Collins, Denise (OAH)

From: Ilan Zeroni <ilan.zeroni@gmail.com>
Sent: Friday, June 22, 2012 3:41 PM
To: Lipman, Eric (OAH)
Cc: Ek, Scott (COMM)
Subject: Public Comments For Hollydale 115kV HVTL
Attachments: Creosote - Competent Authority Report.pdf; creosote railroad tie msds.pdf; Easement and partial release.pdf; EPA - PCP Reregistration Eligibility Decision.pdf; MN PCA Treated Wood.pdf; US Dept Of Health And Human Services - Creosote Toxicological Profile.pdf; Hollydale 115kV Project - EIS Scoping Decision Comments - Ilan Zeroni v1.pdf

Dear Mr. Lipman, I attach my comments in pdf form. The comments refer to several documents, which I attach to this email as well, to please be included in the record. I CC Mr. Ek on this email at his request, so he may have the chance to look at my proposed routes. Mr. Ek, if anything is unclear, particularly regarding the alternate routes, please do not hesitate to reach out.

Please do not hesitate to contact me with any questions or concerns at 763-218-1107 or at this email address. Thanks you for the opportunity to submit comments, and have a wonderful weekend.
Ilan Zeroni

Competent Authority Report

Work Programme for Review of Active Substances in Biocidal Products
Pursuant to Council Directive 98/8/EC

CREOSOTE (PT8)

DOCUMENT I

Evaluation Report

Rapporteur Member State: Sweden

Draft October 2007

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Table of Contents; DOC I

I.1 Statement of Subject Matter and Purpose 3
1.1 Purpose for which the Competent Authority Report was prepared 3
1.2 Identity of active substance 3
1.3 Identity of the biocidal product 4
I.2 Overall Summary and Conclusions 6
2.1 General substance information / general product information 6
2.1.1 Active substance/product properties 6
2.1.2 Analysis of the active substance as manufactured 7
2.1.3 Formulation analysis 7
2.1.4 Residue analysis 7
2.1.5 Classification and labelling 9
2.2 Effectiveness against target organisms / efficacy 11
2.3 Human health risk assessment 12
2.3.1 Human health effects assessment 12
2.3.2 Toxicokinetics and metabolism 12
2.3.3 Acute toxicity 13
2.3.4 Short-term toxicity 13
2.3.5 Genotoxicity 13
2.3.6 Long-term toxicity and carcinogenicity 13
2.3.7 Reproduction toxicity 14
2.3.8 Neurotoxicity 14
2.3.9 Medical data 14
2.3.10 Acceptable daily intake (ADI) and acute reference dose (ARfD) 15
2.3.11 Acceptable Operator Exposure Level (AOEL) 16
2.3.13 Data on exposure for operators 16
2.3.14 Data on exposure for bystanders 17
2.4 Environmental risk assessment 18
2.4.1 Effects assessment 18
2.4.2 Exposure assessment 20
2.4.3 Risk characterisation 20
2.5 Hazard identification for physico-chemical properties 23
I.3 Proposal for the Decision 24
3.1 Background to the proposed decision 24
3.2 Proposed decision regarding the inclusion in Annex I 25
3.3 Justification for the conditions and restriction(s) regarding the planned inclusion in Annex I 25
I.4 Demand for Further Information 26
Appendix: Listing of End Points 27
Appendix: List of Terms and Abbreviations 45

I.1 Statement of Subject Matter and Purpose

1.1 Purpose for which the Competent Authority Report was prepared

This competent authority (CA) report has been prepared for submission to the European Commission to enable a decision to be made on the possible inclusion of creosote in Annex I of Directive 98/8/EC as a part of the review programme referred to in Article 16(2) of the Directive.

1.2 Identity of active substance

Name and address of applicant for inclusion of the active substance in Annex I

Address	Creosote Council Europe (CCE) Subgroup of Coal Chemicals Sector group CEFIC Avenue E. van Nieuwenhuyse 4 B-1160 BRUSSELS
Telephone	+32 26767211
Facsimile	

Manufacturer of the active substance

BILBAINA de ALQUITRANES, S.A. *Obispo Oleachea 49* *E-48903 LUCHANA-BARACALDO Vizcaya* *SPAIN* *+34-94 4970020* *enrique@bilbaina.com*
CINDU CHEMICALS BV. *Postbus 9* *NL-1420 AA UITHOORN* *HOLLAND* *+31-297-545259* *g.weering@cindu.nl*
KOPPERS UK Ltd. *Port Clarence Works, Huntsman Drive* *PORT CLARENCE / Middlesborough, Teeside, TS2 1SD* *(Contact see Koppers Denmark)*
KOPPERS UK Ltd. *Dawes Lane* *SCUNTHORPE / North Lincolshire DN15 8UR* *(Contact see Koppers Denmark)*
KOPPERS Denmark A/S *Avernakke* *DK-5800 NYBORG* *DENMARK* *+45-63313100* *bechp@koppers-eu.com*

RÜTGERS Chemicals AG *Kekuléstr. 30* *D-44579 CASTROP-RAUXEL* *GERMANY* *+49 2305 705-100* *oele@ruetgers-chemicals.de*
VFT Belgium N.V. *Vredekaai 18* *B-9060 ZELZATE* *BELGIUM* *+32-93458831* *luc.dewulf@vft.be*

Common name

Creosote

Chemical name

Creosote

CAS No.

8001-58-9

EINECS No.

232-287-5

Molecular and structural formula, and molecular mass

Not applicable to a complex mixture (i.e. UVCB-substance); information on the individual components are given in Doc IIIAB1-2.

Purity

Not applicable to a complex mixture (i.e. UVCB-substance)

Impurities and additives

Not applicable to a complex mixture (i.e. UVCB-substance)

1.3 Identity of the biocidal product

The biocidal product is the same as the active substance

Current, former and proposed trade names and development code numbers

Creosote

Manufacturer of the biocidal product

Same as for the active substance

Composition of the biocidal product

100% creosote

I.2 Overall Summary and Conclusions

2.1 General substance information / general product information

Creosote [CAS No. 8001-58-9], as defined in the European Standard EN 12303 (CEN 2000), a brownish-black oily liquid, used as wood preservative, is a distillation product of coal tars which themselves are by-products of the high-temperature destructive distillation of bituminous coal to form coke.

The distillation process generally produces several oil cuts starting from 80°C to 450°C. Creosote is the intermediate cut, ranging from 200 to 355°C as described in the European Standard EN 13991 (CEN 2003).

The common product is called Grade B and is intended for treatment of timber by pressure impregnation. Grade C excludes the lower boiling fraction allowable in Grade B, and because of the lower volatility a reduction in odour is achieved. Furthermore the term creosote Grade B composite is used throughout the dossier/report and it is a mixture of single Grade B creosote batches produced by the European producers and mixed at equal parts in order to achieve an average representative Grade B creosote. It also served in more recent testing to cover some data gaps (e.g. the algae test, mouse lymphoma test).

Creosote is a complex mixture of hundreds of distinct compounds, including bi- and polycyclic aromatic hydrocarbons, phenols, as well as heterocyclic, oxygen-, sulphur- and nitrogen-containing compounds. 66 compounds have been identified in the creosotes applied for.

2.1.1 Active substance/product properties

Several of the physical and chemical properties are claimed to have been tested in internal studies of the creosote manufacturers and these parameters were only addressed in Document III-AB (i.e. no study reports were provided in Document IV). This has been considered acceptable as the results are reasonable and in some cases also supported by results on other/undefined types of creosote. The parameters for which no study summaries were provided are summarised in the first section below.

<u>Parameters only addressed in Document III-AB</u>

The two grades of creosote under evaluation (i.e. Grade B and Grade C) are brown liquids with an aromatic odour. The cloud/clarification point is <30°C for both grades and the boiling point is ≥210-400°C and ≥260-400°C for Grade B and Grade C respectively. Creosote is denser than water (i.e. density is 1.02-1.15 for both grades) and it is considered soluble in benzene, toluene, acetone and quinoline. Creosote is not considered auto-flammable, highly flammable or to possess oxidizing properties. The flash-point is >80-105°C. It is claimed not to be explosive but it is also stated that the vapours of creosote may produce explosive mixtures with air. It is considered thermally stable, stable upon storage and not reactive towards any container material. The viscosity is claimed to be <25 mm^2/s for both grades and is probably also within the range 13-16 mm^2/s (i.e. experimentally determined for US-type creosote). The great majority of the components of creosote are not able to dissociate and creosote is thus not considered to be significantly affected by pH.

<u>Parameters for which study-reports were provided</u>

The vapour pressure of the creosotes applied for is extrapolated to be 0.7 Pa and 0.5 Pa at 25°C for Grade B and Grade C respectively. Vapour pressure data for several of the components of creosote is also available from the open literature. Henry's law constant is not considered relevant for the creosote mixtures but individual figures for several of the components are available from the open literature. The water solubility expressed as TOC was found to be dependent on the initial creosote loading and was determined as 2.2-8.1 mg/l for all grades at a loading of 100 mg/l. At a loading of 10 g/l the TOC was

~30 mg/l for Grade B and Grade C and 191 mg/l for Grade B composite. The difference is probably due to the larger fraction of low molecular components in Grade B composite.

Moreover, water solubility data is also available from the open literature for several of the components.

Log P_{ow} was determined for US-types P1/13 and P2 creosote and the results are considered valid also for the EU-creosote under evaluation. The result was shown to be dependent on the octanol concentration with increasing log P_{ow} with decreased octanol:water ratios. The log P_{ow} was found to be in the range 2.7-3.7 for the tested creosotes. However, due to uncertainties in the validity of the experimentally derived log P_{ow}, it has not been used in the evaluation of fate and behaviour (see section 2.4 below).

2.1.2 Analysis of the active substance as manufactured

The method provided for characterisation of the creosote under evaluation is based on GC-FID and was able to determine 63%, 60% and 56% (w/w) of the total content in the Grade B-composite, Grade B and Grade C respectively.

No validation data was provided for the method except for some linearity data. However, due to the complex nature of creosote and as it falls under the definition of substances of unknown or variable composition, complex reaction products or biological materials (i.e. a UVCB-substance) according to the REACH Implementation Project (RIP) 3.10 no further validation data is considered required.

Nevertheless, provided characterisation data on the US-types P1/13 and P2 creosote indicates that the sum of identified components in the creosote under evaluation can be increased. The RMS therefore proposes that further characterisation data for the EU-creosotes applied for is set as a data requirement.

2.1.3 Formulation analysis

See 2.1.2 above. The active substance and the product are the same.

2.1.4 Residue analysis

Numerous methods were provided for the analysis of components of creosote in different compartments, mostly from the open literature.

<u>Soil and sediment</u>
For soil the applicant stated that the provided US-EPA standard for extraction of PAH, phenols and heterocycles could be used in connection with any of the methods used for characterisation of creosote. However, the RMS considers that some validation data is required in support of this statement and therefore proposes that this should be set as a data requirement.

A method based on GC-MS from the open literature was submitted to address the analysis of 24 PAHs in sediment. However the study is only considered acceptable as supplementary information as the reporting and the validation data is insufficient.

<u>Air</u>
Several methods were provided for the analysis of PAHs in air, which are considered to be the most relevant components of creosote to be monitored in air. The method considered most suitable for monitoring in air is based on GC-FID and has been sufficiently validated.

<u>Water</u>
Two acceptable standard methods based on HPLC-FD and GC-FID were provided for the analysis of PAHs in drinking and surface water.

Moreover, a GC-FID method for water using the same principles as in the characterisation of the creosote under evaluation was provided. This method was able to also quantify the polar components of creosote, which is considered required as these substances are more likely to end up in the water

compartment. No sufficient validation data was provided. However, the data derived by the method was in good agreement with the results obtained in a study by an independent laboratory using the same method.

Animal and human body fluids and tissues
An acceptable method based on GC-FID/MS for the analysis of three PAHs (phenanthrene, pyrene and chrysene) and the corresponding OH-metabolites in faeces and urine was provided. No sufficient validation data was provided in the studies used to address the analysis of blood and tissues. However the presence of PAHs and corresponding OH-metabolites in urine and faeces is widely used as an indicator of creosote exposure and no further data is therefore considered required.

Food and feeding stuffs
No method is considered required due to the use pattern of creosote and the fact that that the biomagnification potential of PAH generally is considered low.

2.1.5 Classification and labelling

Creosote is currently classified according to the Commission Directive 2004/73/EC (adapting to technical progress for the twenty-ninth time Council Directive 67/548/EEC) which updates Annex I to Directive 67/548/EEC.

Since the active substance and the biocidal product are identical they have the same classification and labelling requirements.

Hazard symbol and indication of danger	Xi	Irritating
	T	Toxic, carcinogen, Category 2
	N	Dangerous for the environment
Risk Phrases: (for labelling)	Existing and provisionally by manufacturer:	
	R36	Irritating to eyes
	R38	Irritating to skin
	R45	May cause cancer
	R51/53	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
	Additional classification proposed by RMS:	
	R43	May cause sensitization by skin contact
	R60	May impair fertility
	R63	Possible risk of harm to the unborn child
	Classification according to GHS (ECB transitional table)[1]:	Hazard statement according to GHS:
	Eye irrit. 2	H319
	Skin irrit. 2	H315
	Skin sens. 1	H317
	Carc. 1B	H350
	Repr. 1B	H360F
	Repr. 2	H361b
	Aquatic Chronic 2	H411
Safety Phrases: (for labelling)	S24	Avoid contact with skin
	S25	Avoid contact with eyes
	S45	In case of accident or if you feel unwell, seek medical advice immediately. Show the label where possible
	S53	Avoid exposure – obtain special instructions before use
	S57	Use appropriate container to avoid environmental contamination
	S61	Avoid release to the environment. Refer to special instructions/Safety data sheets

1. The current classification has been directly translated into corresponding GHS phrases, using the translation list "Translation between classification in accordance with Directive 67/548/EEC and the new EU C&L Regulation"

i.e Annex VII to Proposal for a Regulation of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures, and amending Directive 67/548/EEC and Regulation (EC) No 1907/2006" (COM(2007) 355 final).

2.2 Effectiveness against target organisms / efficacy

Product type and field of use envisaged

Main group 2: Preservatives

Product type 8: Wood preservative

Creosote is used as a wood preservative for industrial and professional use in use classes 3, 4, and 5 (applications above soil, in soil and freshwater, and in sea water).

User

Professional use only

Function

Repellent, fungicide, and insecticide. Creosote is used as a biocidal active substance against wood rotting fungi, against wood rot in soil and water contact, and against insects.

Effectiveness and organisms to be controlled

The efficacy data show, together with many years of practical experience, adequately that creosote is effective against a broad spectrum of organisms.

Organisms to be controlled:

- wood rotting fungi (wood rotting basidiomycetes, soft rot micro-fungi, wood disfiguring fungi)
- wood rot in soil and water contact
- insects (termites, wood-decaying beetles)
- crustaceae (marine borers)

For example:

- *Lentinus lepideus*, *Coniophora cerebella* (brown-rot fungus), *Poria vaporarla*, *Polystictus* (white-rot fungus)
- Insects Xylophaga larvae: *Hylotrupes bajulus*;
  Anobia larvae/nymphs: *Anobium punctatum*
- Insects Termites: *Calotermes flavicollis*
- Crustaceae: *Limnoria sp*., *Limnoria tripunctata*, *Limnoria lignorum* / *Teredo sp*., e.g. *Teredo utriculus*, *Teredo pedicullata*

Although some of the efficacy data are old, they nevertheless, together with many years of practical experience, adequately show the good efficiency of creosote against a broad spectrum of harmful organisms. Please, note that a full assessment of efficacy will be performed for product authorisation at national level in each Member State.

2.3 Human health risk assessment

2.3.1 Human health effects assessment

The biocidal product creosote and the active substance are one and the same. A database on the toxicity of creosote was submitted by the applicant. It included studies on toxicokinetics, acute toxicity, short-term toxicity, genotoxicity, reproductive and developmental toxicity, combined chronic toxicity and carcinogenicity.

2.3.2 Toxicokinetics and metabolism

Creosote is a complex mixture and is composed of several hundreds and probably several thousands different compounds. Standard ADME studies according to guidelines are therefore not possible to perform. The submitted database consists of published literature describing some parts of ADME of some of the key components of creosote. Great caution has to be taken when interpreting the ADME results obtained with individual components of creosote. The ADME of a complex mixture like creosote can be vastly different even with respect to the single components themselves.

The absorption from the gastrointestinal tract was relatively rapid following oral administration of phenanthrene and pyrene in the rat and was estimated to be higher than 90% based on the presence of the mother compound in the faeces. The oral route is, however, of minor importance in human exposure. Dermal exposure has been shown to account for about 90% of human exposure, and inhalation exposure accounts for the remaining part. Dermal absorption of creosote is, however, extremely difficult to assess depending on a large number of variables. Please see Doc II-B, section 9.1, for a discussion on this matter.

Information regarding distribution of creosote into tissues is scarce. Results regarding the persistence of creosote over a long period are inconclusive. The total recovery of the mother compounds and their metabolites were in some studies very low. For phenanthrene only about 10% was excreted following oral administration and for pyrene only about 50% of pyrene and the metabolites that were analysable with the technique used in the study, were excreted. Either it is, as the applicant suggests, that different species of metabolites are formed and excreted but they are not analysable by the experimental conditions used or, alternatively, substantial parts of phenanthrene and pyrene and metabolites of the respective compounds are retained and possibly accumulated in the body. A combination of these two scenarios is also possible. In contrast, other studies show almost complete elimination of benzo(a)pyrene following dermal administration. Only about 0.5% was retained in the body after 7 days. Generally, metabolites of 2-3 ring aromatic compounds are mainly excreted into urine or to similar extent into urine and faeces, while metabolites of 4 –6 ring PAH are mainly excreted into the faeces.

Aromatic compounds are metabolized by microsomal oxidative enzyme systems in a first step, in particular by the cytochromes P450 system (CYP1A1, CYP2E1 and CYP3A) in liver, lungs and other tissues. Thereby, the PAHs form reactive intermediates (epoxides) that can bind to macromolecules and cause specific toxic effects. Generally, the epoxides are hydrolysed, thereby forming hydroxy-/dihydroxy compounds or are directly conjugated with glutathione. Dihydrodiols may undergo conjugation with glucuronic acid or sulphate. Hydroxylated species may be further oxidised and form quinones. Conjugates of phenols, dihydrodiols, quinones, anhydrides have been the principal metabolic products identified. The metabolic profile varies with compound and species tested.

The primary metabolic reaction of acenaphthene starts with the oxidative cleavage of the 5-membered ring in acenaphthene in rat.

The metabolites following administration with phenanthrene were phenolic and dihydrodiol compounds. In vitro experiments show that a single metabolite, trans-9,10-diOH-9,10-dihydrophenanthrene (K-region oxidation), was formed by liver microsomes from non-induced rats while various inducers stimulated the formation of additional metabolites. Creosote contains several of these potential monooxygenase inducers. Observations by others show that also conjugation with glutathione, may occur to a high degree. Conjugation with methionine may also occur, resulting in

methylthioesters. These types of metabolites escaped analysis under the experimental conditions employed in the investigations outlined above.

In the metabolism of fluoranthene mainly 3-dihydro-2,3-diOH-fluoranthene was formed but also 3-OH-fluoranthene, and 1-OH-fluoranthene were identified. The metabolism of fluoranthene in human and rat liver microsomes was qualitatively roughly similar, but the spectra of metabolites differed a lot.

While the trans-2,3-dihydrodiol was the major metabolite in both systems, many more metabolites were seen in the rat samples. Rat liver microsomes were also more proficient at metabolising fluoranthene. Variability was seen in the human samples, with respect to both the extent of metabolism and the metabolite spectra. This probably reflects interindividual differences. There were also differences between the human and rat systems in the formation of R,R enantiomers of the major metabolite, which may have an impact on the mutagenic potency.

The main metabolite following administration of pyrene is 1-OH-pyrene.

2.3.3 Acute toxicity

Creosote has low acute toxicity when administered orally, dermally and via inhalation to rats.

Creosote is a skin irritant. Furthermore, creosote should, despite the negative results from the eye irritation study, on a precautionary basis, be considered to be potentially irritating to eyes, especially since practical experience with hot vapours of creosote has shown that it may display irritating properties to the eyes.

Creosote should be labelled with **Xi, R38 “Irritating to skin”.**

In the sensitisation studies creosote proved to be sensitising in the Maximisation test (M&K test), and considerations should therefore be taken if creosote should be labelled with **R43 “May cause skin sensitisation by skin contact”**.

2.3.4 Short-term toxicity

For repeated administration of creosote via the dermal and inhalational routes the studies did not reveal any evidence for cumulative toxicity in rats.

Most of the changes observed in the dermal and inhalational studies were mild and did not persist after the recovery periods.

2.3.5 Genotoxicity

The mutagenic potency of creosote was studied *in vitro* in bacteria and mammalian cells and *in vivo* test systems in rats and mice. The results show that the creosote types tested were mutagenic in 2 out of 4 *in vitro* tests in the presence of a metabolising system (S9), while creosote was negative in the *in vivo* test systems with respect to genotoxicity. It has to be kept in mind that there was significant cytotoxicity in most of the experiments. This can eventually mask a mutagenic potential of creosote in these assays.

Different creosote types have been shown to display large differences in genotoxic potency and the composition of creosote today has drastically reduced amounts of genotoxic components compared to former creosote types. However, the overall results from this evaluation regarding the genotoxic potency of the creosote types tested are inconclusive. Risk mitigation procedures are important since since no threshold can be said to exist for substances containing genotoxic compounds.

The complex composition of creosote includes several mutagenic components, and the results in genotoxicity assays varies, depending on for example, cell type, concentration, metabolising capacity etc.

2.3.6 Long-term toxicity and carcinogenicity

One dermal carcinogenicity study was submitted. In addition of oncogenicity a limited number of other endpoints with respect to long-term toxicity were investigated.

The results show that there was a dose-dependent increase in the number of tumours, and the tested creosote types produced 3-5 times more tumours than what could have been expected based on their BaP content.

A threshold cannot be said to exist, and it is generally agreed that there is no threshold for genotoxic substances. Creosote is a complex mixture which contains several substances that are regarded as carcinogenic and mutagenic. A NOAEL could therefore not be set.

Creosote is classified as Canc. Kat. 2, R45.

Regarding other endpoints following long-term exposure, some parameters, in addition of carcinogenesis, were investigated. None of these gave rise to significant findings. Carcinogenesis can, however, be regarded as the most severe endpoint after long-term exposure.

2.3.7 Reproduction toxicity

In the teratology studies in rats there was an increase in post-implantation loss (early resorptions) in the high dose group. There was no difference in maternal body weight and body weight gain between the dose groups and the control when corrected for gravid uterine weight.

It seems that creosote has an impact on early intrauterine development (seen as post-implantation loss) under very mild maternal toxicity.

In the developmental toxicity study performed in rabbits there was an increase in abortions and a reduction in the number of live fetuses in the high dose group. This can either be a result of maternal toxicity or reflect a reproductive/developmental toxicity effect of creosote.

All together these results indicate that creosote has an impact on early intrauterine development. It is unlikely that the increases of post-implantation losses are coupled to the decreased maternal food consumption, and there were virtually no other maternal toxic signs. Creosote should therefore be labelled with **R63 – “Possible risk of harm to the unborn child”**

In the two-generation reproduction study, a significant reduction in the number of live F1 offspring in the mid and high dose groups was observed. There was also a decrease in litter size and in offspring viability in F2, and this effect was even clearer than in F1. The body weight of live pups was decreased among all dose groups and showed a clear dose response (less than 10 % in the low dose group).

Overall, the results of the reproduction studies indicate that creosote has an impact on reproduction and fertility under the influence of very mild maternal toxicity (maternal toxicity mainly seen as as salivation and reduction of body weight and body weight gain (up to 20%) during gestation and lactation, and note, no corrections were made for gravid uterine weight). The decrease of maternal body weight gain during gestation may therefore be an effect of the decreased number of viable offspring.

Creosote should therefore be labelled with **R60 “May impair fertility”**

2.3.8 Neurotoxicity

No specific data submitted. The results from the other studies do not indicate any neurotoxic potential of creosote.

2.3.9 Medical data

Creosote has been used for more than 100 years. Clinical findings thought to result from occupational exposure have mainly been restricted to the presence of various types of skin rashes, such as pustular folliculitis, tar warts, dermatitis, including phototoxic dermatitis after subsequent or simultaneous exposure to sunlight.

Epidemiologists have attempted to determine whether people who are occupationally exposed to creosote are at a greater risk than the general population for certain cancers. In a historical cross-sectional occupational survey (Henry 1947), skin tumour incidences over 26 years amounted to 35 cases for which "creosote oil" was nominated as causal agent out of 3753 skin cancer cases (about 1 %/26 years), notified by the “British Medical Inspector of Factories” in the first half of the 20th century. This low incidence has to be seen in relation to the less stringent working standards and application of creosotes with much higher PAH levels than today.

Studies conducted in Norway and Sweden and in the United States show conflicting results. Some studies point to a connection between creosote exposure and various forms of cancer and there are also a number of studies that fail to show such an association between occupational creosote exposure and any cancers. Simultaneous exposure to sunlight was a confounding factor.

The significance of the results of the epidemiological studies and exposure studies are difficult to interpret. Many of these studies are limited by their date and/or by uncertainty over the composition of the creosote in use at the time. The latter is a problem even for the more recent studies. Some of the studies were based on questionnaires on past occupational activities, giving rise to uncertainty about the reliability of the information gathered maybe several years after exposure occurred. Furthermore, the number of workers available for the studies were uncertain or few. The studies were also hampered by the lack of follow-up and control of confounders.

A recent cohort study which included creosote-exposed workers of 11 wood-treating plants in the USA from 01 Jan. 1979 through 31 Dec. 1999 failed to reveal any exposure-related mortality increases (Wong and Harris 2005).

A large risk assessment was conducted for creosote pressure-treating workers using probabilistic distributional methods (Sapphire 2004). This was not a single study, and it was based on reviews of animal data, case reports, cohort studies, case control studies, cross-sectional studies, and exposure studies. It included some of the studies mentioned above.

The estimates of occupational cancer risk from creosote in the Sapphire study gave the result that the largest part of the cancer risk distribution fell within acceptable risk levels (1×10-6 to 1×10-4) traditionally employed for regulatory purposes by the US EPA (Sapphire 2004). However a small part (95th %-ile) (result of cancer potency factors: $1.5x10^{-4}$ with probabilistic analysis included, and $3.1x10^{-4}$ with probabilistic analysis excluded) actually falls above the acceptable risk (that is $1x10^{-4}$), giving a reason for concern.

Overall, the body of epidemiological data does not indicate an apparent elevated cancer risk for creosote workers.

Direct observations, e.g. clinical cases and poisoning incidents

Fatal cases after ingestion of creosote involves the amount of about 7 g for adults and 1-2 g for children. Death occurs 14 to 36 hours after ingestion of such amounts, and is mainly coupled to cardiovascular collapse.

Symptoms of systemic exposure and illness are salivation, respiratory difficulties, vomiting, headache, irregular pulse, vertigo, hypothermia, cyanosis, and mild convulsions.

2.3.10 Acceptable daily intake (ADI) and acute reference dose (ARfD)

By definition, ADI gives a safety level of daily intake of a substance via ingestion.

Therefore, the setting of ADI for creosote would be considered irrelevant, since creosote is used as wood preservative (PT8).

The route of exposure to creosote is primarily via dermal exposure, and to some extent via inhalation. Creosote is only used by professional users. The exposure via food or drinks to creosote would be practically non-existent. In addition, creosote is a complex mixture and contains several components that are regarded as carcinogenic and mutagenic, and creosote is classified as carcinogenic Cat.2. An ADI cannot be set for substances that are genotoxic and/or carcinogenic unless a threshold mechanism clearly has been demonstrated. Creosote is regarded as a complete carcinogen (i.e., it has both initiating and promoting capacity with respect to tumour formation). The RMS is therefore of the opinion that an ADI or a long-term reference value cannot be established for creosote.

The ARfD of a chemical can be defined as "an estimate of a substance in food and/or drinking water, normally expressed on a body weight basis, that can be ingested in a period of 24 hours or less, without appreciable health risk to the consumer on the basis of all the known facts at the time of evaluation" (EU guidance, 7199/VI/99/rev 6). By this definition, the setting of ARfD for creosote which is used as

wood preservative (PT8) is considered not to be relevant by RMS, since there will be no exposure of creosote to food or drinking water.

2.3.11 Acceptable Operator Exposure Level (AOEL)

Creosote is a complex mixture and contains several components that are regarded as carcinogenic and mutagenic, and creosote is classified as carcinogenic Cat.2. According to the EU Guidance for the setting and application of acceptable operator levels (AOELs) (rev 10), an AOEL cannot be set for substances that are genotoxic and/or carcinogenic unless a threshold mechanism clearly has been demonstrated. Creosote is regarded as a complete carcinogen (i.e., it has both initiating and promoting capacity with respect to tumour formation).

The RMS is therefore of the opinion that an AOEL or a long-term reference value cannot be established for creosote.

2.3.13 Data on exposure for operators

Measurements performed at impregnation plants in North America were presented. A justification was provided describing the similarities of the processes as compared to European conditions. All relevant exposure scenarios and work tasks were covered. Since creosote is a complex mixture consisting of several hundreds, and maybe thousands different compounds, it cannot be measured directly. Instead, eleven of the predominant components of North American Standard Creosote P2 and P1-13 were chosen to represent the entire boiling range of compounds found in creosote (these were: naphthalene, 2-and 1-methylnaphthalene, fluorene, acenaphthene, phenanthrene, dibenzofurane, anthracene, fluoranthene, pyrene, and chrysene).

The main conclusions were that worker exposure occurs primarily via the dermal route and is clearly connected to the proximity of the treating cylinder.

The estimated fraction of total body deposition arising from inhalation was in the range of **0.01- 0.06 mg/kg bw/day** (11 PAH dominated by naphthalene at >50 %), while the dermal creosote deposition ranged from about **0.06 to more than 10 mg per kg bw/day (maximum value 58.6 mg/kg bw/day)** with geometric averages from **0.03 – 1.1 mg/kg bw/day** (Bookbinder 2001). This range of creosote contamination of creosote workers skin is fairly well supported by the results from the other studies.

For both dermal and inhalatioanl uptake a value of 100% is used in the risk characterisation

The RMS is fully aware that this is a very conservative value for dermal absorption.

It is, however, with the submitted data as a basis, impossible to conclude on dermal absorption of creosote as a whole mixture. It is not possible to conclude if the remainder components (majority) of creosote behave the same way as the PAHs or mixtures used in the different studies.

The applicant has suggested to use a dermal absorption value of 20%/24h. However, given the considerable uncertainties present in the submitted data package (see Doc III-A6/B6, and Doc II-B, section 9.1 for more details), and with reference to the EU Guidance document of dermal absorption (Sanco/222/2000 rev 6, 27 november 2002) a default value of 100% for dermal absorption has to be used.

The result of the risk characterisation is that all of the Margin of Exposures (MOEs) indicate reasons for concern, and no safe uses can be identified, based on the animal experimental results, and on the submitted exposure data.

Regarding down-stream users, e.g., pole installers, there are no specific exposure data available for these groups. However, handling of treated wood products is included in the work tasks in the study by Bookbinder (see above), and, furthermore, it was shown that exposure is clearly connected to the proximity of the treating cylinder. Wood handled by down-stream users is much dryer than directly after the impregnation process. It is unlikely that downstream users would exhibit higher exposure than workers at the impregnation plants.

2.3.14 Data on exposure for bystanders

Creosote is exclusively used by professional users. Exposure to non-professionals is therefore considered to be of minor relevance.

Furthermore, the exposure has been shown to be clearly connected to the proximity of the treating cylinder, and inhalational exposure account for only about 10 % of the total exposure levels. Investigations regarding emissions to ambient air at two American pressure treatments plants have shown the ambient air emissions for naphthalene, which is the most significant PAH air emission, are close to background concentrations. Other, more high-molecular weight PAHs are below detection levels. Consequently, there is no apparent elevation in health risks for people living nearby creosote treatment plants.

2.4 Environmental risk assessment

2.4.1 Effects assessment

2.4.1.1 Fate and distribution

Creosote is made up of hundreds of aromatic compounds and from this fact it can be understood that a selection has to be made concerning which and how many compounds that can be studied regarding their fate and distribution in the environment. Since most compounds in creosote are polycyclic aromatic hydrocarbons (PAHs), the data submitted is almost exclusively on PAHs.

Abiotic degradation

No data has been submitted on hydrolysis of creosote components. The justification given is that the components of creosote do not have hydrolysable groups and this has been considered to be acceptable.

PAHs present in creosote are rapidly photolysed under best case, laboratory conditions and an increasing trend in photoreactivity with increasing molecular weight was indicated. Due to effects of light attenuation, simulated realistic case half-life values for photolysis in natural waters were approximately two orders of magnitude longer than best case half-lives and varied between approximately half a day and 300 days depending on the PAH studied. Regardless of water type, direct photolysis is much more important than photosensitized oxygenation of PAHs. One major transformation product from aqueous photolysis of PAHs seems to be quinone derivatives. It has been indicated that photolysis of alkylated PAHs generates a greater number of transformation products than photolysis of parent PAHs.

For volatile PAHs, gas phase reaction with OH radicals is an important removal process. The half-lives of the selected PAHs range from approximately 1 to 7 hours. The mean half-life for the selected PAHs can be estimated to approximately 3 hours. For some PAHs, reactions with NO_3 radicals are very important but for PAHs in general this transformation pathway is of less importance compared to the OH radical-initiated reactions.

Biodegradation

A majority of the compounds present in creosote contain fused polyaromatic ring systems (e.g. PAHs) which are very stable chemical structures, but a wide variety of bacteria, fungi and algae do have the ability to metabolise these compounds.

Results of aquatic screening tests show that under favourable microbial conditions PAHs show significant degradation with rapid or gradual adaptation. This is true for compounds with three rings or less but among compounds with four rings some PAHs do not degrade even under favourable conditions. The rate of degradation in water for PAHs with three rings or less seems to be enhanced when the water has been previously contaminated with hydrocarbons and/or PAHs. Alkylated PAHs seem to degrade slower than parent PAHs.

Dissipation half-lives in water of all PAHs (and creosote) can be estimated to one month. The dissipation of creosote components from the water can most likely be ascribed to a combination of removal processes like volatilisation, adsorption, uptake by biota, photolysis and biodegradation. Mineralisation half-lives in sediment-water systems can be summarised as follows: For non-alkylated PAHs with two rings; $DT_{50} \approx 30$ d, for alkylated PAHs with 2 rings and PAHs with 3 rings; $DT_{50} = >60$ d and finally, for PAHs with four rings, $DT_{50} \approx$ several years - ∞ (all at 22 °C). The rate of aerobic and anaerobic degradation of creosote components like PAHs increase in previously contaminated sediment water environments compared to pristine environments. In pristine, anaerobic sediment water environments mineralisation rates of PAHs are indicated to be too slow to be measured.

Soil degradation half-lives at 20 °C ranged from approximately two days for two ringed PAH compounds to more than a year for the four ringed PAHs. Shorter degradation half-lives were measured for PAHs when incubated as constituents in creosote. No degradation could be measured in anaerobic

soil. PAHs may however be microbially degraded in soil under anaerobic, denitrifying conditions. The rate of degradation under anaerobic denitrifying conditions is slower than under aerobic conditions. Data on route of degradation in soil and the extent and nature of bound residues was missing.

Distribution

For compounds present in creosote, the log K_{oc} values are found in the following approximate intervals; aromatic hydrocarbons range from 2.5 to 5.4, phenolic compounds from 1.0 to 1.8, nitrogen containing heterocycles from 1.1 to 3.0, sulphur containing heterocycles from 2.7 to 3.9 and finally, for the only identified oxygen-containing heterocycle, dibenzofuran, the log K_{oc} is approximately 3.6. All K_{oc} values have been estimated from literature values of K_{ow} by using the following correlation between the two partition coefficients; $K_{oc} = 0.35\ K_{ow}$.

If the log K_{ow} and log K_{oc} values of single compounds are weighted by their content in creosote (in percent), the log K_{ow} and log K_{oc} values of the different creosote oils can be estimated. The results of such calculations indicate that the composite sample of Grade B type (log K_{oc} 3.67) is less hydrophobic than the single Grade B creosote oil (log K_{oc} 3.97). Since the content of low molecular weight PAHs (i.e. most volatile compounds) is lower in Grade C creosote oil its log K_{oc} is higher (4.17) than that for Grade B.

Accumulation

It is not possible to determine a single value for bioaccumulation potential of creosote, since the individual components of creosote all have different bioaccumulation potential. In the aquatic environment, the bioconcentration factors (BCFs) of a number of PAHs in creosote (phenanthrene, fluorene, fluoranthene, and pyrene) ranged from 78 to 540. However, some other components of creosote (naphthalene, methyl-naphthalenes, and anthracene) had higher BCFs of about 1000 and up to almost 5000 at high exposure concentrations. The depuration rate in fish was rather rapid with 95% of the accumulated substance eliminated within 2-5 days for most PAHs. The bioaccumulation potential of creosote components in terrestrial organisms was low.

The results from the bioaccumulation studies in the aquatic environment show that most PAHs that are constituents of creosote are rapidly taken up and bioaccumulated in organisms. Biomagnification in food webs are not to be expected, though, since vertebrates and also some invertebrates have efficient metabolism and/or excretion of PAHs. There are species, however, that metabolise PAHs to little or no extent, like algae, oligochaetes, molluscs, and the more primitive invertebrates (protozoans, porifera, and cnidaria), which can accumulate high concentrations of PAHs. Therefore, predatory organisms may be exposed to significant levels of PAHs when feeding, but organisms from higher trophic levels are expected to eliminate these PAHs rather rapidly.

2.4.1.2 Effects on organisms

Creosote has very high toxicity to aquatic invertebrates and fish and moderate toxicity to algae. Predicted No-Effect Concentration (PNEC) in surface water was 0.1 µg/l, based on the lowest NOEC for both fish and invertebrates, which was 1µg/l. $PNEC_{sw}$ were also calculated for some individual components of creosote and these were in general somewhat higher than the PNEC for creosote, ranging from 0.2-1.5 µg/l.

The effects of creosote-treated pilings on sediment dwelling organisms were assessed in long-term field studies investigating benthic infaunal community composition. $PNEC_{sediment}$ for creosote was estimated to be 2 mg/kg ww sediment, based on measured concentrations of 15 PAHs (assumed to be equivalent to creosote). $PNEC_{sediment}$ derived for two individual PAHs, phenanthrene and fluoranthene, were estimated to 0.4 and 0.6 mg/kg ww, respectively.

The EC_{50} for inhibition of microbial activity in activated sludge by creosote was estimated to be 33 mg TOC/l and the $PNEC_{STP}$ was set to 0.33 mg creosote/l.

Terrestrial toxicity of creosote was studied in three trophic levels (microorganisms, plants, and earth-worm/springtail). The $PNEC_{soil}$ for creosote was estimated to be 0.3 mg/kg ww, based on the NOEC

from a long-term test (28d) with creosote Grade B and springtails. There was also data available to calculate $PNEC_{soil}$ for individual PAHs. These were all higher than the $PNEC_{soil}$ for creosote, with a value of 0.34 mg/kg ww for 1-/2-methylnaphthalene, and between 1.1 and 1.7 mg/kg ww for five PAHs with increasing molecular weight from phenanthrene to pyrene.

2.4.2 Exposure assessment

The environmental exposure assessment of creosote has been performed following the general guidance in the OECDs emission scenario document (ESD) for wood preservatives and the Technical Guidance Document on Risk Assessment (TGD). The exposure assessment of creosote includes the estimation of local emissions to various receiving environmental compartments from only two stages of the life cycle, i.e. industrial product application and treated wood in-service in use classes 3, 4 and 5.

The leaching data used in the exposure assessment originates from experimental data, almost exclusively on pine. For the calculations of PECs, creosote retentions up to 150 kg/m^3 have been taken into consideration since this was the highest retention applied for. Other types of wood as well as higher creosote retentions will have to be assessed by Member State at product authorisation stage.

2.4.3 Risk characterisation

The risk characterisation for the industrial use and for treated wood in-service has been performed both for creosote and for a selection of a few single creosote components (mostly PAHs).

It should be noted that all predicted environmental concentration (PEC) values determined for creosote which have been generated from leaching rate data, are more uncertain than corresponding PEC values for single creosote components since the leaching rates for creosote are extrapolations from single creosote components, i.e. PAHs. Also, in some cases the predicted no-effect-concentration (PNEC) for creosote is more uncertain than corresponding PNECs for individual creosote components.

2.4.3.1 Aquatic compartment

Sewage treatment plant (STP)

There is a risk posed to micro-organisms in a sewage treatment plant (STP) when an industrial application plant is connected to an STP. The PEC/PNEC ratio was 11 for creosote. It is therefore proposed that industrial application facilities should not be connected to a local STP.

The second exposure scenario for a STP is in-service leaching from a noise barrier. For this scenario all PEC/PNEC ratios for creosote and single creosote components were << 1, i.e. no risk was indicated.

Surface water – industrial use

The industrial use of creosote generates two exposure pathways to surface waters, emissions from the application entering a local STP followed by discharge into a local surface water and surface runoff from the storage site for creosote treated wood. PEC/PNEC ratios >>1 showed that there are risks posed to aquatic organisms when exposed to creosote and creosote components via STP outlet. Therefore, it is again proposed that industrial application facilities where wood is treated with creosote should not be connected to a local STP.

PEC/PNEC ratios <1 indicate that no risk is posed to aquatic organisms via exposure to runoff from the storage site. The discharge from a local STP and runoff from the storage site should be assumed to enter the same surface water. In the present case however, there is no point in making this worst-case assumption since the contribution from the storage runoff is negligible compared to the emissions from the application process. In conclusion, the added risk will be the same as the risk for the applications process scenario.

Surface water – in-service leaching

No risks are posed to aquatic organisms via exposure to in-service leaching from a creosote treated noise barrier (via STP outlet) since all PEC/PNEC ratios were <1.

For the jetty-in-lake scenario, PEC/PNEC ratios >1 for creosote showed that there are risks to aquatic organisms when exposed to in-service leaching. The ratios were >1 regardless of assessment period or if removal was considered or not. For individual creosote components however, the PEC/PNEC ratios indicated no risk to aquatic organisms when removal processes (dissipation) were assumed to affect the creosote components in the water. An alternative approach denoted the Hydrocarbon Block Method (HBM) was applied to the PEC/PNEC data for single creosote components in order to assess the risk in a different way. The HBM is based on the assumption that the PEC/PNEC ratio of the whole mixture (i.e. creosote) can be derived from the sum of PEC/PNEC ratios of all single components of the mixture. In the present case, the sums of PEC/PNEC ratios for the selected single components for both assessment periods (i.e. 30 days and 20 years) were adjusted to represent 100% of creosote. The results of the alternative assessment indicated that in-service leaching from a creosote treated jetty in a lake do not pose a risk to aquatic organisms. The applicability of the method needs however to be discussed.

Also, measured water concentrations in large mesocosms mimicking the 'jetty' scenario were used in order to assess the risk from in-service leaching. The result showed that there is a risk for aquatic organisms during the initial assessment period of 30 days and for the long-term assessment period (measured conc. long-term/PNEC = 1.3).

There are risks for aquatic organisms when exposed to in-service leaching from creosote treated sheet pilings in a streaming waterway. The PEC/PNEC ratios were >>1 for creosote and >1 for single creosote components.

For the wharf scenario, all PEC/PNEC ratios for creosote showed that there are risks posed to aquatic organisms when exposed to in-service leaching in a sea water environment. For individual creosote components however, the PEC/PNEC ratios indicated no risk to aquatic organisms when dissipation processes were assumed to affect the creosote components in the water. The PEC/PNEC ratios obtained when applying the HBM on the data for single components were however >1. Data on measured (by semi-permeable membrane device) water concentration adjacent to underwater constructions (piling sites) in a seawater environment was also used to assess the risk for aquatic organisms. The ratio between measured water concentration of creosote and ditto PNEC indicates that no risk is posed to aquatic organisms.

Sediment– industrial use

In a similar manner as for surface water, the PEC/PNEC ratios for the application process showed that there is a risk posed to sediment living organisms when exposed to creosote and creosote components via STP outlet. No risks are however posed to sediment living organisms via exposure to runoff from the storage site.

Sediment– in-service leaching

No risks are posed to sediment living organisms via exposure to in-service leaching from a creosote treated noise barrier (via STP outlet) since all PEC/PNEC ratios were <1.

The PEC/PNEC ratios for creosote and single creosote components were all <1 for the sediment in the jetty-in-lake and wharf scenarios for both assessment periods when assuming removal processes (dissipation) in the water. It should be noted however that the $PEC_{sediment}$ calculated by using the PECs for surface water assuming removal in the water column through dissipation are more or less underestimated. For the sheet-piling-scenario however, all PEC/PNEC ratios were >1 regardless if dissipation in water was assumed or not and regardless of assessment period.

By comparing measured sediment concentration of creosote adjacent to underwater constructions (piling sites) in a seawater environment with the $PNEC_{sediment}$ for creosote it was shown that for the initial assessment period there was a risk for sediment living organisms close (0.5 m) to the piling site

made of newly treated wood. For the long-term assessment period, at the same piling site, the $PNEC_{sediment}$ for creosote was exceeded (i.e. indicating risk) in surface sediments collected in a gradient from close to the construction and up to a distance of >7.5 m - <10 m from the construction. For the piling site made with weathered pilings, the $PNEC_{sediment}$ for creosote was exceeded in sediments collected in a gradient from close to the piling site up to a distance of 2 m for the initial assessment period, and up to a distance of >5 m - < 10 m for the long-term assessment period.

2.4.3.2 Terrestrial compartment

There is risk posed to terrestrial organisms when exposed to leaching of creosote from treated wood at the storage site. It is therefore suggested that all treated wood should be stored on impermeable hard standing to prevent direct losses to soil and allow losses to be collected for re-use or disposal.

There are no risks posed to terrestrial organisms by exposure to in-service leaching from creosote treated house, fence or noise barrier. All PEC/PNEC ratios were <1 when it was assumed that degradation is taking place in the soil.

There are risks posed to terrestrial organisms when exposed to creosote leached out into the ground from a transmission pole or a fence post. For the transmission pole scenario there are risks for both the initial and long-term assessment periods when assuming soil degradation, while for the fence post scenario the risk was only seen for the long-term assessment period (also when assuming degradation in the soil). For individual creosote components however, the PEC/PNEC ratios indicated no risk when degradation was assumed to affect the creosote components in the soil. When applying the HBM on the PEC/PNEC ratios for single creosote components assuming soil degradation in the transmission pole scenario, the alternative PEC/PNEC ratios was <1 for the initial assessment period and slightly >1 for the long-term assessment period. When applying the HBM on data for single creosote components assuming soil degradation in the fence post scenario, the alternative PEC/PNEC ratio was <1 for the long-term assessment period.

Measured concentrations of creosote (i.e. PAHs) at various distances and depths adjacent to a large number of utility (transmission) poles in service were compared to $PNEC_{soil}$ for creosote. The results indicate that there are risks posed to terrestrial organisms at distances up to at least 76.2 cm from the poles. The PAH concentrations measured at a distance of 122 cm from the poles were not elevated compared to background levels but still some of the samples collected at 122 cm from the poles showed ΣPAH concentrations that were above the $PNEC_{soil}$, i.e. indicating risk to soil organisms.

Experimental data showed that creosote components can be mobile in soil which indicates that potential exposure to groundwater cannot be excluded. Simulation results however, indicate that exposure to groundwater for in-service use in use class 3 will not result in unacceptable risk for groundwater.

2.4.3.3 Summary of risk characterisation for in-service leaching

Table summarising the results of the risk characterisation for creosote for all in-service use scenarios. Degradation/removal processes were not assumed for STP and sediment or for water in the ‘noise barrier’ scenario.

		PEC/PNEC >1, Yes / No				**Measured concentrations indicate risk? Yes/No** (Conc./PNEC ratio)
Use class	**Scenario**	**STP**	**Water**	**Sediment**	**Soil**	
3	’House/fence’	-	-	-	No	-
3	’Noise barrier’	No	No	No	No	-
4a	’Transmission pole’ and ‘Fence post’	-	-	-	**Yes**	**Yes** (24)[1]

4b	'Jetty in a lake'	-	**Yes**	No	-	**Yes** (1.3) [2]
4b	'Sheet pilings in waterway'	-	**Yes**	**Yes**	-	-
5	'Wharf'	-	**Yes**	No	-	No -water [3] **Yes** –sediment [4]

[1] The ratio given is for soil at a distance of 45.7 cm from transmission/utility poles (long-term assessment).
[2] The ratio given is for water (large mesocosms) for the long-term assessment period.
[3-4] Equivalent to the long-term assessment period.

2.4.3.4 Atmosphere

Creosote released from the industrial application process and during storage and in-service use of creosote treated wood is not expected to result in air concentrations which can be considered to be of concern.

2.5 Hazard identification for physico-chemical properties

Creosote does not harbour any particularly hazardous physico-chemical properties. It is stable also at elevated temperatures, is not flammable (flash point >80 – 105 °C) and not self-igniting with an ignition temperature above 450 °C. Creosote has no oxidising properties. Creosote has a significant vapour pressure which rises rapidly with increasing temperature. Hydrocarbon vapours may form explosive mixtures with air.

I.3 Proposal for the Decision

3.1 Background to the proposed decision

Creosote is classified as R45, carcinogenic, category 2.

In the risk characterisation for human health all MOEs indicate concern and no safe uses could be identified based on animal experimental results and on the submitted exposure data.

However, the body of epidemiological data does not indicate an apparent elevated cancer risk for creosote workers.

In the TNsG on Annex I inclusion it is stated that: “The risk from active substances that meet criteria for categories 1 or 2 carcinogenicity under 67/548/EEC will not be acceptable where exposure is likely to occur”.

In the TNsG on Annex I inclusion it is also stated that: “The benefits of products containing the active substance should be considered. Especially in cases where there are concerns about the acceptability of the risks, the need for and benefits of biocidal products containing the substance should be considered carefully and weighed against the acceptable level of risk”.

Such a socio-economic benefit analysis has not been performed and is therefore, at present, not part of the background of the proposed decision. However, the withdrawal of creosote from the European market could have substantial impact on European infrastructure and socioeconomics, in particular since creosote treated wood is used in the electrical and telephone supply industries and for railways across much of the European Union. Therefore, it is recommended that a comprehensive analysis of the benefits regarding the use of creosote on a European level is carried out.

If inclusion was proposed on the basis of reduced risk to human health or on other grounds there would remain certain issues with respect to the environmental risk assessment that would need to be addressed. Risks are posed to environmental compartments from exposure from the industrial application process and during storage of creosote treated wood. It is therefore proposed that industrial application facilities would not be connected to a local STP and that all treated wood should be stored on impermeable hard standing to prevent direct losses to soil and allow losses to be collected for re-use or disposal.

For the in-service use of creosote treated wood in use class 3 (not covered and not in contact with soil), the risk assessment showed that no risk is posed to the environment. In-service-leaching from treated wood in contact with the ground (use class 4a) will, according to the risk assessment, result in a risk to terrestrial organisms. The risk assessment also showed that there is risk to the aquatic compartment due to in-service use of creosote treated wood in contact with freshwater (use class 4b) as well as permanently exposed to sea water (use class 5).

The risks identified for the terrestrial and aquatic compartments during in-service use of creosote treated wood should be further discussed and reviewed in relation to the alternative method of assessment presented and to the risk assessment results obtained by the use of measured/monitoring data.

3.2 Proposed decision regarding the inclusion in Annex I

Based on the hazard assessment and risk characterisation for human health; an inclusion in Annex I of Directive 98/8/EC **cannot be recommended** at present for creosote as an active substance in wood preservatives, product type 8.

It is also recommended that the benefits of creosote products are analysed before a final decision is taken.

[Member States shall in the light of new knowledge and information review and, where necessary, amend or withdraw existing authorisations for biocidal products in accordance with Articles 6 and 7 of Directive 98/8/EC. If such amendments or withdrawals are considered necessary the Member State shall immediately notify other Member States and the Commission of such information and the actions taken.]

3.3 Justification for the conditions and restriction(s) regarding the planned inclusion in Annex I

Not applicable at this stage.

I.4 Demand for Further Information

The following data gaps were identified: More detailed data on the composition of the creosotes applied for, validation data for a monitoring method for soil and data on route of degradation in soil and the extent and nature of bound residues.

The information and justifications submitted is however sufficient to propose a decision regarding Annex I inclusion for creosote.

Appendix: Listing of End Points

Chapter 1: Identity, Physical and Chemical Properties, Details of Uses, Further Information, and Proposed Classification and Labelling

Active substance (ISO Common Name)	Creosote
Function (*e.g.* fungicide)	Wood preservative: fungicide, insecticide, repellent

Rapporteur Member State	Sweden (Competent Authority: Swedish Chemicals Agency, KemI)

Identity (Annex IIA, point II.)

Chemical name (IUPAC)	Creosote
Chemical name (CA)	Creosote
CAS No	8001-58-9
EC No	232-287-5
Other substance No.	None
Minimum purity of the active substance as manufactured (g/kg or g/l)	Not applicable to a complex mixture (i.e. an UVCB substance)
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Not applicable to a complex mixture (i.e. an UVCB substance)
Molecular formula	Not applicable to a complex mixture (i.e. an UVCB substance)
Molecular mass	Not applicable to a complex mixture (i.e. an UVCB substance)
Structural formula	Not applicable to a complex mixture (i.e. an UVCB substance)

Physical and chemical properties (Annex IIA, point III, unless otherwise indicated)

Melting point (state purity)	Range: <30 °C (grade B and grade C))
Boiling point (state purity)	Range: ≥210 °C – 400 °C (grade B) ≥260-400°C (grade C)
Temperature of decomposition	none
Appearance (state purity)	Brown liquid with aromatic phenolic odour (purity not applicable)
Relative density (state purity)	1.02 – 1.15 (Grade B and Grade C)
Surface tension	Not possible to determine for a complex mixture with a low solubility in water.
Vapour pressure (in Pa, state temperature)	Measurements in the range 164-255°C (Grade B) and 180-285°C (grade C).

	Extrapolated: 20 °C 0.4 Pa (Grade B) 0.3 Pa (Grade C) 25 °C 0.66 Pa (Grade B) 0.50 Pa (Grade C) 50 °C 4.88 Pa (Grade B) 3.41 (Grade C) 100 °C 120 Pa (Grade B) 72.6 Pa (Grade C)
Henry's law constant (Pa m^3 mol^{-1})	Not possible to determine for the complex creosote mixture Range for single components (literature data for 18 PAHs): 0.007 (6 ring PAH) – about 150 (acenaphthylene) Pa*m^3/mol
Solubility in water (g/l or mg/l, state temperature)	For creosote expressed as TOC: <u>At a loading of 100 mg creosote/l water:</u> 2.25-8.11 mg/l (Grade B, Grade B-composite and Grade C) <u>At a loading of 10 g creosote/l water:</u> 191 mg/l (Grade B-composite) 30.3 mg/l (Grade B) 27.7 mg/l (Grade C) Range for single components (literature data for 18 PAHs): 0.26 µg/l (benzo[ghi]perylene) – 31.7 mg/l (naphthalene) Higher solubilites anticipated for the polar components (i.e. phenolics, N-, S- and O-heterocycles)
Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1)	Completely miscible in benzene or toluene, >99.5 % in acetone, soluble in quinoline
Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2)	Not relevant as creosote is not used in any solvents
Partition coefficient (log P_{OW}) (state temperature)	Experimentally determined for US types creosote P1/13 and P2: 2.8 (o:w 8:1)-3.7 (o:w 1:1.25) o:w = octanol to water ratio

	The experimental value not used in the risk assessment (See Chapter 4)
Hydrolytic stability (DT_{50}) (state pH and temperature) (point VII.7.6.2.1)	See Chapter 4
Dissociation constant (not stated in Annex IIA or IIIA; additional data requirement from TNsG)	No possible to determine for the complex creosote mixture Creosote is not anticipated to be significantly affected by pH, as the great majority of the components cannot dissociate.
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	No specific information due to complex mixture of aromatic compounds
Flammability	Flash point: >80°C-105 °C; ignition point >450 °C
Explosive properties	Not explosive
Oxidizing properties	Not oxidizing

Summary of intended uses[1]

Object and/or situation (a)	Member State or Country	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks:
				Type (d-f)	Conc. of as (i)	method kind (f-h)	number min max (k)	interval between applications (min)	kg as/m^3 wood min max	water L/m^2 min max	g as/m^2 min max	(m)
Wood rotting fungi	No data	creosote	Basidiomyctes: e.g. Lentinus Coniophora, Polystictus	Creosote EN 13991 Grade B and C	100 %	Pressure impregnation	1	none	40 – 150	--	--	
Please, note that the oil retention rates that have been applied for are 40-150 kg/m^3. RMS has nevertheless been informed during the evaluation process that in order to achieve full efficacy for marine applications, higher retention rates will be required. A full assessment regarding efficacy and environmental risk characterisation, in the case of marine applications, has therefore to be performed at Member State level provided that creosote is included in Annex I of Directive 98/8/EC.												
Marine borers	No data	creosote	Crustaceae: Limnoria sp., Limnoria tripunctata, Limnoria lignorum / Teredo sp., e.g. Teredo utriculus, Teredo pedicullata	Creosote EN 13991 Grade B and C	100 %	Pressure impregnation	1	none	300 - 400	--	--	

(a) *e.g.* biting and suckling insects, fungi, molds;
(b) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(c) GCPF Codes - GIFAP Technical Monograph No 2, 1989 ISBN 3-8263-3152-4);
(d) All abbreviations used must be explained
(e) g/kg or g/l;
(f) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench;
(g) Kind, *e.g.* overall, broadcast, aerial spraying, row, bait, crack and crevice equipment used must be indicated;
(h) Indicate the minimum and maximum number of application possible under practical conditions of use;
(i) Remarks may include: Extent of use/economic importance/restrictions

[1] adapted from: EU (1998a): European Commission: Guidelines and criteria for the preparation of complete dossiers and of summary dossiers for the inclusion of active substances in Annex I of Directive 91/414/EC (Article 5.3 and 8,2). Document 1663/VI/94 Rev 8, 22 April 1998

Classification and proposed labelling (Annex IIA, point IX.)

According to the 29th ATP, rev. 19 (Directive 2004/73/EC) and proposed.	
with regard to physical/chemical data	none
with regard to toxicological data	Class of danger: T, Xi R phrases: 36, 38, 43, 45, 60, 63
with regard to fate and behaviour data and ecotoxicological data	Class of danger: N R phrases: 51/53

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method) (Annex IIA, point 4.1)	GC-FID Able to quantify 66 components in the creosote under evaluation (further data is considered required)
Impurities in technical active substance (principle of method) (Annex IIA, point 4.1)	Not relevant as the term “impurities” does not apply to a complex mixture like creosote (i.e. UVCB-substance).

Analytical methods for residues

Soil (principle of method and LOQ) (Annex IIA, point 4.2)	<u>Sediment</u> <u>24 PAHs in sediment</u> SEC for isolation and GC-MS for analysis. LOQ not stated. LOD: 1-4 ng/g dry sediment (i.e. µg/kg) for low-molecular weight PAH and 0.3-0.5 ng/g dry sediment (i.e. µg/kg) for high-molecular weight PAH. However, the reporting and the validation data are not sufficient. <u>Soil</u> No specific method has been submitted. Soxhlet extraction in combination with e.g. GC-FID analysis has been proposed. However, no validation data has been provided in support of the proposal.
Air (principle of method and LOQ) (Annex IIA, point 4.2)	<u>11 PAHs in air</u> GC-FID. LOQ: 19.1-25.8 µg/air sampling tube. Another study for slightly different PAHs indicated LOQs of 1.6-10.2 mg/m^3
Water (principle of method and LOQ) (Annex IIA, point 4.2)	<u>16 PAHs in surface and drinking water:</u> GC-FID or HPLC-UV/FD (US EPA method 610) LOQ not stated. LOD: Naphthalene, acenaphthylene, acenaphthene: 1.8-2.3 µg/l,

	Fluorene-pyrene, chrysene: 0.15-0.66 µg/l, remaning PAHs: 0.017-0.076 µg/l (LOD for benz(a)pyrene is above the EU-drinking water limit (98/83/EC)) <u>6 PAHs in drinking water</u> HPLC-FD (DIN 38407-8), LOQ: 0.005 µg/l <u>Components of creosote in water (deionized)</u> GC-FID, able to quantify 68 components of creosote, LOD: 1 µg/l, LOQ: 3 µg/l
Body fluids and tissues (principle of method and LOQ) (Annex IIA, point 4.2)	<u>Urine and faeces</u> <u>1-OH-pyrene in urine</u> HPLC-FD, LOQ: 8.73 µg/l <u>Phenanthrene, pyrene and chrysene and corresponding OH-metabolites in urine and faeces</u> GC-FID/MS, LOQ not stated, LOD: 0.1 ng injected <u>Blood and tissues</u> <u>10 PAHs in blood</u> HPLC-FD, LOQ: 76 ng/l-10 µg/l. However, the reporting and the validation data are not sufficient <u>24 PAHs in tissues</u> SEC for isolation and GC-MS for analysis. LOQ not stated, LOD: 5-50 ng/g dry tissue (i.e. µg/kg) for low-molecular weight PAH and 0.5-3.5 ng/g dry tissue (i.e. µg/kg) for high-molecular weight PAH. However, the reporting and the validation data are not sufficient.
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not required due to the use pattern of creosote
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not required due to the use pattern of creosote

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals (Annex IIA, point 6.2)

Rate and extent of oral absorption:	Considered as not relevant (impossible to assess, since creosote consists of several 100 compounds)
Rate and extent of dermal absorption:	Impossible to assess, since creosote consists of several 100 compounds. 100% used.
Rate and extent of inhalational absorption	100% used
Distribution:	Pyrene (as model PAH): highest levels in liver, kidney and fat (transient peaks)
Potential for accumulation:	no evidence, reactive metabolites of certain PAH may react with DNA
Rate and extent of excretion:	depending on compound: pyrene elimination rate constant (rat): 0.17 – 0.35/d, 70 – 80 % (6 d)
Toxicologically significant metabolite	epoxides, quinones, phenols

Acute toxicity (Annex IIA, point 6.1)

Rat LD_{50} oral	>3500 mg/kg
Rat LD_{50} dermal	>2000 mg/kg
Rat LC_{50} inhalation	>5000 mg/m^3 (aerosol)
Skin irritation	Irritating
Eye irritation	Not irritating
Skin sensitization (test method used and result)	Positive (Maximization) negative (Buehler)

Repeated dose toxicity (Annex IIA, point 6.3)

Species/ target/critical effect	Rat / liver hypertrophy / inflammation in nasal cavity (inhalation)
Lowest relevant oral NOAEL/LOAEL	no data
Lowest relevant dermal NOAEL/LOAEL	40/400 mg/kg bw/d (90 d)
Lowest relevant inhalation NOAEL/LOAEL	22/128 mg/m^3 (90 d)

Genotoxicity (Annex IIA, point 6.6)

	Result	Creosote-type
• Bacterial reverse mutation test (Ames test)	negative (+/- S9)	EU <50 ppm BaP
• In Vitro mammalian chromosome aberration test (human lymphocytes)	negative (+/- S9)	EU <50 ppm BaP

• In vitro mammalian cell gene mutation test (Mouse lymphoma L5178Y)	positive (weak, + S9)	EU <50 ppm BaP
• In vivo micronucleus assay (mouse, bone marrow)	negative	EU <50 ppm BaP
• Dominant-Lethal Test (rat)	negative	US ~5000 ppm BaP

Long term toxicity and Carcinogenicity (Annex IIA, point 6.7)

Species/type of tumour	Mouse (dermal): skin tumors (papilloma and squamous-cell carcinoma)
lowest dose with tumours	CTP1 (BaP content 10ppm): 3 mg (2x/wk) CTP2 (BaP content 270 ppm): 0.1 mg (2x/wk)

Reproductive toxicity (Annex IIA, point 6.8)

Species/Reproduction target/critical effect	Rat / fertility / decreased litter size in the high dose group, decreased live offspring, and decreased bw of live pups during lactation
Lowest relevant reproductive NOAEL/LOAEL	25/75 mg/kg bw/d
Species/Developmental target / critical effect	Rat, rabbit/ embryonal / post-implantation loss
Lowest relevant developmental NOAEL/LOAEL	50/175 mg/kg bw/d

Neurotoxicity / Delayed neurotoxicity (Annex IIIA, point VI.1)

Species/target/critical effect	no data
Lowest relevant developmental NOAEL/LOAEL	--

Other toxicological studies (Annex IIIA, VI/XI)

No data

Medical data (Annex IIA, point 6.9)

Fatal cases after ingestion of creosote involve the amount of about 7 g for adults and 1-2 g for children. Overall, the body of epidemiological data does not indicate an apparent elevated cancer risk for creosote workers.

Summary (Annex IIA, point 6.10)

ADI (if residues in food or feed)	By definition, ADI gives a safety level of daily intake of a substance via ingestion. Therefore, the setting of ADI for creosote would be considered irrelevant, since creosote is used as wood preservative (PT8). Furthermore, creosote is classified as R45 canc. Cat.2. An ADI cannot be set for substances that are genotoxic and/or carcinogenic unless a threshold mechanism clearly has been demonstrated.
AOEL (Operator/Worker Exposure/Bystander)	Creosote is classified as R45 canc. Cat.2. According to the EU guidance on AOEL setting (rev 10), an AOEL cannot be set for substances that are genotoxic and/or carcinogenic unless a threshold mechanism clearly has been demonstrated.
Drinking water limit	0.1 µg/L (As set by EU Drinking Water Directive (98/83/EC))
ARfD (acute reference dose)	The setting of ARfD for creosote which is used as wood preservative (PT8) is considered not to be relevant.

Acceptable exposure scenarios (including method of calculation)

Professional users	Creosote is classified as R45 canc. Cat.2. No acceptable exposure scenarios can be identified. All MOEs indicate concern.
Workers (re-entry)	Creosote is classified as R45 canc. Cat.2. No acceptable exposure scenarios can be identified. All MOEs indicate concern.
Non-professional users	Not relevant
Indirect exposure as a result of use	Not relevant

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water (Annex IIA, point 7.6, IIIA, point XII.2.1, 2.2)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	Not applicable for creosote (PAH compounds not expected to be hydrolytically degraded).
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Not applicable for creosote. Direct photochemical transformation (latitude 40°N, midday, midsummer) for different PAH compounds in creosote: Compound / DT_{50} (h) / Quantum yield x 10^3 Naphthalene 71 15±1 1-Methylnaphthalene 22 18±1 2-Methylnaphthalene 54 5.3±0.2 Phenanthrene 8.4 10±1.6 Anthracene 0.75 3.0±0.2 9-Methylanthracene 0.13 7.5±0.5 9,10-Methylanthracene 0.35 4.0±0.4 Pyrene 0.68 2.0±0.3 Fluoranthene 21 0.12±0.001 Chrysene 4.4 2.8±0.7 One major transformation product of PAHs seems to be quinone derivatives.
Readily biodegradable (yes/no)	No
Disappearance in water	Dissipation DT_{50} = 30 d for creosote and individual creosote components.
Biodegradation in water / sediment systems	Not applicable for creosote. Mineralisation half-lives (at 22 °C) and total percentage mineralised of ^{14}C-labelled PAHs after 56 days. Values in brackets for 2-methylnaphthalene and phenanthrene show estimated half-lives as given in the study report: DT_{50}, days / % mineralised Naphthalene 30.8 54.5 2-Methyl-naphthalene >56 (140) 18.8 phenanthrene >56(126) 22.3 Pyrene nd <0.2 nd = no mineralisation detected.
Non-extractable residues	Not applicable for creosote. Between approx. 2% for naphthalene / methylnaphthalene to 7.5% for phenanthrene (56 days).
Distribution in water / sediment systems (active substance)	Not applicable for creosote. For naphthalene, methylnaphthalene, phenanthrene and pyrene: Between 3.1 and 8.4% was found in the water phase

	and between 8.2 and 75% was found in the sediment phase. (Measured as recovered ^{14}C in the water and sediment phases, respectively, after 56 d)
Distribution in water / sediment systems (metabolites)	No data (polar metabolites of PAHs accounted for 0.1 to 6% of the original PAHs).

Route and rate of degradation in soil (Annex IIIA, point VII.4, XII.1.1, XII.1.4; Annex VI, para. 85)

Mineralization (aerobic)	No data
Laboratory studies (range or median, with number of measurements, with regression coefficient)	Not applicable for creosote. For PAHs the following half-lives were determined (highest value of two soils) at 20 °C: DT_{50} (d) Naphthalene 2.2 1-Methylnaphthalene 2.2 Phenanthrene 35 Anthracene 134 Fluoranthene 377 Pyrene 260 Benz[a]anthracene 261 Chrysene 387 The kinetic calculations resulting in first order rate constants and half-lives gave r^2 values ranging from 0.71-0.95 and 0.57-0.93 for the two soils, respectively
Field studies (state location, range or median with number of measurements)	No data
Anaerobic degradation	No degradation could be measured in anaerobic soil
Soil photolysis	No data
Non-extractable residues	No data
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	No data

Adsorption/desorption (Annex IIA, point VII.7.7; Annex IIIA, point XII.1.2)

Ka, Kd Ka_{oc}, Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	Data on log K_{ow}- and log K_{oc} values for 42 single components present in creosote have been compiled and presented in the report. The log K_{ow}- and log K_{oc} values for single components were weighted by their content in creosote (in percent), in order to estimate the corresponding partition coefficients for the different creosote oils, respectively.

Creosote Oil	Log K_{ow}	Log K_{oc}	Proportion of creosote used in the estimate [a]
Composite Grade B	4.12	3.67	61%
Grade B	4.43	3.97	58%
Grade C	4.63	4.17	53%

[a] The total sum of all analysed/identified compounds in the oils were approx. 63, 60 and 56% for 'composite Grade B', Grade B and Grade C, respectively (see Document III-A1-2).

No pH dependence of partition coefficients.

Fate and behaviour in air (Annex IIIA, point VII.3, VII.5)

Direct photolysis in air: No data

Quantum yield of direct photolysis: No data

Photo-oxidative degradation in air:

Not applicable for creosote.

Half-lives of selected PAHs due to gas-phase reactions with hydroxyl (OH) radicals and nitrate (NO_3) radicals for hypothetical summertime conditions in clean air:

	DT_{50} (OH)	DT_{50} (NO_3)
Naphthalene	4.0 h	10 years
1-Methylnaphthalene	2.4 h	5 years
2-Methylnaphthalene	1.9 h	3 years
1-Ethylnaphthalene	2.8 h	3 years
2-Ethylnaphthalene	2.4 h	5 years
Dimethylnaphthalenes	1.2-1.7 h	0.1-3 years
Acenaphthylene	0.76 h	4.2 min
Acenaphthene	1.2 h	0.97 h
Fluorene	6.9 h	20 h
Phenanthrene	5.3 h	3.0 h

Volatilization:

A laboratory study simulated emissions to air during storage of creosote treated timber. For this purpose, a climate–controlled enclosure was constructed into which test pieces of wood were placed. The air in the enclosure was circulated. There was constant supply of clean air and equal amount of air was extracted from the enclosure. The emissions were measured for their content of 21 PAHs by sampling the extracted air. The results showed that the loss rate of creosote (estimated from ΣPAH conc.) to air was approximately 8-74 mg/m² wood and day.

Monitoring data, if available (Annex VI, para. 44)

Soil (indicate location and type of study): No data for creosote.

PAH concentrations in soil at various depths and distances from creosote treated utility poles in service were determined in the USA (EPI, 1997; III- A2.10.2/12). The age of the poles ranged from less than 5 years to 40 years although most of the poles of the study were less than 20 years old. Twenty-two pole sites were investigated and from each site 40-44 samples were analysed for their content of 18 PAHs. Median ΣPAH concentrations of all maximum values at each distance (independent of depth) from each pole site:

Distance from the pole	Median creosote[1] concentration (mg/kg wet weight)
7.6 cm	3320
20.3 cm	973
45.7 cm	7.1
76.2 cm	4.0
122 cm	0.25 [2]

[1] Assuming that the proportion of the PAHs analysed was 40% of the creosote content.
[2] Background levels of ΣPAHs.

Surface water (indicate location and type of study)

No data for creosote.

In Sooke Basin, British Colombia, Canada, sea water concentrations of PAHs were measured with SPMD (semi-permeable membrane device) adjacent to underwater constructions (piling sites = dolphins) made of creosote treated wood (Goyette and Brooks, 1998 and 2002; III-A2.10.2/10). The highest water concentration of creosote (estimated from ΣPAH conc.) was 0.08 µg/l approx. 6 months after construction.

Sediment (indicate location and type of study)

In Sooke Basin, British Colombia, Canada, surface sediment concentrations of 16 PAHs were measured adjacent to underwater constructions (piling sites = dolphins) made of creosote treated wood (Goyette and Brooks, 1998 and 2002; III-A2.10.2/10). The following concentrations of creosote (estimated from Σ16PAH concentrations) were found (mg/kg wet weight):

Day from installation	Day 14	Day 384	Day 14	Day 384
Distance from site	*0.5 m*	*0.5 m*	*1.5 m*	*7.5 m*
Site-BMP*	12	31	1.5	6.3
Distance from site	*0.5 m*	*0.5 m*	*2 m*	*5 m*
Site-WP#	142	17	4.1	3.2

* Newly treated pilings
# Weathered pilings

Ground water (indicate location and type of

No data

study)	
Air (indicate location and type of study)	No data

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)
(Annex IIA, point 8.2, Annex IIIA, point 10.2)

Species	Test substance	Time-scale	Endpoint	Toxicity (mg/l)
Fish				
O. latipes (fresh water) *Pagrus major* (seawater)	creosote	96 h semi-static	LC_{50}	0.7 mg/l (measured conc. of 19 PAHs)
Brachydanio rerio	PAH-mixture	42 d	$NOEC_{growth}$	0.0021 mg Σ6PAHs/l (m)
Clupea pallasi	creosote from treated wood	9 d	$NOEC_{hatching\ success}$	0.001 mg creosote (Σ Aromatic compounds)/l
B. rerio	phenanthrene/ fluoranthene	28/41 d	$NOEC_{reproduction}$	0.011/0.0044 mg/l (estimated/m)
P. promelas	anthracene	77 d	$NOEC_{reproduction}$	0.006 mg/l (m)
Invertebrates				
Daphnia magna	anthracene, fluorene, phenanthrene	21 d	$NOEC_{reproduction}$	0.002, 0.015, and 0.018 mg/l
zooplankton community	creosote from treated wood	83 d	$NOEC_{abundance}$	0.011 mg creosote (Σ15PAHs)/l
Algae				
(*Desmodesmus subspicatus*)	creosote	72 h	E_rC_{50} NOEC	2.1 mg/l (measured TOC) 0.9 mg/l (measured TOC)
Sediment dwelling organisms				
Benthic community	creosote from treated wood pilings	1-4 years	NOEC abundance/ diversity	creosote (Σ15PAHs): 10 mg/kg dw = 22 mg/kg ww phenanthrene: 2 mg/kg dw = 4.4 mg/kg ww fluoranthene: 3 mg/kg dw = 6.5 mg/kg ww (in ww after conversion to TGD standard susp. matter)
Microorganisms				
Activated sludge	creosote	3 h	EC_{50} resp. inhibition	33 mg/l (TOC/creosote, estimated conc.)

Effects on earthworms or other soil non-target organisms
(Annex IIIA, point XIII.3.2)

	Test substance	Endpoint/toxicity (mg/kg)
Acute toxicity to: earthworms (*E. fetida*)	PAH- or creosote-contaminated soil	LC_{50} (14d): 286-1354 (ΣPAH) (ww)
springtails (*F.candida*)	1-/2-methyl-naphthalene isomer mixture	LC_{50} (14d): 42 (ww)
earthworms (*E. fetida*)	fluorene/phenol	LC_{50} (14d): 51.2/56.6 (ww)
	chrysene	LC_{50} (14d): > 301 (ww) (after conversion to standard TGD soil)
Long-term toxicity to: springtails (*F. candida*)	creosote Grade B	$NOEC_{mortality}$ (28d): 10 (dw) = 3 (ww)
	1-/2-methylnaphthalene isomer mixture	$NOEC_{reproduction}$ (28d): 56 (dw) = 16.8 (ww)
	phenanthrene	$NOEC_{reproduction}$ (28d): <75 (dw) = 22.6 (ww)
earthworms (*E. crypticus*)	naphthalene, fluorene, fluoranthene, pyrene, carbazole, dibenzofuran	$NOEC_{reproduction}$ (28d): 11- 36 (dw) = 12- 40 (ww)
	anthracene	$NOEC_{reproduction}$ (28d): >897 (dw) = >690 (ww) (in ww after conversion to standard TGD soil)

dw = dry weight, ww = wet weight

Effects on terrestrial plants (Annex IIIA, point 3.4)

	Test substance	Endpoint/toxicity (mg/kg)
Acute toxicity to: lettuce (*L. sativa*)	PAH-contaminated soil	$NOEC_{seed\ germination}$ (5 d): 180 (dw) = 54 (ww) (Σ 9PAH)
tomato	PAH-mixture	$NOEC_{growth\ inhibition}$ (20 d): 10 (dw) = 24 (ww) (Σ 4PAH/creosote)
red clover, ryegrass, mustard	phenanthrene, pyrene, fluorene, carbazole, dibenzofuran (tested ind.)	$NOEC_{growth\ inhibition}$ (14 d): 10 (dw) = 11.1 (ww)
	fluoranthene	$NOEC_{growth\ inhibition}$ (14 d): 100 (dw) = 111 (ww)
oat	anthracene	$NOEC_{growth\ inhibition}$ (14 d): 10 (dw) = 15 (ww) (in ww after conversion to standard TGD soil)

dw = dry weight, ww = wet weight

Effects on soil micro-organisms (Annex IIA, point 7.4)

	Test substance	Toxicity (mg/kg)
Nitrogen mineralization	creosote Grade B 1-/2-metylnaphthalene	NOEC (14 d): 316 (dw) = 373 (ww) NOEC (28 d): 1000 (dw) = 1180 (ww) NOEC (28 d): 100 (dw) = 80 (ww) (in ww after conversion to standard TGD soil)
Carbon mineralization	creosote Grade B	NOEC (28d): 1000 dw = 1180 ww (in ww after conversion to standard TGD soil)

dw = dry weight, ww = wet weight

Effects on terrestrial vertebrates

Acute toxicity to mammals (Annex IIIA, point XIII.3.3)	> 3500 mg creosote/kg (rat)
Acute toxicity to birds (Annex IIIA, point XIII.1.1)	No data
Dietary toxicity to birds (Annex IIIA, point XIII.1.2)	No data
Reproductive toxicity to birds (Annex IIIA, point XIII.1.3)	No data

Effects on honeybees (Annex IIIA, point XIII.3.1)

Acute oral toxicity	Not applicable
Acute contact toxicity	Not applicable

Effects on other beneficial arthropods (Annex IIIA, point XIII.3.1)

Acute oral toxicity	Not applicable
Acute contact toxicity	Not applicable

Bioconcentration (Annex IIA, point 7.5)

	Creosote substance	BCF/BAF
Bioconcentration factor (BCF)	naphthalene 1-methyl-naphthalene 2-methyl-naphthalene phenanthrene anthracene fluoranthene fluorene pyrene	~70 – 1000 ~100 ~140 – 4300 ~1600 ~750 – 5000 ~380 ~540 ~50 – 70
Depuration time (DT_{50})	naphthalenes anthracene fluoranthene	2 days (in oyster) 3 days (in oyster) 5 days (in oyster)

(DT_{95})	Most PAHs in creosote	2-5 days (in fish)
Level of metabolites (%) in organisms accounting for > 10 % of residues	No data	

Chapter 6: Other End Points

Appendix: List of Terms and Abbreviations

List of terms and abbreviations (standard and report related)

Term / Abbreviation	**Explanation**
A	ampere
ACh	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADME	administration distribution metabolism and excretion
ADP	adenosine diphosphate
AE	acid equivalent
AF	assessment factor
AFID	alkali flame-ionisation detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD_{50}	approximate median lethal dose, 50%
ALT	alanine aminotransferase (SGPT)
Ann.	Annex
AOEL	acceptable operator exposure level
AMD	automatic multiple development
ANOVA	analysis of variance
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	Adenosine triphosphate
B	Bioaccumulative (used in the PBT assessment)
BAF	bioaccumulation factor
BaP	Benzo(a)pyrene
B[b]F	benzo[b]fluoranthene
BCF	bioconcentration factor
bfa	body fluid assay
B[k]F	benzo[k]fluoranthene
B[ghi]P	benzo[ghi]perylene
BOD	biological oxygen demand
bp	boiling point
BP	biocidal product
BPD	Biocidal Products Directive
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathy
BSP	bromosulfophthalein
Bt	*Bacillus thuringiensis*
Bti	*Bacillus thuringiensis israelensis*
Btk	*Bacillus thuringiensis kurstaki*
Btt	*Bacillus thuringiensis tenebrionis*
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degrees Celsius (centigrade)
CA	Competent Authority

Term / Abbreviation	**Explanation**
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application
cDNA	complementary DANN
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
CTPV	Coal Tar Pitch Volatiles
cv	coefficient of variation
Cv	ceiling value
d	day(s)
DES	diethylstilboestrol
DIS	draft international standard *(ISO)*
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days post inoculation
DRP	detailed review paper *(OECD)*
DT_{50}	period required for 50 percent disappearance (degradation, dissipation, or depuration)
DT_{90}	period required for 90 percent disappearance (degradation, dissipation, or depuration)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC_{50}	median effective concentration
ECD	electron capture detector
ED_{50}	median effective dose
EDI	estimated daily intake
EINECS	European inventory of existing commercial substances
ELINCS	European list of notified chemical substances
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EN	European norm
EPMA	electron probe micro-analysis
EqP	equilibrium partitioning
ERL	extraneous residue limit
ESPE46/51	evaluation system for pesticides
EUSES	European Union system for the evaluation of substances
F	field
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FBS	full base set
FELS	fish early-life stage

Term / Abbreviation	**Explanation**
FIA	fluorescence immuno-assay
FID	flame ionisation detector
F_{mol}	fractional equivalent of the metabolite´s molecular weight compared to the active substance
FOB	functional observation battery
f_{oc}	fraction of organic carbon (compartment dependent)
fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram(s)
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionisation detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPS	global positioning system
GSH	glutathione
GV	granulosevirus
h	hour(s)
H	Henry’s Law constant (calculated as a unitless value)
ha	hectare(s)
Hb	haemoglobin
HBM	Hydrocarbon Block Method
HC5	concentration which will be harmless to at least 95 % of the species present with a given level of confidence (usually 95 %)
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionisation detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography - mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
H_S	Shannon-Weaver index
Ht	haematocrit
HUSS	human and use safety standard
I	indoor
I_{50}	inhibitory dose, 50%
IC_{50}	median immobilisation concentration or median inhibitory concentration

Term / Abbreviation	**Explanation**
ICM	integrated crop management
ID	ionisation detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
INT	2-p-iodophenyl-3-p-nitrophenyl-5-phenyltetrazoliumchloride testing method
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
IUCLID	International Uniform Chemical Information Database
iv	intravenous
IVF	*in vitro* fertilisation
k *(in combination)*	kilo
k	rate constant
K	Kelvin
Ka	acid dissociation constant
Kb	base dissociation constant
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
kg	kilogram
K_H	Henry´s Law constant (in atmosphere per cubic metre per mole)
K_{oc}	organic carbon – water partition coefficient
K_{om}	organic matter - water partition coefficient
K_{ow}	octanol-water partition coefficient
Kp	solid-water partition coefficient
kPa	kilopascal(s)
l, L	litre
LAN	local area network
LASER	light amplification by stimulated emission of radiation
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography- mass spectrometry
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDH	lactate dehydrogenase
ln	natural logarithm
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
log	logarithm to the base 10
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre

Term / Abbreviation	**Explanation**
M	molar
µm	micrometre (micron)
MAC	maximum allowable concentration
MAK	maximum allowable concentration
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram
MHC	moisture holding capacity
MIC	minimum inhibitory concentration
min	minute(s)
MKC	minimum killing concentration
mL	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
MMAD	mass median aerodynamic diameter
mo	month(s)
MOE	margin of exposure
mol	mole(s)
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
MRL	maximum residue level or limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MT	material test
MW	molecular weight
n.a.	not applicable
n-	normal (defining isomeric configuration)
n	number of observations
NAEL	no adverse effect level
nd	not detected
NEDI	national estimated daily intake
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometre
NMR	nuclear magnetic resonance
no, n°	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase

Term / Abbreviation	**Explanation**
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OEL	occupational exposure limit
OH	hydroxide
1-OHN	1-hydroxynaphthalene
1-OHP	1-hydroxypyrene
OJ	Official Journal
OM	organic matter content
P	persistent
Pa	pascal
PAC	polycyclic aromatic compound
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
PAH	polycyclic aromatic hydrocarbon
PBT	Persistent Bioaccumulative Toxic
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration (compartment to be added as subscript)
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PIC	prior informed consent
pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the acid dissociation constant
pKb	negative logarithm (to the base 10) of the base dissociation constant
PNEC	predicted no effect concentration (compartment to be added as subscript)
po	by mouth
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})
PPP	plant protection product
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion (10^{-12})
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	product type
PT(CEN)	project team CEN
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QA	quality assurance
QAU	quality assurance unit
(Q)SAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RA	risk assessment
RBC	red blood cell
REI	restricted entry interval
RENI	Registry Nomenclature Information System
Rf	retardation factor

Term / Abbreviation	**Explanation**
RfD	reference dose
RH	relative humidity
RL_{50}	median residual lifetime
RMS	Rapporteur Member State
RNA	ribonucleic acid
RP	reversed phase
rpm	revolutions per minute
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RSD	relative standard deviation
s	second
S	solubility
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SCAS	semi-continous activated sludge
SCTER	smallest chronic toxicity exposure ratio (TER)
SD	standard deviation
se	standard error
SEC	size exclusion chromatography
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
S/L	short term to long term ratio
SMEs	small and medium sized enterprises
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
SPMD	semi-permeable membrane devise
spp	subspecies
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STER	smallest toxicity exposure ratio (TER)
STMR	supervised trials median residue
STP	sewage treatment plant
Σ	sum of
T	toxic
t	tonne(s) (metric ton)
$t_{½}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
T_{25}	tumorigenic dose that causes tumours in 25 % of the test animals
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TEL	threshold effect level
TG	technical guideline, technical group
TGD	Technical Guidance Document

Term / Abbreviation	**Explanation**
TID	thermionic detector, alkali flame detector
TDR	time domain reflectrometry
TER	toxicity exposure ratio
TER_I	toxicity exposure ratio for initial exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
Tlm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TNsG	technical notes for guidance
TOC	total organic carbon
TPAH	Total polycyclic aromatic hydrocarbons (16 EPA priority PAH)
Tremcard	transport emergency card
tRNA	transfer ribonucleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TTC	2,3,5-triphenylterazoliumchloride testing method
TWA	time weighted average
UC	use class
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UR	unit risk
UV	ultraviolet
UVC	unknown or variable composition, complex reaction products
UVCB	undefined or variable composition, complex reaction products in biological material
vB	very bioaccumulative
vP	very persistent
v/v	volume ratio (volume per volume)
vis	visible
W	Watt
WBC	white blood cell
WBD	Whole body dosimeter
wk	week
WSF	Water-soluble fraction
wt	weight
w/v	weight per volume
ww	wet weight
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Abbreviations of organisations and publications

Abbreviation	**Explanation**
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
BBA	German Federal Agency of Agriculture and Forestry
CA(S)	Chemical Abstracts (System)
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CEC	Commission of the European Communities
CEFIC	European Chemical Industry Council
CEN	European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CIPAC	Collaborative International Pesticides Analytical Council Ltd
CMA	Chemicals Manufacturers Association
COREPER	Comite des Representants Permanents
COST	European Co-operation in the field of Scientific and Technical Research
DG	Directorate General
DIN	German Institute for Standardisation
EC	European Commission
ECB	European Chemicals Bureau
ECCO	European Commission Co-ordination
ECDIN	Environmental Chemicals Data and Information Network of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre
EDEXIM	European Database on Export and Import of Dangerous Chemicals
EEC	European Economic Community
EHC	Environmental Health Criteria
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPAS	European Producers of Antimicrobial Substances
EPFP	European Producers of Formulated Preservatives
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organization
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
EWMP	European Wood Preservation Manufacturers
FAO	Food and Agriculture Organization of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques (now known as GCPF)
GCOS	Global Climate Observing System

Abbreviation	**Explanation**
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GRIN	Germplasm Resources Information Network
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
ICBP	International Council for Bird Preservation
ICCA	International Council of Chemical Associations
ICES	International Council for the Exploration of the Seas
ILO	International Labour Organization
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
ISCO	International Soil Conservation Organization
ISO	International Organization for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JECFA FAO/WHO	Joint Expert Committee on Food Additives
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
MITI	Ministry of International Trade and Industry, Japan
NATO	North Atlantic Treaty Organization
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Center for Toxicological Research (USA)
NGO	non-governmental organisation
NTP	National Toxicology Program (USA)
OECD	Organization for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
OPPTS	Office of Prevention, Pesticides and Toxic Substances (US EPA)
OSPAR	Oslo Paris Convention (Convention for the Protection of the Marine Environment of the North-East Atlantic)
PAN	Pesticide Action Network
RIVM	Netherlands National Institute of Public Health and Environmental Protection
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment
SETAC	Society of Environmental Toxicology and Chemistry
SI	Système International d'Unitès
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UBA	German Environmental Protection Agency
UN	United Nations
UNEP	United Nations Environment Programme
WFP	World Food Programme
WHO	World Health Organization
WPRS	West Palearctic Regional Section
WTO	World Trade Organization
WWF	World Wildlife Fund

Universal Forest Products

TO: Railroad Tie Purchaser

FROM: Legal Compliance Department DATE: March 15, 2011

SUBJECT: Creosote Treated Wood Railroad Tie MSDS

Purchaser:

Used railroad ties are not manufactured by Universal Forest Products, Inc. or its operating affiliates and subsidiaries ("UFP"); consequently, UFP does not produce and maintain an MSDS. Instead UFP relies on receiving MSDS's from its suppliers. Attached is an MSDS from one manufacturer of creosote railroad ties.

In addition, end users can refer to the Creosote Treated Wood Consumer Information Sheet for use and handling information. This Consumer Information Sheet contains language approved by the U.S. Environmental Protection Agency. You can find it by going to www.ufpi.com and typing "creosote consumer information sheet" in the search box at the top of the page.

Universal Forest Products®, Inc.
2801 East Beltline NE Grand Rapids, MI 49525 (616) 364-6161 FAX (616) 364-5558

KOPPERS

Safety Data Sheet

Material Name: CREOSOTE PRESSURE TREATED WOOD **SDS ID: 00228327**

* * * Section 1 - PRODUCT AND COMPANY IDENTIFICATION * * *

Manufacturer Information

KOPPERS INC.
436 Seventh Avenue
Pittsburgh, PA 15219-1800
Mfg Contact: 412-227-2001 (SDS Requests: 866-852-5239)

CHEMTREC: 800-424-9300 (Outside USA: +1 703-527-3887)
Emergencies (Medical in USA): 877-737-9047
Emergencies (Medical Outside of USA): 651-632-9269
Email: naorgmsds@koppers.com

Material Name: CREOSOTE PRESSURE TREATED WOOD

Product Use

Industrial wood products; specifically railroad ties, utility poles, and marine pilings.

* * * Section 2 - HAZARDS IDENTIFICATION * * *

EMERGENCY OVERVIEW

Physical Form: Pressure treated poles and crossties - treated at a retention level of 7-9 lbs/ft3 with a wood density of 45-55 lbs/ft3. Pressure treated piling - treated at a retention level of 12-20 lbs/ft3 with a wood density of 45 lbs/ft3. Actual retention level dependent on wood stock, moisture levels, and customer specifications.
Color: dark, brown to black
Odor: tar odor
Signal Word: WARNING!
Major Health Hazards: harmful if inhaled, harmful on contact with the skin, respiratory tract irritation, skin irritation, eye irritation, allergic reactions, nasal/sinus cancer, lung cancer, skin cancer
Physical Hazards: Dust/air mixtures may ignite or explode.
Precautionary Statements: Avoid breathing dust. Avoid contact with eyes, skin and clothing. Use only with adequate ventilation. Wash thoroughly after handling. Protective clothing must be changed when it shows signs of contamination. Observe good hygiene and safety practices when handling this product. There is an EPA approved Consumer Information Sheet (CIS) available for this product, do not use this product until the CIS and MSDS have been read and understood.

POTENTIAL HEALTH EFFECTS

Inhalation

Short Term: Creosote may cause irritation. Wood dust may cause irritation and allergic reactions.
Long Term: Creosote may cause nausea, vomiting, and headache. Wood dust may cause irritation, allergic reactions, nosebleed, nausea, vomiting, loss of appetite, chest pain, difficulty breathing, headache, drowsiness, dilated pupils, visual disturbances, irregular heartbeat, lung damage, liver damage, kidney damage, and nasal/sinus cancer.

Skin

Short Term: Creosote may cause irritation, skin discoloration, skin disorders, sensitivity to sunlight, changes in body temperature, nausea, vomiting, headache, difficulty breathing, irregular heartbeat, bluish skin color, and convulsions. Wood dust may cause irritation, allergic reactions, skin disorders, difficulty breathing, irregular heartbeat, headache, visual disturbances and kidney damage.
Long Term: Creosote may cause dermatitis, skin discoloration, skin disorders, sensitivity to sunlight, changes in body temperature, nausea, vomiting, headache, difficulty breathing, irregular heartbeat, bluish skin color, lung cancer, and skin cancer. Wood dust may cause irritation, allergic reactions, and skin disorders.

Eye

Short Term: Creosote may cause irritation and sensitivity to sunlight. Wood dust may cause irritation and eye damage.
Long Term: Creosote may cause irritation and sensitivity to sunlight. Wood dust may cause irritation and eye damage.

Ingestion

Short Term: Creosote may cause irritation, nausea, vomiting, changes in body temperature, difficulty breathing, irregular heartbeat, headache, dizziness, bluish skin color, cardiovascular collapse, and convulsions. Wood dust may cause nausea, vomiting, loss of appetite, difficulty breathing, irregular heartbeat, and drowsiness.
Long Term: Creosote may cause irritation, nausea, vomiting, headache, gastrointestinal effects, dizziness, changes in body temperature, visual disturbances, difficulty breathing, irregular heartbeat, bluish skin color, and cardiovascular collapse. No information is available for wood dust.

* * * Section 3 - COMPOSITION / INFORMATION ON INGREDIENTS * * *

CAS	Component	Percent
Not Available	WOOD DUST, SOFTWOODS	<85
Not Available	WOOD DUST, HARDWOODS	<85
8001-58-9	COAL TAR CREOSOTE	<15

Component Related Regulatory Information

This product may be regulated, have exposure limits or other information identified as the following: Wood dust, all soft and hard woods, Wood dusts-hard wood, Wood dusts (all other wood dusts), Wood dusts (birch, mahoghany, teak, walnut), Wood dust, western red cedar, Creosotes.

* * * Section 4 - FIRST AID MEASURES * * *

Inhalation

If adverse effects occur, remove to uncontaminated area. Give artificial respiration if not breathing. Get immediate medical attention.

Skin

Wash skin with soap and water for at least 15 minutes while removing contaminated clothing and shoes. DO NOT rub until skin is free of sawdust and preservative material. Get medical attention, if needed. Thoroughly clean and dry contaminated clothing and shoes before reuse.

Eyes

Flush eyes with plenty of water for at least 15 minutes. DO NOT rub eyes. Then get immediate medical attention.

Ingestion

If a large amount is swallowed, get medical attention.

* * * Section 5 - FIRE FIGHTING MEASURES * * *

See Section 9 for Flammability Properties

NFPA Ratings: Health= 2 **Fire=** 1 **Reactivity=** 0
Hazard Scale: 0 = Minimal 1 = Slight 2 = Moderate 3 = Serious 4 = Severe

Flammable Properties

Dust/air mixtures may ignite or explode. During fire conditions, vapors and decomposition products may be released, forming flammable/explosive mixtures in air. Contact with heat may generate toxic and/or flammable gases.

Sensitivity to Mechanical Impact

Not available

Sensitivity to Static Discharge

Not available

Extinguishing Media

carbon dioxide, regular dry chemical, regular foam, water spray

Protective Equipment and Precautions for Firefighters

Full fire fighting turn-out gear (bunker gear).

Fire Fighting Measures

Avoid inhalation of material or combustion by-products. Stay upwind and keep out of low areas. Use extinguishing agents appropriate for surrounding fire.

* * * Section 6 - ACCIDENTAL RELEASE MEASURES * * *

Water Release

Subject to California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

Occupational Spill / Release

Collect debris and used material in appropriate container for disposal. Due to the concentration of Creosote and the CERCLA (40 CFR 302.4) reportable quantity of 1 pound, the release of 6 pounds of this product requires National Response Center notification.

* * * Section 7 - HANDLING AND STORAGE * * *

Handling Procedures

Use methods to minimize dust. Avoid frequent or prolonged inhalation of sawdust from treated wood. When sawing and machining treated wood, wear a dust mask. When power-sawing and machining, wear goggles to protect eyes from flying particles. Whenever possible, these operations should be performed outdoors to avoid indoor accumulations of airborne sawdust from treated wood. Avoid frequent or prolonged skin contact with creosote-treated wood; when handling the treated wood, wear long-sleeved shirts and long pants and use gloves impervious to the chemicals (for example, gloves that are vinyl-coated). Use protective skin cream on exposed skin before and during work shift. To reduce sun sensitivity a sun-blocking lotion (SPF 15+) can also be applied prior to application of a protective cream. After working with the wood, and before eating, drinking and use of tobacco products, wash exposed areas thoroughly. If oily preservative or sawdust accumulate on clothes, launder before reuse. Wash work clothes separately from other household clothing.

Storage Procedures

No special requirements.

* * * Section 8 - EXPOSURE CONTROLS / PERSONAL PROTECTION * * *

Exposure Guidelines

Creosote is a complex mixture of variable composition, and while no odor threshold for creosote has been established, work done at the University of California has measured the odor thresholds for one of the more volatile components in creosote and determined that the involved odor threshold is in the part per billion range, and well below applicable exposure limits. On the basis of these data the perception of creosote odor in and of itself should not be taken as an indication of exposure in excess of accepted exposure limits.
Exposure to wood dust would not be expected under normal use conditions. If handling or use patterns associated with creosote treated wood involve the use of a power saw, sander, drill or any tool or activity resulting in the generation of airborne particulate the following wood dust exposure limits should be observed and appropriate steps taken to minimize exposure.

Component Exposure Limits

WOOD DUST, HARDWOODS (Not Available)

ACGIH: 1 mg/m3 TWA (inhalable fraction)
NIOSH: 1 mg/m3 TWA
Mexico: 1 mg/m3 TWA

WOOD DUST, SOFTWOODS (Not Available)

ACGIH: 0.5 mg/m3 TWA (inhalable fraction)
Sensitizer
NIOSH: 1 mg/m3 TWA

COAL TAR PITCH VOLATILES (65996-93-2)

OSHA (US): 0.2 mg/m3 TWA (benzene soluble fraction)
ACGIH: 0.2 mg/m3 TWA (as benzene soluble aerosol)
NIOSH: 0.1 mg/m3 TWA (cyclohexane-extractable fraction)
Mexico: 0.002 mg/m3 TWA; 0.02 mg/m3 TWA (as Particulate polycyclic aromatic hydrocarbons)
0.015 ppm STEL; 0.03 mg/m3 STEL

Ventilation

Ensure adequate ventilation. Ensure compliance with applicable exposure limits.

PERSONAL PROTECTIVE EQUIPMENT

Eyes / Face

ANSI Z87.1-1989 approved safety glasses with side shields.

Protective Clothing

Wear tightly woven long-sleeved shirts and long pants. Remove and launder contaminated clothing separately from other laundry before reuse.

Glove Recommendations

Individuals must wear gloves impervious to the wood treatment formulations in all situations where dermal contact with creosote is expected.

Protective Material Types

Examples of impervious materials for protective clothing (e.g. overalls, jackets, gloves and boots) required during application and handling of creosote are polyvinyl acetate (PVA), polyvinyl chloride (PVC), Neoprene and NBR (Buna-N).

Respiratory Protection

If the applicable TLVs and/or PELs are exceeded, use canister or cartridge respirators, which are MSHA/NIOSH-approved, with high-efficiency particulate filters.

* * * Section 9 - PHYSICAL AND CHEMICAL PROPERTIES * * *

Physical State:	Solid	**Color:**	dark, brown to black
Physical Form:	Pressure treated poles and crossties - treated at a retention level of 7-9 lbs/ft3 with a wood density of 45-55 lbs/ft3. Pressure treated piling - treated at a retention level of 12-20 lbs/ft3 with a wood density of 45 lbs/ft3. Actual retention level dependent on wood stock, moisture levels, and customer specifications.	**Odor:**	tar odor
pH:	Not available	**Freezing / Melting Point:**	Not available
Boiling Point:	Not available	**Flash Point:**	Not applicable
Decomposition Temperature:	Not available	**Evaporation Rate:**	Not available
Lower Explosive Limit:	Not available	**Upper Explosive Limit:**	Not available
Vapor Pressure:	Not available	**Vapor Density:**	Not available
Specific Gravity (water=1):	Not available	**Water Solubility:**	Not available
Coefficient of Water/Oil Dist:	Not available	**Autoignition:**	Not available
Viscosity:	Not available	**Volatility:**	Not available

* * * Section 10 - STABILITY AND REACTIVITY * * *

Chemical Stability

Stable at normal temperatures and pressure.

Conditions to Avoid

Avoid heat, flames, sparks and other sources of ignition. Avoid contact with incompatible materials.

Materials to Avoid (Incompatibilities)

oxidizing materials, acids

Decomposition Products

carbon monoxide, carbon dioxide, oxides of nitrogen

Possibility of Hazardous Reactions

Will not polymerize.

* * * Section 11 - TOXICOLOGICAL INFORMATION * * *

Irritation / Corrosive Information

RTECS Irritation

The components of this material have been reviewed and RTECS publishes no applicable data as of the date on this document.

Local Effects

WOOD DUST, HARDWOODS (Not Available)
Irritant: inhalation, skin, eye.
WOOD DUST, SOFTWOODS (Not Available)
Irritant: inhalation, skin, eye.
COAL TAR CREOSOTE (8001-58-9)
Irritant: inhalation, skin, eye.

Acute and Chronic Toxicity

Component Analysis - LD50/LC50

The components of this material have been reviewed in various sources and the following selected endpoints are published:
COAL TAR CREOSOTE (8001-58-9)
Oral LD50 Rat 2524 mg/kg

RTECS Acute Toxicity (selected)

The components of this material have been reviewed, and RTECS publishes the following endpoints:
COAL TAR CREOSOTE (8001-58-9)
Oral: 725 mg/kg Oral Rat LD50

Acute Toxicity Level

COAL TAR CREOSOTE (8001-58-9)
Moderately Toxic: ingestion.

Carcinogenicity (Product)

OSHA: No
NTP: Yes
IARC: Yes
(See below for additional information on component carcinogen status)

Component Carcinogenicity

WOOD DUST, HARDWOODS (Not Available)
ACGIH: A1 - Confirmed Human Carcinogen
NIOSH: potential occupational carcinogen
NTP: Known Human Carcinogen (Select Carcinogen)
IARC: Monograph 100C [in preparation]; Monograph 62 [1995] (Group 1 (carcinogenic to humans))
WOOD DUST, SOFTWOODS (Not Available)
ACGIH: A4 - Not Classifiable as a Human Carcinogen
NIOSH: potential occupational carcinogen
NTP: Known Human Carcinogen (Select Carcinogen)
IARC: Monograph 100C [in preparation]; Monograph 62 [1995] (Group 1 (carcinogenic to humans))
COAL TAR CREOSOTE (8001-58-9)
NIOSH: potential occupational carcinogen
IARC: Monograph 92 [2010]; Supplement 7 [1987]; Monograph 35 [1985] (Group 2A (probably carcinogenic to humans))

RTECS Tumorigenic

The components of this material have been reviewed, and RTECS publishes data for one or more components.

RTECS Mutagenic

The components of this material have been reviewed, and RTECS publishes data for one or more components.

RTECS Reproductive Effects

The components of this material have been reviewed, and RTECS publishes data for one or more components.

Target Organs (Product)

respiratory system, skin, eyes, immune system (sensitizer)

Target Organs (Components)

WOOD DUST, HARDWOODS (Not Available)
immune system (sensitizer).
WOOD DUST, SOFTWOODS (Not Available)
immune system (sensitizer).

Medical Conditions Aggravated by Exposure Based on Product and Component Information

respiratory disorders, skin disorders and allergies

Additional Information (Product)

This product contains coal tar creosote. Volume 35 of the IARC monograph states that there is limited evidence that coal tar derived creosotes are carcinogenic in humans and sufficient evidence for the carcinogenicity of creosote in experimental animals. Limitations in the human exposure studies reviewed by IARC (including the presence of other chemicals, small study populations and not well documented exposure levels) contributed to IARC's conclusions regarding human exposure to creosote. When applied to the skin of mice in experimental studies, creosote produced skin tumors and in one study produced lung tumors.

Most available information on the effects of coal tar creosote in humans comes from older occupational studies in the wood-preserving and construction industries. Today, with the use of engineering controls and personal protective equipment, occupational exposure to creosote components is expected to be below permissible exposure limits (measured as CTPVs). Wood dust is particles of varying size produced from processing or handling wood. Cancer of the nasal cavities and sinuses is associated with exposure to hardwood dust. IARC concluded that there were too few studies to evaluate cancer risks attributable to exposure to softwood alone and to any particular species of wood. In view of the overall lack of consistent findings, IARC also concluded that there is no indication that occupational exposure to wood dust has a causal role in cancers of the throat, lung, lymphatic and blood systems, stomach, colon or rectum.

Different woods produce different health effects and there is evidence that wood from different trees of the same species can produce varying health effects. Woods other than Western Red Cedar (WRC) seem unlikely to be responsible for large numbers of cases of respiratory allergies. Other common wood dusts produce asthma/pulmonary effects that are less well described than the responses to WRC. These other wood species (e.g., oak and pine) are considered somewhat allergenic.

* * * Section 12 - ECOLOGICAL INFORMATION * * *

Component Analysis - Aquatic Toxicity

COAL TAR CREOSOTE (8001-58-9)

Fish: 96 Hr LC50 Brachydanio rerio: 2.6 - 6.6 mg/L [static]; 96 Hr LC50 Oncorhynchus mykiss: 0.57 mg/L [static]

Invertebrate: 48 Hr EC50 Daphnia magna: 1.04 mg/L; 48 Hr EC50 Daphnia magna: 0.065 - 0.082 mg/L [Static]

* * * Section 13 - DISPOSAL CONSIDERATIONS * * *

Disposal Methods

Dispose in accordance with all applicable regulations. Treated wood should not be burned in open fires or in stoves, fireplaces or residential boilers, because toxic chemicals may be produced as part of the smoke and ashes. Treated wood from commercial or industrial use (e.g., construction sites) may be burned only in commercial or industrial incinerators or boilers in accordance with state and federal regulations. For more information please see Koppers Consumer Information Sheet for this product.

Component Waste Numbers

COAL TAR CREOSOTE (8001-58-9)

RCRA: waste_number U051

* * * Section 14 - TRANSPORT INFORMATION * * *

US DOT Information

No Classification assigned.

TDG Information

No Classification assigned.

* * * Section 15 - REGULATORY INFORMATION * * *

U.S. Federal Regulations

This material contains one or more of the following chemicals required to be identified under SARA Sections 302/304 (40 CFR 355 Appendix A), SARA Section 313 (40 CFR 372.65), TSCA 12(b), and/or require an OSHA process safety plan.

COAL TAR CREOSOTE (8001-58-9)

SARA 313: 0.1 % de minimis concentration

SARA 311/312 Hazardous Categories (40 CFR 370 Subparts B and C)

Acute Health: Yes **Chronic Health:** Yes **Fire:** No **Pressure:** No **Reactive:** No

U.S. State Regulations

The following components appear on one or more of the following state hazardous substances lists:

Component	CAS#	CA	MA	MN	NJ	PA	RI
WOOD DUST, HARDWOODS ([1]related to: Wood dust, all soft and hard woods) ([2]related to: Wood dusts-hard wood)	Not Available	No	No	Yes[1]	No	Yes[2]	Yes[1]
WOOD DUST, SOFTWOODS ([1]related to: Wood dust, all soft and hard woods)	Not Available	No	No	Yes[1]	No	No	Yes[1]
COAL TAR CREOSOTE ([1]related to: Creosotes)	8001-58-9	Yes	Yes	Yes[1]	Yes	Yes	No

The following statement(s) are provided under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65):

WARNING! This product contains a chemical known to the state of California to cause cancer.

Canadian Regulations

WHMIS Classification

Not a Controlled Product under Canada's Workplace Hazardous Material Information System.

WHMIS Ingredient Disclosure List

There are no components listed on the Ingredient Disclosure List.

Canada Inventory Information (Product)

This product is exempt.

U.S. Inventory (TSCA) Information (Product)

This product is exempt.

Inventory Status (Components)

Component Analysis - Inventory

Component	CAS#	US	CA
COAL TAR CREOSOTE	8001-58-9	Yes	DSL

* * * Section 16 - OTHER INFORMATION * * *

Key / Legend

ACGIH - American Conference of Governmental Industrial Hygienists; ADR - European Road Transport; AU - Australia; BOD - Biochemical Oxygen Demand; C - Celsius; CA - Canada; CAS - Chemical Abstracts Service; CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act; CN - China; CPR - Controlled Products Regulations; DFG - Deutsche Forschungsgemeinschaft; DOT - Department of Transportation; DSL - Domestic Substances List; EEC - European Economic Community; EINECS - European Inventory of Existing Commercial Chemical Substances; EPA - Environmental Protection Agency; EU - European Union; F - Fahrenheit; IARC - International Agency for Research on Cancer; IATA - International Air Transport Association; ICAO - International Civil Aviation Organization; IDL - Ingredient Disclosure List; IDLH - Immediately Dangerous to Life and Health; IMDG - International Maritime Dangerous Goods; JP - Japan; Kow - Octanol/water partition coefficient; KR - Korea; LEL - Lower Explosive Limit; LOLI - List Of LIsts™ - ChemADVISOR's Regulatory Database; MAK - Maximum Concentration Value in the Workplace; MEL - Maximum Exposure Limits; NFPA - National Fire Protection Agency; NIOSH - National Institute for Occupational Safety and Health; NJTSR - New Jersey Trade Secret Registry; NTP - National Toxicology Program; NZ - New Zealand; OSHA - Occupational Safety and Health Administration; PH - Philippines; RCRA - Resource Conservation and Recovery Act; RID - European Rail Transport; RTECS - Registry of Toxic Effects of Chemical Substances®; SARA - Superfund Amendments and Reauthorization Act; STEL - Short-term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; UEL - Upper Explosive Limit; US - United States

Other Information

The information set forth in this Safety Data Sheet does not purport to be all-inclusive and should be used only as a guide. While the information and recommendations set forth herein are believed to be accurate, the company makes no warranty regarding such information and recommendations and disclaims all liability from reliance thereon.

"RTECS®" is a United States trademark owned and licensed under authority of the U.S. Government, by and through Symyx Software, Inc. Portions ©Copyright 2010, U.S. Government. All rights reserved.

End of Sheet 00228327

3714289

39A

Easement

KNOW ALL MEN BY THESE PRESENTS, that ~~I~~ (We) the undersigned William C. Mitchell and Nancy G. Mitchell (husband and wife) / Merrill H. Pearson and Wilma Pearson (~~Unmarried~~) (Husband and Wife) whose post office address is R#1-Box 572 Excelsior, Minn. 55331 in consideration of one dollar and other good and valuable considerations, the receipt whereof is hereby acknowledged, do hereby grant unto The RURAL COOPERATIVE POWER ASSOCIATION, whose post office address is Elk River, Minnesota, and to its successors or assigns the right to enter upon the following described lands of the undersigned, situated in Hennepin County, Minnesota, to wit:

The South one-half of the Southwest quarter (S½ of SW¼) of Section 18, Township 118, Range 22.

The South one-half of the Northeast quarter of the Southwest quarter (S½ of NE¼ of SW¼) of Section 18, Township 118, Range 22, lying South of County Road No. 48.

and to construct, operate and maintain thereon, and in or upon all streets, roads or highways abutting said lands, an electric transmission line or system consisting of single pole wood structures.

DEED TAX $2.20 STATE DEED TAX DUE HEREON $ 2.20

The grant of this easement shall include the right to cut down, trim, or in any manner eliminate all trees, shrubbery or brush to a distance of 35 feet on either side of said electric transmission line or system, and further to cut down from time to time all other dead, weak, leaning or dangerous trees that are tall enough to strike the wires in falling.

The Cooperative agrees to pay to the undersigned, when construction of said line or system is commenced on the above described lands the further sum of $ [illegible]

Further, the Cooperative agrees to pay a reasonable sum for any damage caused to crops or fences by the operation, maintenance, or repair of said line or system.

All facilities installed and placed by the Cooperative on said lands shall remain the property of the Cooperative, removable at the option of the Cooperative.

IN WITNESS WHEREOF ~~I~~ (We) have duly executed this instrument this 17th day of March, 1968.

In presence of:

[illegible]

William C. Mitchell

Nancy G. Mitchell (SEAL)

Merrill H. Pearson (SEAL)

Wilma Pearson (SEAL)

STATE OF MINNESOTA
COUNTY OF Hennepin) SS

On this 17th day of March 1968, before me a Notary Public, within and for Hennepin County, personally appeared William C. Mitchell and Nancy G. Mitchell husband and wife and Merrill H. Pearson and Wilma Pearson (~~Unmarried~~) (Husband and Wife), to me known to be the persons described in and who executed the foregoing instrument and acknowledged that they executed the same as their free act and deed.

[illegible]

Notary Public Hennepin County, Minn.

My Commission expires [illegible] 1971

ESMT

3714289

Mi-PE

MAY 13-68 4 2 8 9 $ 002.00 B

RJ

OFFICE OF REGISTER OF DEEDS
STATE OF MINNESOTA
COUNTY OF HENNEPIN

I hereby certify that the within instrument was filed for record in this office on the 13 day of MAY A. D. 1968 at 3 o'clock P M., and was duly recorded in book 68 of Hennepin County Records page 3714289

REGISTER OF DEEDS

By

DEPUTY REGISTER OF DEEDS

TRANSFER ENTERED
MAY 9 1968
GEORGE R. HICKEY, AUDITOR
HENNEPIN COUNTY, MINN.
BY DEPUTY

RCPA
Eng. #76-1

3802934

Easement No. BD-B-39A

PARTIAL RELEASE OF EASEMENT

KNOW ALL MEN BY THESE PRESENTS, that The Rural Cooperative Power Association, an incorporated Cooperative Association under the laws of the State of Minnesota, (Grantor) in consideration of the sum of one dollar and other good and valuable considerations, the receipt of which is hereby acknowledged, does hereby release the following described land situated in Hennepin County, Minnesota, to wit:

The South one-half of the Northeast quarter of the Southwest quarter, (S 1/2 of the NE 1/4 of the SW 1/4) of Section 18, Township 118, Range 22, lying Southerly of County Road number 48 as it is now laid out and constructed, EXCEPTING THEREFROM the East 37 feet thereof;

The South one-half of the Southwest quarter (S 1/2 of the SW 1/4) of Section 18, Township 118, Range 22, EXCEPTING THEREFROM the East 37 feet and the South 50 feet thereof;

from that certain easement executed on March 19, 1968 by William C. Mitchell and Nancy G. Mitchell and Merritt H. Pearson and Mima L. Pearson, husband and wife husband and wife, ~~unmarried~~, to The Rural Cooperative Power Association, its successors and assigns, and filed for record in the office of the Register of Deeds for Hennepin County on May 13, 1968 as Document No. 3714289 and recorded in Book 68 of Hennepin County Records on page 3714289

As to the lands herein excepted all rights acquired by Grantor by said easement herein described dated March 19, 1968 are hereby expressly retained and reserved unto Grantor, its successors and assigns.

As to the lands hereby released, Grantor hereby reserves unto itself, its successors and assigns, the right to cut down or trim from time to time any dead, weak, leaning or dangerous trees located thereon that are tall enough to strike the wires of Grantor's transmission line in falling; also reserving unto Grantor, its successors and assigns, the right of reasonable ingress and egress from its right-of-way (being the lands herein excepted) over and across the lands hereby released by the most convenient route which will cause the least possible interference with the owners or occupants use thereof.

Dated at Elk River, Minnesota, this ..... day of ....., 19.....

In Presence of:

.....

.....

The Rural Cooperative Power Association

By .....
O.N.Gravgaard, Its President

By .....
J.Mauritz Nelson, Its Secretary

(Seal)

STATE OF MINNESOTA)
) ss
COUNTY OF SHERBURNE)

On this ..... day of ....., 19....., before me a Notary Public, within and for ..... County, personally appeared O.N.Gravgaard and J. Mauritz Nelson, to me personally known, who, being each by me duly sworn did say that they are respectively the President and the Secretary of the corporation named in the foregoing instrument and that the seal affixed to said instrument is the corporate seal of said corporation and that said instrument was signed and sealed in behalf of said corporation by authority of its Board of Directors and said O.N.Gravgaard and J.Mauritz Nelson acknowledged said instrument to be the free act and deed of said corporation.

(Return this document to The Rural Cooperative Power Assn., Elk River, Mn., 55330, after recording)

.....
Notary Public

KENNETH J. WAHL
Notary Public, Anoka County, Minnesota
My Commission Expires Sept. 9, 1970

United States
Environmental Protection
Agency

Prevention, Pesticides
and Toxic Substances
(7510P)

EPA 739-R-08-008
September 25, 2008

Reregistration Eligibility Decision for Pentachlorophenol

REREGISTRATION ELIGIBILITY
DECISION
for
Pentachlorophenol
List B
CASE 2505

Approved By:

Frank T. Sanders
Director, Antimicrobials Division
September 25, 2008

Attachment

I. INTRODUCTION ..... - 1 -

II. CHEMICAL OVERVIEW ..... - 3 -

A. REGULATORY HISTORY ..... - 3 -
B. CHEMICAL IDENTIFICATION ..... - 4 -
C. USE PROFILE ..... - 5 -
D. METHODS AND RATES OF APPLICATION: ..... - 6 -
E. DISPOSAL INFORMATION ..... - 6 -
1. TREATED WOOD ..... - 6 -

III. SUMMARY OF RISK ASSESSMENTS ..... - 7 -

A. BACKGROUND ON WOOD PRESERVATIVE RISK ASSESSMENT ..... - 7 -
B. HUMAN HEALTH RISK ASSESSMENT ..... - 9 -
1. TOXICITY OF PENTACHLOROPHENOL ..... - 10 -
a. Acute Toxicity ..... - 10 -
b. Carcinogenicity ..... - 11 -
c. Toxicological Endpoints ..... - 12 -
2. TOXICITY OF DIOXIN/FURAN ..... - 13 -
a. Acute and Chronic Toxicity ..... - 13 -
b. Carcinogenicity ..... - 13 -
3. TOXICITY OF HEXACHLOROBENZENE ..... - 14 -
a. Acute and Chronic Toxicity ..... - 14 -
b. Carcinogenicity ..... - 14 -
c. Toxicological Endpoints ..... - 15 -
4. DIETARY EXPOSURE AND RISK FROM FOOD AND DRINKING WATER ..... - 17 -
a. Dietary and Drinking Water ..... - 17 -
b. Pentachlorophenol ..... - 18 -
c. Dioxins and Furans ..... - 18 -
d. Hexachlorobenzene ..... - 19 -
5. RESIDENTIAL POST-APPLICATION EXPOSURE AND RISK ..... - 20 -
a. Residential Post-application Non-cancer Exposure and Risk Using NHANE- 20 -
b. Residential Post-application Non-cancer Exposure and Risk Using CTEPP- 21 -
c. Residential Post-application Cancer Exposure and Risk Using NHANES and CTEPP ..... - 21 -
6. AGGREGATE RISK ASSESSMENT ..... - 22 -
7. OCCUPATIONAL EXPOSURE AND RISK ..... - 22 -
a. Pentachlorophenol Occupational Handler Exposure and Risk ..... - 24 -
b. Dioxin Occupational Handler Exposure and Risk ..... - 24 -
c. Hexachlorobenzene Handler Exposure and Risk ..... - 25 -
d. Pentachlorophenol Occupational Post-application Exposure and Risk ..... - 25 -
e. Dioxin/Furan Occupational Post-application Exposure and Risk ..... - 26 -
f. Hexachlorobenzene Post-application Exposure and Risk ..... - 26 -
8. PENTACHLOROPHENOL HUMAN INCIDENT DATA ..... - 27 -
D. ENVIRONMENTAL RISK ASSESSMENT ..... - 28 -

1. ENVIRONMENTAL FATE AND TRANSPORT ..... - 29 -
a. **Pentachlorophenol** ..... - 29 -
b. **Dioxins/Furans** ..... - 30 -
c. **Hexachlorobenzene** ..... - 31 -
2. TERRESTRIAL AND AQUATIC ORGANISM EXPOSURE AND RISK ..... - 31 -
a. **Pentachlorophenol** ..... - 31 -
b. **Dioxins/Furans** ..... - 31 -
c. **Hexachlorobenzene** ..... - 34 -
3. RISKS TO LISTED SPECIES ..... - 35 -

IV. REREGISTRATION ELIGIBILITY AND RISK MANAGEMENT DECISIONS - 37 -

A. REREGISTRATION ELIGIBILITY DECISION ..... - 37 -
1. REGULATORY RATIONALE ..... - 37 -
a. **Summary of Risks** ..... - 37 -
b. **Summary of Benefits and Alternatives** ..... - 38 -
c. **Risk/Benefit Finding** ..... - 39 -
2. ENDOCRINE DISRUPTOR EFFECTS ..... - 39 -
3. CUMULATIVE RISKS ..... - 39 -
4. PUBLIC COMMENTS AND RESPONSE ..... - 40 -
B. RISK MANAGEMENT DECISION ..... - 40 -
1. DIOXIN/FURAN REDUCTION ..... - 45 -
2. MANAGEMENT OF PENTACHLOROPHENOL-TREATED MATERIALS ..... - 45 -
3. REGISTRATION REVIEW OF PENTACHLOROPHENOL ..... - 46 -

V. WHAT REGISTRANTS NEED TO DO ..... - 47 -

A. MANUFACTURING USE PRODUCTS ..... - 47 -
1. GENERIC DATA REQUIREMENTS ..... - 47 -
B. END-USE PRODUCTS ..... - 48 -
1. PRODUCT SPECIFIC DATA REQUIREMENTS ..... - 48 -
2. LABELING FOR END-USE PRODUCTS ..... - 50 -

APPENDIX A: USE PATTERNS ELIGIBLE FOR REREGISTRATION PENTACHLOROPHENOL 56

APPENDIX B: PENTACHLOROPHENOL CASE (2505) 57

APPENDIX C. TECHNICAL SUPPORT DOCUMENTS 61

APPENDIX D. CITATIONS SUPPORTING THE REREGISTRATION ELIGIBILITY DECISION (BIBLIOGRAPHY) 63

APPENDIX E. GENERIC DATA CALL-IN 91

APPENDIX F. PRODUCT SPECIFIC DATA CALL-IN 92

APPENDIX G. BATCHING OF PENTACHLOROPHENOL PRODUCTS FOR MEETING ACUTE TOXICITY DATA REQUIREMENTS FOR REREGISTRATION 93

APPENDIX H. LIST OF ALL REGISTRANTS SENT THE DATA CALL-IN 94

Pentachlorophenol Reregistration Team

Office of Pesticide Programs

Health Effects Risk Assessment
Jonathan Chen
Timothy McMahon
Timothy Leighton
Najm Shamim
Timothy Dole

Ecological Risk Assessment
Rick Petrie

Environmental Fate Risk Assessment
Siroos Mostaghimi

Biological and Economics Assessment Division
Jonathan Becker
Steve Hopkins
Timothy Kiely

Risk Management
Sherrie Kinard
Diane Isbell

Office of General Counsel:

Pesticides and Toxic Substances Law Office
Philip Ross

Office of Enforcement and Compliance Assistance:

David Stangel

Office of Solid Waste:

Ross Elliot

GLOSSARY OF TERMS AND ABBREVIATIONS

a.i.	Active Ingredient
aPAD	Acute Population Adjusted Dose
APHIS	Animal and Plant Health Inspection Service
ARTF	Agricultural Re-entry Task Force
BCF	Bioconcentration Factor
CDC	Centers for Disease Control
CDPR	California Department of Pesticide Regulation
CFR	Code of Federal Regulations
ChEI	Cholinesterase Inhibition
CMBS	Carbamate Market Basket Survey
cPAD	Chronic Population Adjusted Dose
CSFII	USDA Continuing Surveys for Food Intake by Individuals
CWS	Community Water System
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DL	Double layer clothing {i.e., coveralls over SL}
DWLOC	Drinking Water Level of Comparison
EC	Emulsifiable Concentrate Formulation
EDSP	Endocrine Disruptor Screening Program
EDSTAC	Endocrine Disruptor Screening and Testing Advisory Committee
EEC	Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EP	End-Use Product
EPA	U.S. Environmental Protection Agency
EXAMS	Tier II Surface Water Computer Model
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FOB	Functional Observation Battery
FQPA	Food Quality Protection Act
FR	Federal Register
GL	With gloves
GPS	Global Positioning System
HIARC	Hazard Identification Assessment Review Committee
IDFS	Incident Data System
IGR	Insect Growth Regulator
IPM	Integrated Pest Management
RED	Reregistration Eligibility Decision
LADD	Lifetime Average Daily Dose
LC_{50}	Median Lethal Concentration. Statistically derived concentration of a substance expected to cause death in 50% of test animals, usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LCO	Lawn Care Operator
LD_{50}	Median Lethal Dose. Statistically derived single dose causing death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation), expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOC	Level of Concern
LOEC	Lowest Observed Effect Concentration
mg/kg/day	Milligram Per Kilogram Per Day
MOE	Margin of Exposure
MP	Manufacturing-Use Product
MRID	Master Record Identification (number). EPA's system of recording and tracking studies submitted.
MRL	Maximum Residue Level

N/A	Not Applicable
NASS	National Agricultural Statistical Service
NAWQA	USGS National Water Quality Assessment
NG	No Gloves
NMFS	National Marine Fisheries Service
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NPIC	National Pesticide Information Center
NR	No respirator
OP	Organophosphorus
OPP	EPA Office of Pesticide Programs
ORETF	Outdoor Residential Exposure Task Force
PAD	Population Adjusted Dose
PCA	Percent Crop Area
PDCI	Product Specific Data Call-In
PDP	USDA Pesticide Data Program
PF10	Protection factor 10 respirator
PF5	Protection factor 5 respirator
PHED	Pesticide Handler's Exposure Data
PHI	Pre-harvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
PRZM	Pesticide Root Zone Model
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RPA	Reasonable and Prudent Alternatives
RPM	Reasonable and Prudent Measures
RQ	Risk Quotient
RTU	(Ready-to-use)
RUP	Restricted Use Pesticide
SCI-GROW	Tier I Ground Water Computer Model
SF	Safety Factor
SL	Single layer clothing
SLN	Special Local Need (Registrations Under Section 24C of FIFRA)
STORET	Storage and Retrieval
TEP	Typical End-Use Product
TGAI	Technical Grade Active Ingredient
TRAC	Tolerance Reassessment Advisory Committee
TTRS	Transferable Turf Residues
UF	Uncertainty Factor
USDA	United States Department of Agriculture
USFWS	United States Fish and Wildlife Service
USGS	United States Geological Survey
WPS	Worker Protection Standard

ABSTRACT

The Environmental Protection Agency (EPA or the Agency) has completed the human health and environmental risk assessments for pentachlorophenol and is issuing its risk management decision. The risk assessments, which are summarized below, are based on the review of the required target database supporting the use patterns of currently registered products and additional information received through the public docket. After considering the risks identified in the revised risk assessments, comments received, and mitigation suggestions from interested parties, the Agency developed its risk management decision for uses of pentachlorophenol that pose risks of concern. As a result of this review, EPA has determined that pentachlorophenol containing products are eligible for reregistration, provided that risk mitigation measures are adopted and labels are amended accordingly. That decision is discussed fully in this document. The Agency is aware that research is ongoing regarding pentachlorophenol. The Agency may revisit this decision in the future.

I. INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was amended in 1988 to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984 and amended again by the Pesticide Registration Improvement Act of 2003 to set time frames for the issuance of Reregistration Eligibility Decisions. The amended Act calls for the development and submission of data to support the reregistration of an active ingredient, as well as a review of all submitted data by the U.S. Environmental Protection Agency (EPA or the Agency). Reregistration involves a thorough review of the scientific database underlying a pesticide's registration. The purpose of the Agency's review is to reassess the potential hazards arising from the currently registered uses of the pesticide; to determine the need for additional data on health and environmental effects; and to determine whether or not the pesticide meets the "no unreasonable adverse effects" criteria of FIFRA.

Pentachlorophenol (PCP) is a general biocide which has been used extensively as a fungicide, bactericide, herbicide, molluscicide, algaecide and insecticide by agriculture and other industries including textiles, paints, oil drilling and forestry. Pentachlorophenol also contains chlorinated dibenzodioxins and chlorinated dibenzofurans (CDDs and CDFs) and hexachlorobenzene (HCB) as contaminants formed during the manufacture process. These compounds are inherently toxic, as well as environmentally persistent, and their presence may increase the ecological risk associated with the use of pentachlorophenol. Pentachlorophenol is only one of many sources of CDDs, CDFs, and HCB in the environment making it difficult to quantify the portion of the aggregate environmental risk from CDDs, CDFs, and HCB that is attributable to pentachlorophenol wood treatment uses. The main use of pentachlorophenol, as a heavy duty wood preservative, is to treat utility poles. Although its only remaining use in the U.S. is as a heavy duty wood preservative, pentachlorophenol has been used in rice and sugar production, in water treatment, as a pre-harvest defoliant in cotton, and as a general pre-emergence herbicide. It has also been utilized in numerous products including adhesives, construction materials, leather and paper. Pentachlorophenol is currently classified as a Restricted Use Product (RUP) when used as a heavy duty wood preservative and is predominately used to treat utility poles and cross arms.

This document presents the Agency's revised human health and ecological risk assessments and the Reregistration Eligibility Decision (RED) for pentachlorophenol. The pentachlorophenol case consists of one PC Code: 063001. Pentachlorophenol has been used as a wood preservative since 1936; however, the first pesticidal product containing pentachlorophenol was registered in 1950. For a list of the current products, please see Appendix A.

Currently, all of the pentachlorophenol produced in the U.S. is utilized in wood preservation. There are approximately 60 million utility-owned wood poles and 54 million crossarms in service across the United States which have been treated with wood preservatives (mainly pentachlorophenol and creosote; EPRI 1993). Approximately 36 million of the wood poles in service have been treated with pentachlorophenol (Malecki, 1992), and approximately

95.8% of the crossarms in service were treated with pentachlorophenol (EPRI 1993). An estimated 3% of the treated poles are replaced annually.

The Agency has determined that analysis of the potential need for a special hazard-based safety factor under the FQPA is not needed at this time. The Agency does not anticipate dietary or drinking water exposures based on the registered use patterns and there are no tolerances or tolerance exemptions for the use of pentachlorophenol as an active ingredient. Therefore, an FQPA hazard analysis is not necessary at this time.

This document presents the Agency's decision regarding the reregistration eligibility of the registered uses of pentachlorophenol. In an effort to simplify the RED, the information presented herein is summarized from more detailed information which can be found in the technical supporting documents for pentachlorophenol in this RED. The revised risk assessments and related addenda are not included in this document, but are available in the Public Docket at www.regulations.gov (Docket ID EPA-HQ-OPP-2004-0402).

This document consists of six sections. Section I is the Introduction. Section II provides a Chemical Overview, a profile of the use and usage of pentachlorophenol and its regulatory history. Section III, Summary of pentachlorophenol Risk Assessments, gives an overview of the human health and environmental assessments, based on the data available to the Agency. Section IV, Risk Management and Reregistration, presents the reregistration eligibility and risk management decisions. Section V, What Registrants Need to Do, summarizes the necessary label changes based on the risk mitigation measures outlined in Section IV. Finally, the Appendices list all use patterns eligible for reregistration, bibliographic information, related documents and how to access them, and Data Call-In (DCI) information.

II. Chemical Overview

A. Regulatory History

Pentachlorophenol was first registered as an active ingredient by the United Sates Department of Agriculture (USDA) on December 1, 1950. In 1970, the Environmental Protection Agency (EPA) was established and was charged with protecting human health and the environment, and assumed all pesticide registrations from USDA. Currently, there are six products containing pentachlorophenol as an active ingredient. Pentachlorophenol is a fungicide, bactericide, herbicide, molluscicide, algaecide and insecticide and is only registered for use as a heavy duty wood preservative.

The production of pentachlorophenol for wood preserving began on an experimental basis in the 1930s. In 1947 nearly 3,200 metric tons of pentachlorophenol was reported to have been used in the U.S. by the commercial wood preserving industry. Pentachlorophenol was one of the most widely used biocides in the U.S. prior to regulatory actions to cancel and restrict certain non-wood preservative uses of pentachlorophenol in 1987. Prior to the 1987 Federal Register Notice (Vol. 52, No. 13) which canceled and restricted certain non-wood uses, pentachlorophenol was registered for use as an herbicide, defoliant, mossicide, and as a disinfectant.

Indoor applications of pentachlorophenol are prohibited. These restrictions were imposed on pentachlorophenol registrations as part of the Agency's Special Review process as indicated in the *U.S.EPA Position Document 4 for Wood Preservative Pesticides: Creosote, Pentachlorophenol and Inorganic Arsenicals (1984, amended 1986)*. PD 4 announcing the termination of the Special Review for the non-wood uses of pentachlorophenol was signed 12/29/92 and was published 2/93.

The use of pentachlorophenol to treat wood intended for use in interiors is also prohibited, except for a few low exposure uses (i.e., those support structures which are in contact with the soil in barns, stables, and similar sites and which are subject to decay or insect infestation). Pentachlorophenol is a restricted use pesticide for sale and use by certified applicators only.

In 2000, the Agency canceled 12 products containing pentachlorophenol due to the registrant's failure to pay registration maintenance fees. This resulted in cancellation of all uses of pentachlorophenol as a remedial treatment (a non-pressure treatment using a brush) of utility poles.

The Agency has received requests by the registrants of pesticide products containing pentachlorophenol to voluntarily amend to terminate certain uses of affected products. Two registrants, KMG Chemicals, Inc. and Vulcan Chemicals, requested this action to be effective immediately. KMG Chemicals, Inc. requested that all non-pressure treatment and non-thermal treatments for their product (Pentacon 40) be deleted. Vulcan Chemicals requested to voluntarily cancel spray uses for two of their products (Vulcan GLAZD Penta and Vulcan Premium Four Pound [PCP-2] Concentrate). The Agency has processed these requests. These voluntary use cancellations leave only pressure and thermal wood treatment uses of pentachlorophenol.

B. Chemical Identification

Technical Pentachlorophenol

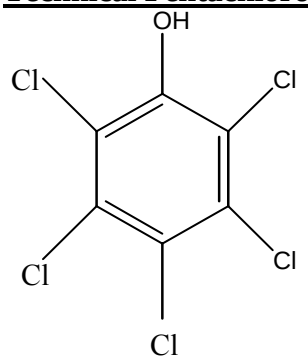


Figure #1. Molecular Structure of Pentachlorophenol

Common name: Pentachlorophenol

Chemical name: 2,3,4,5,6-pentachlorophenol

Chemical family: Aromatic Hydrocarbon Chlorophenol

Empirical formula: $C_6H\,Cl_5O$

CAS Registry No.: 87-86-5

Case number: 2505

OPP Chemical Code: 063001

Molecular weight: 266.34 g/mol

Other names: Pentachlorophenol is abbreviated as PCP. Product names include Dowicide EC-7, Penchlorol, Penta, Pentacon, Penwar, Priltox, Sinituho and Weedone.

Basic manufacturer: KMG-Bernuth, Inc.

Chemical properties: Pentachlorophenol is light brown to tan (Pure pentachlorophenol, however, is white needle-like crystals). It is a solid with a phenolic odor. Pentachlorophenol has a density of 1.978 g/ml; a dissociation constant (K_a) of 1.6×10^{-14}; has a pH of 4.99; and sublimes at 54 ± 2°C. Pentachlorophenol has a melting point of 190-191° C; and has a boiling point of 309° C (decomposes). The vapor pressure is 1.1×10^{-4} mm Hg at 25°C. Pentachlorophenol has a Log K_{OW} of 5.05 at pH 5.1; a Log K_{OC} of 2430 (Georgia, sandy loam), 3420 (Ohio, clay loam), 706 (California, sandy loam), 1410 (Nebraska, blue sandy loam); and its solubility at 20°C is 14 mg/L in water, 1.7 g/g in methanol, and 0.014 g/g in benzene.

C. Use Profile

The following information is a description of the currently registered uses of pentachlorophenol products, and an overview of use sites and application methods. A detailed table of the pentachlorophenol uses that are eligible for reregistration can be found in Appendix A.

Type of Pesticide: Pentachlorophenol is a restricted use pesticide used as a heavy duty wood preservative (fungicide, bactericide, herbicide, molluscicide, algaecide and insecticide).

Carpenter Ants
Mold
Lyctus Powderpost Beetles
Powderpost Beetles
Termites
Wood Rot/Decaying Fungus
Wood Rot/Decaying Organisms
Wood Stain Fungus

Use Classification: Restricted use.

Use Sites: The only registered use of pentachlorophenol is as a heavy duty wood preservative.

Lumber
Seasoned Lumber
Timbers
Wood
Wood Poles/Posts
Wood Products
Wood Pressure Treatment

Formulation Types: soluble concentrate and ready to use

D. Methods and Rates of Application:

A summary of the pentachlorophenol registered uses is given in Table 1 and a more detailed listing is included in Appendix A. Pentachlorophenol is registered for use as a heavy duty wood preservative. All other uses have been canceled.

Table 1: Pentachlorophenol Use Site and Application Rates

Company Name	Label #	Product Name	Formulation
KMG-Bernuth, Inc.	61483-1	Penta 5 Sure-Treat Wood Preserver	RTU
	61483-2	Dura-Treet 40 Wood Preserver	SC
	61483-3	KMG-B Penta Ol Technical Pentachlorophenol	Intermediate
	61483-58	Pentacon-7	RTU
	61483-59	Pentacon-10	RTU
	61483-62	Vulcan GLAZD Penta	Technical

Note: RTU is Ready to Use, and SC is Soluble Concentrate.

E. Disposal Information

In a broad sense, two types of waste are generated through the use of pentachlorophenol wood preservatives: wood treated with pentachlorophenol and industrial waste generated through the application of pentachlorophenol. The disposal requirements differ for each type of waste.

1. Treated Wood

Discarded pentachlorophenol treated lumber is usually land disposed in either construction and demolition landfills, municipal solid waste landfills, or industrial non-hazardous waste landfills. Many state and local governments may have specific regulations, guidelines, or recommendations for the management and disposal of discarded pentachlorophenol treated wood, either explicitly, or sometimes under the larger category of "treated wood." Therefore, EPA recommends that persons contact their state and local authorities regarding specific policies or regulations concerning the disposal of pentachlorophenol treated wood.

EPA estimates that there will remain a supply of pentachlorophenol treated wood that will ultimately require disposal, considering the amount of this building material currently in use, and its typical service life (which can be many years). EPA continues to evaluate the potential impacts of land disposal of discarded pentachlorophenol treated wood.

2. Waste Generated at Wood Treatment Facilities

There are also hazardous waste regulations under the Resource Conservation and Recovery Act (RCRA) that apply specifically to wastes generated at facilities where wood preservatives are used to treat wood. On December 6, 1990 EPA promulgated several hazardous waste listings applicable to wastes generated by wood treaters using certain wood preservative chemicals. (55 *FR* 50450; December 6, 1990 *Federal Register*). One of these hazardous waste listings (Hazardous Waste Number F032) can be found in the hazardous waste regulations at 40 CFR 261.31, and reads as follows:

- ***F032:*** Wastewaters (except those that have not come into contact with process contaminants), process residuals, preservative drippage, and spent formulations from wood preserving processes generated at plants that currently use or have previously used chlorophenolic formulations (except potentially cross-contaminated wastes that have had the F032 waste code deleted in accordance with Sec. 261.35 of this chapter or potentially cross-contaminated wastes that are otherwise currently regulated as hazardous wastes (i.e., F034 or F035), and where the generator does not resume or initiate use of chlorophenolic formulations). This listing does not include K001 bottom sediment sludge from the treatment of wastewater from wood preserving processes that use creosote and/or pentachlorophenol.

Because pentachlorophenol preservative is a "chlorophenolic formulation," wastes generated from its use falls within the scope of this hazardous waste listing. Thus, wood treaters using pentachlorophenol preservatives would be hazardous waste generators (with respect to any in-scope wastewaters, process residuals, preservative drippage, etc. that are generated) and would be subject to the applicable requirements under RCRA Subtitle C, for example, notification of hazardous waste activity, obtaining an EPA Identification number, use of a hazardous waste manifest for off-site shipments of waste, and most significantly, the use and maintenance of a drip pad as described in 40 CFR 262.34(a)(1)(iii) and part 265, subpart W.

III. Summary of Risk Assessments

A. Background on Wood Preservative Risk Assessment

The purpose of this summary is to assist the reader by identifying the key features and findings of these risk assessments and to help the reader better understand the conclusions reached in the assessments. The human health and ecological risk assessment documents and supporting information listed in Appendix C were used to formulate the safety finding and regulatory decision for pentachlorophenol. While the risk assessments and related addenda are not included in this document, they are available from the OPP Public Docket EPA-HQ-OPP-2004-0402, and may also be accessed from www.regulations.gov. Hard copies of these documents may be found in the OPP public docket. The OPP public docket is located in Room S-4900, One Potomac Yard, 2777 South Crystal Drive, Arlington, VA 22202, and is open Monday through Friday, excluding Federal holidays, from 8:30 a.m. to 4:00 p.m.

The Agency's use of human studies in the pentachlorophenol risk assessment is in accordance with the Agency's Final Rule promulgated on January 26, 2006, related to Protections for Subjects in Human Research, which is codified in 40 CFR Part 26.

For almost all pesticides subject to reregistration, EPA employed an active ingredient-focused approach rather than an application method-focused approach. That is, EPA typically evaluated and made reregistration eligibility decisions for each active ingredient and its associated use sites rather than each use site and its associated active ingredients ("RED for active ingredient X" rather than "RED for applications made by application method X"). However, due to the unique nature in which the chemicals are applied, EPA made the decision

early in the reregistration process (circa 1988) to evaluate heavy duty wood preservative uses collectively using an application method-focused approach.

The term "heavy duty" wood preservative is used to differentiate wood preservatives applied using specialized high pressure treatment cylinders (also called "retorts") from those applied using non-specialized methods (e.g., brush, dip). Figure 1 presents a photograph of a treatment retort. There are three heavy duty wood preservative cases subject to reregistration: chromated arsenicals (Case 0132), pentachlorophenol (Case 2505), and creosote (Case 0139). Because these cases include only heavy duty wood preservatives, to improve readability the words "heavy duty" are often omitted in favor of the generic term "wood preservative" throughout the RED and supporting documents. The Agency notes that other heavy duty wood preservatives exist outside Case 0132, 2505, and 0139; however, uses of these preservatives were not subject to reregistration because the chemicals were not registered prior to November 1, 1984 and are therefore outside the scope of the three heavy duty wood preservative REDs. Heavy duty wood preservatives not included in Case 0132, 2505, and 0139 will be evaluated in the future under the registration review program.

Figure 1. Heavy Duty Wood Preservative High Pressure Treatment Cylinder (Retort)

Again, due to the unique nature in which heavy duty wood preservatives are applied, wood preservative risk assessment requires a different approach than those used for standard agricultural or antimicrobial pesticides. For example, unlike agricultural pesticide handlers who may be exposed to pesticides when mixing/loading, applying, or re-entering an area treated with

a pesticide, treatment facility workers may be exposed to pesticides when handling treated wood and/or performing activities related to operating the treatment cylinder.

This presents two challenges for risk assessment. First, because very few chemicals are applied using retorts, limited data are available to estimate worker exposure. Second, because many of the Agency's exposure models were designed to assess risk from agricultural chemicals, exposure estimates are expected to be conservative and may not be representative of "real world" exposure. The Agency acknowledges these challenges and considered these and other factors when making its reregistration and risk management decisions.

B. Human Health Risk Assessment

Pentachlorophenol is a general biocide which has been used extensively as a fungicide, bactericide, herbicide, molluscicide, algaecide and insecticide by agriculture and other industries including textiles, paints, oil drilling and forestry. However, the only remaining uses of pentachlorophenol are as a heavy duty wood preservative. Pentachlorophenol also contains chlorinated dibenzodioxins and chlorinated dibenzofurans (CDDs and CDFs) and hexachlorobenzene (HCB) as contaminants formed during the manufacture process. However, pentachlorophenol is only one of many sources of CDDs, CDFs, and HCB in the environment making it difficult to quantify the portion of the aggregate environmental risk from CDDs, CDFs, and HCB that is attributable to pentachlorophenol wood treatment uses.

CDDs and CDFs have been identified as micro-contaminants in technical grade pentachlorophenol. CDDs and CDFs have been found throughout the world at low concentrations in air, soil, water, sediment, fish and shellfish, and other food products such as meat and dairy products. CDDs and CDFs are members of a family of polychlorinated isomers of "dioxin-like" compounds. Physical and chemical properties and toxicity vary with the degree of chlorination. The most toxic congener of the family is 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD).

The dioxin/furan contaminants of pentachlorophenol present a unique case for purposes of risk characterization. Up to 17 CDD/CDF congeners are produced as contaminants in the manufacture of technical grade pentachlorophenol. All of these contaminants have chlorine substitution in at least the 2,3,7, and 8 positions, thus imparting these contaminants with "dioxin like" activity. Thus, all must be considered in the risk assessment for the contaminants of pentachlorophenol.

HCB has also been identified as a micro-contaminant in technical grade pentachlorophenol, and is not a naturally occurring compound. It is present in the environment through emissions into the atmosphere due to the manufacture of PCP and numerous emission processes, industrial discharge of HCB containing wastes into waterways as well as due to the manufacturing processes of some pesticides. Since HCB is a micro-contaminant in technical grade pentachlorophenol, it must also be considered in the risk assessment for the contaminants of pentachlorophenol.

1. Toxicity of Pentachlorophenol

A brief overview of the toxicity studies used for determining endpoints in the risk assessment is outlined below in Table 1. Further details on the toxicity of pentachlorophenol can be found in the "Pentachlorophenol-Toxicology Chapter for the Reregistration Eligibility Decision Document.," dated August 29, 2008; and the "***PENTACHLOROPHENOL:*** - Revised Toxicology Endpoint Report.," dated February 11, 2008. These documents are available on the Agency's website in the EPA Docket at: http://www.regulations.gov (Docket ID EPA-HQ-OPP-2004-0402).

The Agency has reviewed all toxicity studies submitted for pentachlorophenol and has determined that the toxicological database is sufficient for reregistration. The studies have been submitted to support guideline requirements. Major features of the toxicology profile are presented below. Table 1 gives a summary of the acute toxicity data and the toxicological endpoints selected for the exposure scenarios are summarized in Table 3. As stated previously, the Agency is aware that research is ongoing regarding pentachlorophenol. The Agency may revisit this decision in the future.

a. Acute Toxicity

The acute toxicity database for pentachlorophenol is considered complete. The acute toxicity of pentachlorophenol is low for dermal toxicity (Toxicity Category IV) and primary dermal irritation (Toxicity Category III) but shows higher toxicity for acute oral toxicity and primary eye irritation (Toxicity Category II). No dermal sensitization was observed with the technical test material. Acceptable acute inhalation toxicity data for pentachlorophenol were not available, but waivers were granted for these data.

The Pentachlorophenol Task Force previously submitted data to the Agency on efforts to develop methods to conduct inhalation studies. This effort was without success, based on an inability to generate consistent chamber concentrations of pentachlorophenol. The Agency has reviewed the documents in its possession regarding requests for waivers of inhalation toxicity data requirements, attempts at generating respirable atmospheres of pentachlorophenol, and conclusions reached in the Position Document 4 for Wood Preservatives (USEPA, 1984). Several difficulties were apparently encountered in the attempt to generate respirable particles of pentachlorophenol. It is concluded that, other issues notwithstanding, the real issue is the ability to maintain a consistent chamber concentration of pentachlorophenol. The previous decision to allow waivers for the acute and 90-day inhalation toxicity studies is upheld, but a Toxicity Category I for inhalation hazard will be assigned. The assignment of a Toxicity Category I is also consistent with regulatory decisions made previously for use of respirators from occupational exposure to pentachlorophenol (USEPA, 1984).

The following table summarizes the acute toxicity of pentachlorophenol. It is noted that the studies cited are older data, in which the test material may contain measureable concentrations of contaminants such as hexachlorodioxins and hexachlorobenzene.

Table 2. Summary of Acute Toxicity Data for Pentachlorophenol

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
Acute Toxicity				
870.1100 (§81-1)	Acute Oral	00101715	LD50 = 155 mg/kg (M); LD50 = 137 mg/kg (F)	II
870.1200 (§81-2)	Acute Dermal Toxicity	00101715	LD50 > 3980 mg/kg	IV
870.1300 (§81-3)	Acute Inhalation Toxicity	waiver granted		I
870.2400 (§81-4)	Primary Eye Irritation	00101715	Corneal involvement at day 7 post-instillation	II
870.2500 (§81-5)	Primary Dermal Irritation	00101715	Moderate irritation at 72 hours post-application	III
870.2600 (§81-6)	Dermal Sensitization	42594301	no sensitization observed using Buehler method	NA

b. Carcinogenicity

Pentachlorophenol was classified as a B2 carcinogen (probable human carcinogen) at a joint February 1990 meeting of the FIFRA Science Advisory Panel and Science Advisory Board. The SAP/SAB concluded that the liver tumors, pheochromocytomas, and hemangiosarcomas were treatment-related and supported the B2 classification. These tumors were observed in female mice from a study conducted by the National Toxicology Program in 1989 (NTP Technical Report 349, March 1989) using pure pentachlorophenol or a technical grade formulation, Dowicide EC-7. In November of 1990, the Health Effects Division's Carcinogenicity Assessment Review Committee met and concurred with the B2 classification and also recommended quantification of risk using the combined incidence of hemangiosarcomas, liver tumors, and pheochromocytomas in female mice from the two data sets generated with the two pentachlorophenol formulations used in the NTP study (Health Effects Division document # 013274, HED archive record series). Using a 3/4 scaling factor, an oral cancer risk estimate (q_1*) of 7.0 x 10^{-2} was calculated on this basis The slope factor was calculated as the geometric mean of the individual slope factors derived from two data sets: female mouse data for technical grade and Dowicide EC-7 pentachlorophenol.

EPA is currently completing a new Integrated Risk Information System (IRIS) assessment that will include a cancer unit risk value for pentachlorophenol. Based on the ongoing re-evaluation of the science to estimate carcinogenic potential of pentachlorophenol, OPP will use the current risk estimate for pentachlorophenol until any new risk estimates are fully peer reviewed. However, the EPA process of regulating pesticides allows for reevaluation at any time if new information from the peer review process of the carcinogenic potential of pentachlorophenol warrants.

c. Toxicological Endpoints

On November 25, 1997, the Health Effects Division's Hazard Identification Review committee evaluated the toxicology data base of pentachlorophenol, selected doses and endpoints for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure risk assessments, assessed the carcinogenic potential and addressed the sensitivity of infants and children from exposure to Pentachlorophenol as required by the Food Quality Protection Act (FQPA). In February of 2008, the Agency evaluated updated information with respect to the carcinogenicity of pentachlorophenol. The toxicity endpoints used in the current risk assessment are summarized below in Table 3.

Table 3. Toxicological Endpoints for Pentachlorophenol

Exposure Scenario	Dose Used in Risk Assessment, UF	Target MOE, Uncertainty Factory (UF) for Risk Assessment	Study and Toxicological Effects
Dietary Risk Assessments			
Acute Dietary (all populations)	An acute dietary assessment is not needed for the registered antimicrobial uses of pentachlorophenol, however, an acute endpoint of 30 mg/kg/day was selected from a developmental toxicity study in rats (MRID 43091702), with an uncertainty factor of 100 to calculate the acute RfD.		
Chronic Dietary (all populations)	A chronic dietary assessment is not needed for the registered antimicrobial uses of pentachlorophenol; however, a chronic endpoint of 1.5 mg/kg/day, the LOAEL from a chronic toxicity study in dogs (MRID 43882701), was previously selected, with an uncertainty factor of 300 to calculate the chronic RfD.		
Non-Dietary Risk Assessments			
Incidental Oral	An incidental oral risk assessment is not required for the registered antimicrobial uses of pentachlorophenol.		
Dermal (short- and intermediate-term)	NOAEL = 30 mg/kg/day	MOE = 100	Developmental Toxicity study – rats MRID 43091702
Dermal (long-term)	LOAEL = 1.5 mg/kg/day UF: 3X for lack of a NOAEL	MOE = 300	Chronic Toxicity study – dogs MRID 43982701
Inhalation (all durations)	No inhalation data available for pentachlorophenol. Inhalation risks for occupational exposure were not performed because most inhalation values derived from the biomonitoring study in workers were below the level of quantitation, thus implying that the majority of worker exposure is through dermal contact with pentachlorophenol		

Exposure Scenario	Dose Used in Risk Assessment, UF	Target MOE, Uncertainty Factory (UF) for Risk Assessment	Study and Toxicological Effects
Carcinogenicity (oral)	Classified as a B2 (probable human carcinogen) carcinogen by the Health Effects Division Carcinogenicity Assessment Review Committee and EPA's Science Advisory Board. An oral cancer risk estimate (q_1*) of 7.0 x 10^{-2} was calculated based on the incidences of hepatocellular neoplasms, adrenal medullary neoplasms, and hemangiosarcomas that developed in female mice treated with technical grade PCP or Dowicide EC-7 (NTP, 1989). The slope factor was calculated as the geometric mean of the individual slope factors derived from two data sets: female mouse data for technical grade and Dowicide EC-7 pentachlorophenol.		

Notes: UF = uncertainty factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose.

2. Toxicity of Dioxin/Furan

The concept of toxic equivalency factors (TEFs) has been developed to facilitate risk assessment of exposure to chemical mixtures of CDDs and CDFs. In this procedure, individual TEFs are assigned to the various congeners of CDDs and CDFs. These values have been published by both the USEPA and the World Health Organization (Younes, 1998) and are based on assigning relative values in relation to 2,3,7,8-TCDD, which is assigned a TEF value of 1.0, it being the most potent congener. Multiplying the exposure concentration of individual congeners by their respective TEFs yields a toxic equivalency, which, when summed for all the components of the mixture, gives the toxic equivalency quotient (TEQ) for that mixture and is an indication of the additional exposure from the pentachlorophenol contaminants.

Recent developments in science policy in the Agency have resulted in a shift towards calculation of non-cancer risk from dioxins and furans using a body burden approach rather than a dose or intake approach. This is appropriate for dioxin/furan contaminants of pentachlorophenol due to the long half-life of these chemicals. The Agency's Office of Research and Development (ORD) has led the effort in characterizing hazards and risks from exposure to dioxins and dioxin-like compounds, and the OPP, in its assessment of non-cancer risks posed by the dioxin/furan contaminants in pentachlorophenol, is working with ORD to express these risks using the methodologies developed in ORD for calculation of body burdens from exposure to the contaminants in pentachlorophenol treated wood.

a. Acute and Chronic Toxicity

Acute and chronic non-cancer toxicity have not been determined and are pending assessment using models developed by the Agency's Office of Research and Development (ORD) to determine actual body burdens. Only long-term dioxin absorbed doses are presented for calculation of the lifetime average daily doses (LADDs).

b. Carcinogenicity

A carcinogenic endpoint related to absorbed doses of CDD and CDF micro-contaminants has been identified. A cancer risk greater than one in a million is of concern.

In 1985, EPA classified 2,3,7,8-TCDD and related compounds as "probable" human carcinogens based on the available data. Since that time, the database relating to the carcinogenicity of dioxin and related compounds has grown and strengthened considerably. Under EPA's current approach, 2,3,7,8-TCDD is best characterized as a "human carcinogen." This means that, based on the weight of all of the evidence (human, animal, mode of action), 2,3,7,8- TCDD meets the stringent criteria that allows EPA and the scientific community to accept a causal relationship between 2,3,7,8-TCDD exposure and cancer hazard. Other dioxin-like compounds are characterized as "likely" human carcinogens primarily because of the lack of epidemiological evidence associated with their carcinogenicity, although there is a strong inference based on toxic equivalency that they would behave in humans as 2,3,7,8-TCDD does.

At this time, the knowledge of the mechanism of action of dioxin, receptor theory, and the available dose-response data do not firmly establish a scientific basis for replacing a linear procedure for estimating cancer potency. Therefore, for purposes of cancer risk assessment, the Agency is using the currently published slope factor of 1.0×10^{5} $(mg/kg/day)^{-1}$ for the 2,3,7,8 congener.

For additional information, please see the *Pentachlorophenol- Risk Assessment for the Reregistration Eligibility Decision (RED) Document*, dated August 29, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

3. Toxicity of Hexachlorobenzene

The Agency has identified HCB as a persistent, bio-accumulative, and toxic (PBT) environmental pollutant contaminating water and food-chain sources. Human health effects associated with exposure to HCB include skin lesions, nerve and liver damage as short-term effects. Long-term effects from lifetime exposures include damage to liver and kidneys, reproductive effects, benign tumors of endocrine glands, and cancer.

The manufacturing process of pentachlorophenol produces several known contaminants of toxicological concern including HCB. The exposure and risk assessment for HCB in pentachlorophenol will focus on the use of pentachlorophenol as a wood preservative and the potential occupational exposure to HCB through this use.

a. Acute and Chronic Toxicity

The toxicology of hexachlorobenzene is discussed in detail within the 1991 "Drinking Water Criteria Document for Hexachlorobenzene", prepared by the U.S. EPA's Office of Health and Environmental Assessment (U.S. EPA, 1991) and the "ATSDR Toxicological Profile for Hexachlorobenzene" (ATSDR, 2002). Both assessments characterize the acute toxicity of HCB as low, with oral LD50 values in the range from 3500-10,000 mg/kg in rats, and other data citing 1700 mg/kg in rats, 2600 mg/kg in rabbits, and 4000 mg/kg in mice.

b. Carcinogenicity

The Agency has classified HCB as a B2 (probable human) carcinogen, based on data sets that showed induction of tumors of the thyroid, liver, and kidney in three rodent species (U.S.EPA, IRIS, 1996). In the IRIS database, the oral cancer slope factor was 1.7 $(mg/kg/day)^{-1}$ based on hepatocellular carcinomas in female Sprague-Dawley rats using a 2/3's animal to human scaling factor. However, based on current Agency policy a 3/4's scaling factor is applied to adjust the slope factor. The cancer slope factor for HCB was modified by 0.6X to account for the newer factor. For this evaluation, carcinogenic risk was assessed for non-dietary exposure to HCB using the modified cancer slope factor of 1.02 $(mg/kg/day)^{-1}$.

c. Toxicological Endpoints

The Agency has selected toxicity endpoints for HCB for use in exposure and risk assessments. These endpoints were selected using the available scientific literature on HCB (U.S. EPA, 2003). A summary of these endpoints is shown below in Table 4.

Table 4. Toxicological Endpoints for Hexachlorobenzene

Exposure Scenario	Dose	Endpoint	Study	Target MOE
Non-Dietary Risk Assessments				
Incidental Oral: Short-Term	NOAEL= 40 mg/kg/day	body weight loss, hyperesthesia, tremors, convulsions in maternal rats at 60 mg/kg/day.	Developmental Toxicity- Rat (Khera, 1974)	100
Incidental Oral: Intermediate-Term	NOAEL= 0.5 mg/kg/day	increased incidence of liver porphyrin levels in female rats at 2 mg/kg/day	15 Week Oral Toxicity- Rat (Kuiper- Goodman et al, 1977)	100
Dermal: Short-Term	Oral NOAEL = 40 mg/kg/day	body weight loss, hyperesthesia, tremors, convulsions in maternal rats at 60 mg/kg/day.	Developmental Toxicity- Rat (Khera, 1974)	100
Dermal: Intermediate-Term	Oral NOAEL = 0.5 mg/kg/day	increased incidence of liver porphyrin levels in female rats at 2 mg/kg/day	15 Week Oral Toxicity- Rat (Kuiper- Goodman et al, 1977)	100
Dermal: Long-Term	Oral NOAEL =0.08 mg/kg/day	hepatic centrilobular basophilic chromogenesis at 0.29 mg/kg/day	Chronic Toxicity - Rat (Arnold et al., 1985)	100
Inhalation: Short-, Intermediate-, and Long-Term	No route-specific endpoints are available for HCB. Therefore, in accordance with Agency policy, oral endpoints and route extrapolation are employed to estimate inhalation risks as needed.			1000
Oral Cancer Slope Factor (CSF)	Q*=1.02 $(mg/kg/day)^{-1}$ (Extrapolated using a Q*of 1.7 $(mg/kg/day)^{-1}$ derived from a linearized multistage model to which a 3/4 scaling factor was applied: 1.7 x 0.6 =1.02)	B2 (probable human carcinogen) based on data showing significant increases in liver and renal tumor incidences in hamsters and rats	Sourced to EPA REDs for DCPA, November 1998, and Chlorothalonil, April 1999 and EPA's IRIS Database.	The Agency typically will not allow Occupational non-dietary risks to exceed 10^{-6}.

Recommended MOEs of 100 are based on applied uncertainty factors used to account for inter-species extrapolation (10x) and intra-species variability (10x).

For additional information, please see the *Pentachlorophenol- Risk Assessment for the Reregistration Eligibility Decision (RED) Document*, dated August 29, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

4. Dietary Exposure and Risk from Food and Drinking Water

There are no existing food uses for the wood preservative uses of pentachlorophenol. Dietary monitoring data assembled by the Food and Drug Administration indicated the presence of pentachlorophenol in certain food items (i.e. milk, pears, pork, but these data are old (i.e. 1991), and FDA discontinued monitoring for pentachlorophenol residues after 1992 based on lack of detectable residue. Since wood treated with pentachlorophenol is not available for sale to the general public, and play activities in children around treated utility poles is not likely to occur, residential risk assessment is not necessary for pentachlorophenol and a FQPA analysis is not needed. However, population-based biological monitoring data from the National Health and Nutrition Surveys (NHANES) were available to assess the exposure of the general population to pentachlorophenol. The NHANES data provides an encompassing review of all pentachlorophenol exposures; the specific pentachlorophenol treated wood contribution to total pentachlorophenol exposure cannot be differentiated. Because NHANES does not include exposures to children under the age of 6 years old, the Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) study (Wilson, et al. 2007) was used to include estimates of exposures to children under 6 years old. For additional information on the potential risks resulting from residential exposure, please see section 6 Residential Exposure and Risk.

It should be noted that the majority of developmental toxicity studies on pentachlorophenol show no teratogenic effects, but some older studies, especially those of Schwetz et al. (1974) and Welsh et al. (1987), showed toxic effects of pentachlorophenol in offspring that occurred at dose levels below those producing maternal toxicity. In addition, it is recognized that the contaminants hexachlorodioxin and 2,3,7,8 tetrachlorodioxin are considered teratogenic chemicals. Due to this reason combined with the knowledge that hexachlorodioxin is a contaminant of pentachlorophenol, the warning labels on pentachlorophenol formulations with respect to potential teratogenic effects have remained.

For additional information, please see the *Previous Pentachlorophenol Dietary Exposure and Risk Chapter Used In 2004 for the Reregistration Eligibility Decision (RED) Document*, dated March 7, 2008; *Previous Polychlorinated dibenzo-p-dioxins (CDDs) and Polychlorinated dibenzofurans (CDFs) Dietary Exposure Chapter Developed in 2005 for the Pentachlorophenol Reregistration Eligibility Decision (RED) Document*, dated March 7, 2008; *Previous Hexachlorobenzene (HCB) Dietary Exposure Chapter Developed in 2005 for the Pentachlorophenol Reregistration Eligibility Decision (RED) Document*, dated March 7, 2008; and *Revised PCP Human Exposure RED Chapter*, dated September 8, 2008 located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

a. Dietary and Drinking Water

Dietary risk is characterized in terms of the Population Adjusted Dose (PAD), which reflects the reference dose (RfD), either acute or chronic. This calculation is performed for each population subgroup. A risk estimate that is less than 100% of the acute or chronic PAD is not of concern.

b. Pentachlorophenol

Typically a dietary risk assessment would not be necessary for pentachlorophenol based upon the current restrictions on use of this pesticide that have been in place since 1984. However, monitoring data from FDA from 1991 showed levels of pentachlorophenol in only a few food items, and at levels that approached the limit of detection. Therefore, the Agency conducted a dietary assessment based on available monitoring data. Using conservative assumptions and the dietary monitoring data collected when pentachlorophenol was still present in certain foods (1991), exposure to pentachlorophenol through food (based on FDA monitoring data) represents 2.4% of the chronic RfD for the most exposed subpopulation in the U.S. (Children ages 1-6). Exposure to all other groups represents less than 0.5% of the chronic RfD.

Surface water runoff from pentachlorophenol treated utility poles may be a possible source for pentachlorophenol or its transformation products in drinking water or in foods. Estimated Environmental Concentrations (EECs) for surface water have been calculated by the Agency. Drinking water levels of concern (DWLOCs) for acute and chronic dietary risk from drinking water were calculated. DWLOCs calculated for surface water for pentachlorophenol were 10,465 ppb for adult males and females and 2,990 ppb for children ages 1-6. Using the PRZM-EXAMS model, available environmental fate data, and conservative assumptions, the estimated environmental concentrations calculated by the Agency for surface water were less than 1 ppb. EECs for groundwater were not available for comparison against DWLOC values; however, based on pentachlorophenol's physical/chemical characteristics and available monitoring data, it is not expected to add significantly to this risk assessment.

For additional information, please see the *Previous Pentachlorophenol Dietary Exposure and Risk Chapter Used in 2004 for the Reregistration Eligibility Decision (RED) Document*, dated March 7, 2008; and, *Estimated Environmental Concentrations (EECs) for Pentachlorophenol Using PRZM-EXAMS Models*, dated March 3, 2008 located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

c. Dioxins and Furans

A dietary risk assessment was not necessary for pentachlorophenol; however, the Agency has examined residue data that demonstrates there are potential sources of dietary exposure to low concentrations of dioxins/furans found throughout the world.

Dietary intake is generally recognized as the primary source of human exposure to CDDs and CDFs. Residue data are available for meat, fish, dairy products, eggs and fruits and vegetables. Residue data are reported in terms of both parts per trillion (ppt) and in terms of toxicity equivalents for both CDDs and CDFs.

Very little residue data are available for crops for residues of CDD and CDF; however, there is a limited amount of residue data available for foods of Canadian and U.S. origin for fruits, vegetables and wheat. The only residues reported for these commodities were for the octachlorodibenzodioxin congener and ranged from 0.6 - 8 ppt.

Samples of vegetable oil from the U.S. were analyzed for CDD and CDF cogence. No residues of tetrachlorodibenzodioxin (TCDD) were detected in the samples. Residues of the other cogence of CDDs and CDFs analyzed for ranged from 0.22 ppt - 33.1 ppt. The 33.1 ppt value is for the octachlorodibenzodioxin congener.

Toxicity equivalent residue data are reported for both environmental media and food. Food residue data are for levels found in both Canadian and U.S. vegetable fats, fish, shellfish, milk and dairy products, eggs, meat and poultry. Mean residues are all reported at levels of less than 2 ppt CDD and CDF toxicity equivalents. The maximum mean CDD/CDF toxicity equivalent residues were reported in freshwater fish at 1.2±1.2 ppt.

For additional information, please see the *Previous Polychlorinated dibenzo-p-dioxins (CDDs) and Polychlorinated dibenzofurans (CDFs) Dietary Exposure Chapter Developed in 2005 for the Pentachlorophenol Reregistration Eligibility Decision (RED) Document*, dated March 7, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

d. Hexachlorobenzene

A dietary risk assessment was not necessary for pentachlorophenol; however, there are other potential sources of dietary exposure to HCB. Therefore, the Agency has also examined residue monitoring data for HCB in food commodities.

There are currently no HCB pesticide tolerances established for food commodities and there are no registered uses for HCB on food commodities. However, dietary exposure to residues of HCB will likely occur as an incidental residue on terrestrial crops as a result of direct application of a pesticide containing HCB as an impurity to agricultural crops in the field. Dietary exposure to HCB residues on terrestrial crops and aquatic organisms can also occur as a result of HCB emission into the atmosphere from various sources followed by deposition of HCB onto agricultural crops, and from industrial discharge or agricultural pesticide run-off into waterways. The source of HCB residues occurring in food commodities cannot be distinguished in an analysis for residues. Therefore, it is not certain that these residues result from use of PCP-treated wood.

Residue monitoring data for HCB are available from the USDA Pesticide Data Program; the USDA Field Safety and Inspection Service; the FDA Pesticide Residue Monitoring Program on meat, milk, fish and various other agricultural commodities; and the FDA Total Diet Study. The monitoring data reflect the analyses of thousands of food samples and cover a period of several years.

The data show few residues of HCB were detected in monitoring samples from FDA or USDA. The majority of detected residues were reported in fish. Detectable residues were more likely to be found in domestic monitoring samples than in imported samples. The majority of reported HCB residues are trace amounts (0.01 ppm range).

For additional information, please see the *Previous Hexachlorobenzene (HCB) Dietary Exposure Chapter Developed in 2005 for the Pentachlorophenol Reregistration Eligibility Decision (RED) Document*, dated March 7, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

5. Residential Post-application Exposure and Risk

The opportunity for residential consumer contact is limited since pentachlorophenol treated wood is not sold to the general public; however, population-based biological monitoring data from the National Health and Nutrition Surveys (NHANES) were available to assess the exposure of the general population to pentachlorophenol. The NHANES data provides an encompassing review of all pentachlorophenol exposures; the specific pentachlorophenol treated wood contribution to total pentachlorophenol exposure cannot be differentiated. Because NHANES does not include exposures to children under the age of 6 years old, the Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) study (Wilson, et al. 2007) was used to include estimates of exposures to children under 6 years old. For additional information, please see the "Revised PCP Human Exposure RED Chapter," September 8, 2008.

Sources of pentachlorophenol other than the currently registered pressure treatment of wood include hexachlorobenzene and lindane, as an emission from incineration of chlorine-containing waste, and also during pyrolysis of polyvinyl chlorides (ATSDR 2001). In the past, PCP was also registered as a termiticide, fungicide, herbicide, molluscicide, algaecide, disinfectant, and for antifoulant paint. It was also used as a preservative for timber used in the construction of log homes. The use of PCP was restricted to wood treatment in 1984.

a. Residential Post-application Non-cancer Exposure and Risk Using NHANES

The following information has been excerpted from Cohen (2008). Since the 1960s, the National Center for Health Statistics, a division of the Centers for Disease Control and Prevention has conducted the National Health and Nutrition Surveys (NHANES), a series of US national surveys of the health and nutrition status of the non-institutionalized civilian population. NHANES 2001 to 2002 included laboratory measurements on 9,929 subjects. This analysis uses urinary concentrations of pentachlorophenol measured in urine spot samples of at least 20 mL collected from a random one-third sample of 3,028 subjects of ages 6 and older. The dose conversion calculations also used the NHANES measurements of creatinine concentrations, body weight, body height, as well as the age, gender, and race of each subject. The NHANES 2001-2002 data were obtained from the NHANES website: www.cdc.gov/nchs/nhanes.htm. Although pentachlorophenol data have been collected for the 2003-2004, these data have not yet been publicly released. The data are expected to be released by the end of 2008.

EPA evaluates health effects in terms of toxicity endpoints that represent an exposure level in mg or µg per kilogram body weight that is not expected to be associated with adverse health effects. The conversion of measured spot urine concentrations to daily doses can be difficult because of variable dilution caused by wide fluctuations in fluid intake and excretion. Dose calculation is also difficult because there is no way to determine from the NHANES data

from what route of exposure (i.e., oral, dermal, inhalation) and when (i.e., duration and time interval prior to measurement) the exposure to PCP occurred, and because of uncertainty and variability in the absorption, distribution, metabolism, and excretion (ADME) parameters.

The long-term target MOE of 300 was used to assess the pentachlorophenol non-cancer risks. The non-cancer risk drivers are for pentachlorophenol, not HCB (i.e., pentachlorophenol non-cancer risks are greater than those of HCB). Therefore, only the non cancer risks for pentachlorophenol were provided. The Agency is following the outcome of the current EPA's Office of Research and Development (ORD) body burden approach/research for the non-cancer risks to dioxin. The Agency is aware that research is ongoing regarding pentachlorophenol. The Agency may revisit this decision in the future.

Total potential exposures and risks from NHANES are presented for the following age groups and subpopulations: all age groups (MOE of 70730); ages 6-11 (MOE of 69544); ages 12-19 (MOE of 58512); ages 20-59 (MOE of 74329); ages ≥ 60 (MOE of 69980); male (MOE of 75512); females (MOE of 66666); Mexican-American (MOE of 134690); white (MOE of 71396), non-Hispanic (MOE of 71396); and black, non-Hispanic (MOE of 47774). The total exposure and risk calculated using the NHANES data demonstrates that for pentachlorophenol (e.g., assuming all pentachlorophenol exposure results from pentachlorophenol treated poles, presentation of various dose conversion methods including the assumption that all individuals excrete a daily urine volume of the 95th percentile of the population), the total risks result in no unreasonable adverse effects from the currently registered wood preservative use.

b. Residential Post-application Non-cancer Exposure and Risk Using CTEPP

The long-term target MOE of 300 was used to assess the non-cancer risks to children 1.5 to 5 years old. The CTEPP data indicate 89 and 99 percent of the samples had detectable levels of pentachlorophenol in NC and OH, respectively. However, the total potential exposure and risk calculated using the CTEPP data demonstrates that for children 1.5 to 5 years old, risks resulting from pentachlorophenol exposure below the Agency's level of concern. MOEs range from 2,400 to 95,000.

c. Residential Post-application Cancer Exposure and Risk Using NHANES and CTEPP

The lifetime average daily dose (LADD) is estimated by combining the results of both the CTEPP and NHANES data sets. The LADD is estimated by averaging the estimated daily dose for each year in a lifetime of 75 years. This assumes the frequency and lifetime duration of exposure is constant (i.e., exposed 365 days per year and 75 years of exposure). CTEPP data are used to estimate the ages 0 to 5 years and NHANES is used to estimate ages 6 to 75 years. In addition to the LADD, the 95th percent lower and upper confidence intervals are also provided for the means. A detailed description of the LADD estimate combining both CTEPP and NHANES data sets are provided in Cohen (2008).

There are currently other sources of pentachlorophenol exposure that are not attributable to pentachlorophenol pressure treated wood; however, the general population biological monitoring data do not allow for the proportioning of exposure to source of contamination. Therefore, the exposures and risks reported are based on the total exposure to pentachlorophenol. Direct measurements of dioxins/furans and HCB exposures for the general population attributed to pentachlorophenol pressure treated wood are not available for this assessment. Therefore, to be inclusive of determining potential exposures to pentachlorophenol contaminants, the amounts of dioxins/furans and HCB in pentachlorophenol are used to extrapolate pentachlorophenol measured exposures to estimate dioxin/furan and HCB exposures.

The potential cancer risks for pentachlorophenol, HCB, and dioxin are 9.8E-7, 1.1E-9, and 5.8E-7, respectively. The risks at the 95th percent upper confidence interval for pentachlorophenol, HCB, and dioxin are 1.5E-6, 1.6E-9, and 8.7E-7, respectively. Future refinements to this assessment should focus on determining contributions of sources to total pentachlorophenol exposure.

6. Aggregate Risk Assessment

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food and drinking water), residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation). Typically in a case such as pentachlorophenol, the Agency would not conduct acute and chronic aggregate assessments based on the lack of dietary exposure, the lack of pentachlorophenol to enter or persist in groundwater, and the lack of residential applications.

However, as discussed above, the Agency used the NHANES and CTEPP data to estimate the exposure of the general public to pentachlorophenol from a national survey of random individuals. Based on the wide survey and number of samples, these data provide a broad view of pentachlorophenol exposure from all sources. Although a typical aggregate assessment was not conducted, the NHANES and CTEPP data have provided actual aggregate exposure information for pentachlorophenol. Additional information can be found in the *Revised PCP Human Exposure RED Chapter*, dated September 8, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

7. Occupational Exposure and Risk

Workers can be exposed to pentachlorophenol through mixing, loading, applying a pesticide or re-entering treated sites. There are potential exposures from use in commercial and industrial settings *via* the dermal and inhalation routes.

Significant exposure is not expected due to mixing/loading per se because treatment plants utilize automated methods for chemical preservative delivery (metered feed/pump) and closed application techniques (treatment cylinder). However, there is the potential for workers near the treatment cylinder door to inhale treatment solution mist when the door is opened following treatment and/or to contact treatment solution residue on equipment such as charge cables and the treated wood itself. Although in many cases treated wood is moved mechanically (e.g., forklifts), this is not required on current product labeling and is currently accomplished manually in some cases.

For treatment facility exposure scenarios, where possible the Agency estimated risk for each job function that could be performed at a typical treatment facility. Although an effort was made to differentiate risk estimates by job function, the Agency acknowledges that the studies used to estimate exposure reflect actual treatment facility practices in that one person often performed more than one job function. Therefore, estimated risks presented by job function are not considered representative of one individual performing one job function and may reflect additional exposure and risk incurred by performing tasks outside the definitions presented below.

- ***Treatment Operator (TO):*** Primary duties for a pressure treatment operator include opening closing valves transferring treatment liquids, opening and closing treatment vessel doors, cleaning pentachlorophenol residues on doors and latches, performing tram maintenance and positioning, and handling leads, chains and cleanup.

- ***Treatment Assistant (TA):*** TAs perform many of the same functions as the TO including opening and closing valves and doors, cleaning pentachlorophenol residues on doors and latches, performing tram maintenance and positioning, and handle leads and chains and cleanup. However, TAs may perform more manual duties such as drip pad and filter cleaning.

- ***Loader Operator (LO):*** LOs operate open-cab forklifts used to load untreated wood onto charge trams, move charges into and out of treatment cylinders, remove charge leads and bands from treated wood, distributed treated wood to load-out area, and load treated wood for shipment. Most work is done in and around drip pad area. LOs may perform certain out-of-cab tasks such as collecting tank samples and performing test boring and lab analysis of treatment solutions in wood.

- ***Tram Setter (TS):*** TSs manually position trams for loading, place wood spacers on trams where needed to elevate wood to be treated and place drawbridges for treatments. TSs also performs lead and chain handling and operates cylinder door controls. They perform various labor and cleanup duties in treatment and drip pad area including sweeping pressure-washed drip pad and tracks; removing and shredding all bands from treated stacks of lumber, picking up and disposing of treated CCA wood waste, cleaning cylinders, and handling hazardous waste.

- ***Stacker Operator (SO):*** SOs work at a fixed position at a facility that mechanically remove wood spacers from stacks of treated (including freshly treated) lumber. They operate lumber stacking devices which arrange treated boards in stacks for banding and shipment to customers, and remove wood spacer sticks from bundles of treated boards. The major task is to manually position ends of all treated loose boards moving through device so they are evenly positioned. They also perform minor maintenance on the equipment and site.

- ***Supervisor (S):*** The Supervisors mainly perform the duties of a second LO when the LO at this site is busy performing other tasks. They take test borings and pressure-wash the drip pad. In addition, Ss perform tasks away from the treatment areas including bringing untreated wood to the treatment loading dock from other parts of the plant.

- ***Test Borer (TB):*** The TB bores lumber after treatment. TB cuts borings from treated poles or ties for on-site analysis to test for preservative penetration. They also perform other QC laboratory duties. Most time is spent away from the treatment area.

- ***Tally Man (TM):*** The main duties of the TM include counting and inspecting incoming and outgoing truckloads of wood products (untreated and treated wood), and supervision of loading and unloading of lumber trucks at drip pad and elsewhere. They also perform some treatment-related duties, such as end-marking of treated items or chaining of charges for treatment and removal of lead cables after treatment.

a. Pentachlorophenol Occupational Handler Exposure and Risk

The Agency has determined that there are potential worker risks of concern for mixers, loaders, applicators, and handlers associated with the currently registered uses of pentachlorophenol. For occupational handlers, potential short and intermediate-term non-cancer risks are not of concern (i.e., MOE greater than 100); however, potential non-cancer long-term dermal risks (i.e., MOE less than 300) for the pressure treatment operators using liquid formulation (MOE of 230) are of concern. For pressure treatment assistants using both crystalline grade product (MOE of 130) and liquid formulation (MOE of 79) potential long-term non-cancer risks are also of concern.

Total potential cancer risks for all four handler scenarios assessed are of concern (i.e., risks greater than 1.0×10^{-6}). (insert 10-4 to 10-6 is ok when benefits are seen) The results for the cancer risk estimates indicate that cancer risks are of concern for the treatment operator handling both crystalline grade product (7.9×10^{-5}) and liquid formulation (1.7×10^{-4}), and for the treatment assistant handling both crystalline grade product (3.1×10^{-4}) and liquid formulation (4.9×10^{-4}).

b. Dioxin Occupational Handler Exposure and Risk

Handler exposure to pentachlorophenol wood preservatives, as product concentrates and treatment solutions result in potential exposure to CDDs and CDFs during handler operations (mixers, loaders, and applicators of pentachlorophenol) in pressure treatment plants.

Non-cancer handler risks have not been calculated and are pending assessment using models developed by the Agency's Office of Research and Development (ORD) to determine actual body burdens. Only long-term dioxin/furan absorbed doses are presented for calculation of the lifetime average daily doses (LADDs) used for the handler cancer risk assessment.

Occupational handler cancer risk estimates have been calculated for dioxin/furan exposures resulting from the registered uses of pentachlorophenol. A cancer risk estimate greater than one in a million ($1.0x10^{-6}$) is of concern. Most of the assessed occupational handler scenarios exceed the Agency's level of concern for potential worker cancer risks. Potential cancer risks are greater than $1.0x10^{-4}$ for the pressure treatment operator handling liquid formulation ($2.0x10^{-4}$), the pressure treatment assistant handling crystalline product ($3.6x10^{-4}$), and the liquid formulation ($5.6x10^{-4}$). Potential cancer risks are greater than $1.0x10^{-5}$for the treatment operator handling the crystalline product ($9.0x10^{-5}$).

c. Hexachlorobenzene Handler Exposure and Risk

Handler exposure to pentachlorophenol wood preservatives, as product concentrates and treatment solutions result in potential exposure to HCB during handler operations (mixers, loaders, and applicators of pentachlorophenol) in pressure treatment plants.

For absorbed short-, intermediate- and long-term exposures to HCB, the Agency's level of concern are MOEs that are less than 100. None of the occupational handler scenarios assessed exceeded the Agency's level of concern for potential non-cancer risks.

Occupational handler cancer risks have been calculated for HCB exposures resulting from the registered uses of pentachlorophenol. A cancer risk greater than one in a million ($1.0x10^{-6}$) is of concern. None of the occupational handler scenarios assessed exceeded the Agency's level of concern (i.e., $1.0x10^{-6}$).

d. Pentachlorophenol Occupational Post-application Exposure and Risk

The Agency has determined that there are no potential non-cancer risks of concern relating to occupational post-application exposure to individuals following pentachlorophenol applications in wood pressure treatment facilities. However, potential post-application cancer risks for pressure treatment loader operator ($6.9x10^{-5}$), pressure treatment test borer ($6.1x10^{-5}$), general helpers ($3.6x10^{-5}$), and electrical utility linemen ($2.5x10^{-5}$) are of concern. A potential cancer risk that is greater than one in a million (i.e., $1.0x10^{-6}$) is of concern.

For additional information, please see the *Revised PCP Human Exposure RED Chapter*, dated September 8, 2008, located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

e. Dioxin/Furan Occupational Post-application Exposure and Risk

Occupational post-application exposure scenarios for dioxins and furans resulting from the registered uses of pentachlorophenol were identified primarily for pressure treatment workers. In addition, a scenario was included for utility linemen. Post-application or reentry exposures in treatment plants may occur after the wood has been pressure treated. Individuals may be exposed to dioxins and furans through contact with pentachlorophenol treated wood products or equipment used to pressure treat wood. Exposure activities include sampling pentachlorophenol retort mixtures, moving trams and treated poles, boring wood cores, and performing cleanup activities on drip pads. The industrial workers involved in post-application activities for this assessment include the test borer, loader operator, and general helper (as representative of pressure treatment plant workers), and the utility linemen involved with post-application handling of pentachlorophenol treated utility poles. The average doses for the pressure treatment operator and treatment assistant were used to estimate long-term exposure to dioxins and furans resulting from the uses of pentachlorophenol. Where applicable, the pentachlorophenol exposures were converted into CDD and CDF equivalents using the TEQ approach in order to estimate exposure and assess risk. These long-term dioxin absorbed doses were calculated for the representative scenarios by adjusting the pentachlorophenol absorbed doses by the EPA-TEQ factor of 0.813 ng/mg as derived from EPA industry monitoring data for pentachlorophenol production years 1998-1999.

Potential non-cancer post-application risks have not been quantified and are pending assessment using models developed by the Agency's Office of Research and Development (ORD) to determine actual body burdens. Only long-term dioxin absorbed doses are presented for calculation of the lifetime average daily doses (LADDs) used for the post-application cancer risk assessment.

Potential occupational post-application cancer risks have been calculated for dioxin/furan exposures resulting from the registered uses of pentachlorophenol. A cancer risk estimate greater than one in a million (1.0×10^{-6}) is of concern. Most of the assessed occupational handler scenarios exceed the Agency's level of concern for potential worker cancer risks. Potential cancer risks are greater than 1.0×10^{-5} for the pressure treatment loader operator (8.0×10^{-5}), pressure treatment test borer (6.5×10^{-5}), general helpers (4.7×10^{-5}), and electrical utility linemen (3.0×10^{-5}).

For additional information, please see the *Occupational Exposure and Risk Assessment of Dioxins and Furans (CDDs/CDFs) in Pentachlorophenol*, dated September 8, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

f. Hexachlorobenzene Post-application Exposure and Risk

Occupational post-application exposure scenarios for HCB resulting from the registered uses of pentachlorophenol were identified primarily for pressure treatment workers. In addition, a scenario was included for utility linemen. Post-application or reentry exposures in treatment plants may occur after the wood has been pressure treated. Individuals may be exposed to HCB

through contact with pentachlorophenol treated wood products or equipment used to pressure-treat wood.

The Agency has determined that Margins of Exposure (MOEs) of 100 or greater are appropriate for acceptable risks from absorbed short-, intermediate- and long-term exposures to HCB. None of the occupational post-application scenarios assessed exceeded the Agency's level of concern for non-cancer aggregate risks.

Potential occupational post-application cancer risks have been calculated for HCB exposures resulting from the registered uses of pentachlorophenol. A cancer risk estimate greater than one in a million ($1.0x10^{-6}$) is of concern. None of the occupational post-application scenarios assessed exceeded the Agency's level of concern (i.e., $1.0x10^{-6}$) for potential cancer risks.

For additional information, please see the *Occupational Exposure and Risk Assessment of Hexachlorobenzene (HCB) in Pentachlorophenol*, dated March 6, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

8. Pentachlorophenol Human Incident Data

An extensive body of literature exists on the health effects (acute and chronic) of pentachlorophenol in humans. Many of the pentachlorophenol incident reports are well structured and appear in the literature to be well executed. Populations are well defined, controls are generally selected appropriately, and analyses are appropriate and adequate. However, major weaknesses in exposure assessment methods often limit the validity of reported findings, either positively or negatively. Of the 24 original articles reviewed for this document, a large majority used questionnaire or interview data, provided either by the study participants or by surrogates, as exposure variables. Often, this information was for mixed exposures including known or unknown contaminants rather than for pentachlorophenol alone. Industrial hygiene monitoring data was rarely available for the assessment of individual exposures. Therefore, in some instances, industrial hygiene expertise was used to judge exposures.

Even considering the above limitations, a reasonably strong argument can be made that exposure to pentachlorophenol is associated with increased risks of a number of diseases, namely chloracne, soft tissue sarcoma (STS), and non-Hodgkin's lymphoma (NHL). Increased risks of developing STS were reported in six studies, although statistical significance was reached in only three. Of five studies reporting increased risk for NHL, only one was statistically significant. Increased risks were also reported for lymphatic cancer, hematopoietic cancer, and Parkinson's Disease, but the associations were generally not significant. While it is known that nerve conduction velocity is slowed by exposure to chlorophenols, as well as many other chemicals, studies with this dysfunction as an endpoint showed ambivalent results. Two studies showed associations between exposure of parents to chlorophenols and negative effects in subsequently born offspring, but results in these studies were not statistically significant.

Considering the number of studies, the consistency among a number of outcomes, as well as the general absence of statistical significance, there appears to be reasonable evidence that exposure to chlorophenols may often be associated with chloracne, STS, NHL, and possibly abnormal births. Whether these health effects result from exposure to pentachlorophenol specifically, or to one or more other chemicals typically found as contaminants, is not clear. Based on the evidence collected to date, careful control of exposures to chlorophenols, including pentachlorophenol, is certainly warranted.

For additional information, please see the *Epidemiology and Incident Reports Associated with Pentachlorophenol*, dated March 9, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

D. Environmental Risk Assessment

Pentachlorophenol is used mainly as a wood preservative and is usually applied to wood as a liquid formulation (5% solution) composed of pentachlorophenol plus hydrocarbon diluents such as P-9 oil, No. 2 fuel oil, kerosene or mineral spirits. Formulated products may include from 5% to greater than 80% active ingredient and typically include water repellents such as paraffin. Introduction of pentachlorophenol into the environment may occur from spills and runoff, and through releases from treated wood by leaching and/or volatilization; these may occur at wood treatment, storage and disposal sites as well as at the locations of wood usage. Pentachlorophenol may also enter the environment by wastewater discharge or holding pond overflow, both of which may occur at wood treating facilities.

Pentachlorophenol contains chlorinated dibenzodioxins and chlorinated dibenzofurans (CDD and CDFs) as contaminants formed during the manufacture process. The main use of pentachlorophenol, a wood preservative, is to treat utility poles. There are an estimated 36 million pentachlorophenol treated utility poles in service in the United States. Annually, nearly 1 million additional utility poles are replaced (3 percent replacement rate) on land and in water. The Agency has estimated that the utility poles in service contain approximately 374 kg of dioxin toxicity equivalents (I-TEQs). The CDD and CDFs in these poles may be released into the environment via volatilization and leaching. In addition, CDD and CDFs may enter the environment during the pressure-treatment of the utility poles when the utility poles are removed from service and are disposed in landfills. These compounds are inherently toxic, as well as environmentally persistent, and their presence may increase the ecological risk associated with the use of pentachlorophenol. There are many congeners of CDDs and CDFs, ranging from monochlorinated to octachlorinated. The most toxic for each compound seems to be the 2, 3, 7, 8-tetrachlorinated congener, referred to as TCDD or TCDF for dioxin or furan, respectively.

Pentachlorophenol is only one of many sources of CDDs and CDFs in the environment making it difficult to quantify the portion of the aggregate environmental risk from CDDs and CDFs that is attributable to pentachlorophenol wood treatment uses.

Hexachlorobenzene (HCB) is also a contaminant formed during the manufacturing process of pentachlorophenol and is a very stable chlorinated aromatic compound that was commonly used as a pesticide until 1965. Currently, there are no commercial uses of the

substance in the United States. HCB may be formed as a byproduct during the manufacture of chemicals used as solvents, pesticides and other chlorine-containing compounds. Small amounts of this compound can also be produced during combustion processes such as burning of city wastes.

HCB is widely distributed throughout the global ecosystem because if its mobility and resistance to degradation. It has been detected in all environmental media and in numerous types of living organisms including insects, aquatic biota, birds and mammals. HCB has also been shown to bioaccumulate in both aquatic and terrestrial organisms.

A summary of the Agency's environmental risk assessment is presented below. The following risk characterization is intended to describe the magnitude of the estimated ecological hazards and environmental risks for the currently registered antimicrobial uses of pentachlorophenol and its micro-contaminants.

1. Environmental Fate and Transport

In general, the environmental fate and transport of pentachlorophenol in soil and water will depend on the pH of the systems. The chemical behavior and the physical properties of pentachlorophenol will depend on whether it exists primarily as the phenol (under more acidic conditions) or the phenolate anion (under basic conditions).

a. Pentachlorophenol

- ***Water:*** Pentachlorophenol is hydrolytically stable in water at pH 4 to pH 9, precluding hydrolysis as a major degradation process in the environment. Chemical degradation of pentachlorophenol in water will occur mainly through photo-degradation. In surface water, pentachlorophenol will rapidly photo-degrade when exposed to direct sunlight, with more rapid degradation occurring with increased pH (when the compound is dissociated).

- ***Soil:*** Wood treated with pentachlorophenol may release the compound through volatilization or leaching. Additionally, pentachlorophenol may be photo-degraded on the wood surface, making degradates available for leaching. All three processes are affected by the solvent systems/carriers used in the application of the compound. The leaching of pentachlorophenol out of utility poles may also partially depend on the method of application (pressure or thermal treatment). Pentachlorophenol may be leached from the poles as the compound moves with either aqueous solution (as from rain) or with the solvent down the pole, either at the surface or within the pole. Based on experimental data, it was determined that the main mechanism for the leaching of pentachlorophenol and its micro-contaminants is the downward migration of the oil carrier along the vertical axis of the pole, designated as "Gravitational Induced Downward Migration of Oil" (GIDMO). Leaching of pentachlorophenol in aqueous solution from rainwater is not considered to be as important as GIDMO, as the replenishment rate at pole surfaces is a limiting factor with respect to the availability of the compound for leaching. Thus, contamination of subsurface soil found in the vicinity of utility poles may result from the downward movement of pentachlorophenol within the

pole, with subsequent leaching from the bottom part of the pole to the soil surface or to the subsoil near the underground portion of the pole, as well as from the downward movement of pentachlorophenol from the surface soils to the subsoil. When leaching of pentachlorophenol from treated poles occurs, the simultaneous leaching of the carrier solvents may affect the mobility of the compound in the soil. Literature and laboratory studies indicate that pentachlorophenol applied in oil is rapidly transported from the upper portion of the poles to the underground portion for the first few years of use, and became relatively constant with time.

Because of the demonstrated tendency for pentachlorophenol to adsorb to soils and the moderately rapid degradation of the compound in the environment, it is not likely that groundwater contamination will result from usage of utility poles, except in situations where the bottom of the pole is directly in contact with the water table (or with a fluctuating water table) or where the leaching occurs from multiple poles in a wood storage or treatment area.

- ***Air:*** Pentachlorophenol is a relatively volatile compound, while its sodium salt in nonvolatile. In the atmosphere, volatilized pentachlorophenol may undergo photolytic degradation or may react with photo-chemically produced hydroxyl radicals. Atmospheric pentachlorophenol which is associated with particulate matter or moisture will be lost from the atmosphere through wet deposition. Based on pentachlorophenol's low Henry's law constant, volatilization from aqueous systems will not be a significant mode of transport in the environment.

For detailed discussions of the environmental fate and transport of pentachlorophenol, see the *Environmental Fate and Transport Assessment of Pentachlorophenol (PCP) for Reregistration Eligibility Decision (RED) Process*, dated February 16, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

b. Dioxins/Furans

Presence of CDDs and CDFs in the environmental compartments resulting from the wood preservative use is due to volatilization into air; leaching from PCP treated poles into water and soil; dry and wet deposition onto air, water, and soils; and sorption into soils. The available data indicate that CDDs and CDFs, particularly the tetras- and higher chlorinated congeners, are extremely stable under most environmental conditions. However, some of these congeners, under certain conditions, are photolytically unstable and in some cases undergo photo-oxidation. Most of the congeners are also resistant to biodegradation under aerobic or anaerobic soil conditions and most are persistent in soils**.**

The process of bioaccumulation has been observed in the benthic organisms, however, bio-transformation processes up the food chain have not been observed. Fish and invertebrates can likely bioaccumulate 2,3,7,8-substituted CDD and CDFs from water columns and sediments. However, because most CDD and CDFs in a water column and sediment are associated with particulate matter and dissolved organic matter, bioaccumulation most likely starts with uptake

of CDD and CDFs by benthic organisms directly from sediment pore waters and by ingestion of contaminated particles. Organisms preying on benthic organisms would possibly transfer the CDD and CDFs up the food chain but no sound scientific data have been obtained.

For detailed discussions of the environmental fate and transport of dioxins/furans, see the *Environmental Fate Modeling of Dioxin in Technical Grade Pentachlorophenol*, dated March 4, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

c. Hexachlorobenzene

HCB is a stable and highly persistent molecule and does not hydrolyze in aqueous medium and is likely to become immobile in soils. It has large sorption partition coefficients. Aerobic and anaerobic biodegradation half lives are long and therefore the main route of dissipation would possibly be through sorption to soils in the terrestrial settings and to sediment organic and inorganic particulate matter in aqueous medium. Because the K_{OC} is high it has a tendency to bind strongly with soil particles and therefore less mobile, the possibility of contamination by HCB of ground water does not seem likely. Because of high binding constants with soils, HCB may possibly accumulate in benthic sediment and bioaccumulate in benthic organisms. Based on monitoring data, it is unlikely that HCB concentration in surface water would exceed 10 ppt (0.01 µg/L).

For detailed discussions of the environmental fate and transport of hexachlorobenzene, see the *Environmental Fate Modeling of Hexachlorobenzene in Technical Grade Pentachlorophenol*, dated March 4, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

2. Terrestrial and Aquatic Organism Exposure and Risk

An ecological risk assessment was conducted to assess impacts of pentachlorophenol residues from treated wood uses. Risk characterization integrates the results of the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects.

a. Pentachlorophenol

The environmental risk assessment indicates that typical concentrations of pentachlorophenol in terrestrial and aquatic environments from wood treatment uses are not expected to be of sufficient quantity or duration to adversely impact terrestrial or aquatic organisms.

b. Dioxins/Furans

Currently there are no FIFRA guideline studies required for the micro-contaminants dioxin/furan, since they are not currently registered, and data on the ecological effects of CDDs and CDFs are relatively limited. Most research efforts have been focused primarily on 2,3,7,8-chlorinated CDD and CDFs, especially 2,3,7,8-TCDD. CDDs and CDFs are very highly toxic to

birds, mammals and aquatic organisms. CDDs (and possibly furans) are capable of producing lasting toxic effects; even a relatively short exposure to TCDD (as little as 6 hours) can result in mortality of fish eggs occurring as much as 80 days later. TCDD is a known endocrine disruptor, and it is likely that other dioxin congeners and furans produce similar effects. Available literature indicates that there are potential acute and chronic risks to birds and chronic risks to mammals from CDDs and CDFs from pentachlorophenol treated wood, especially considering the tendency of CDDs and CDFs to persist and bioaccumulate.

Acute and chronic risks to aquatic organisms are unlikely to occur from runoff of CDDs and CDFs from pentachlorophenol treated wood. However, due to uptake of these compounds by sediment, coupled with the persistence and bioaccumulation of CDDs and CDFs, they may eventually reach toxic levels and pose risks to aquatic organisms through the food web.

Pentachlorophenol is only one of many sources of CDDs and CDFs in the environment making it difficult to quantify the portion of the aggregate environmental risk from CDDs and CDFs that is attributable to pentachlorophenol wood treatment uses.

All environmental exposure and risk assessments are associated with uncertainties which may range from low to high, thus affecting the reliability or certainty of the risk estimations. In the case of the environmental assessment for CDDs and CDFs the uncertainties associated with this assessment are considered high. However, there are no well-established environmental exposure models or methods for determining wildlife (and, particularly, terrestrial wildlife) exposures to 2, 3, 7, 8-TCDD, CDDs, or CDFs released from pentachlorophenol-treated utility poles into the environment.

For the terrestrial environmental assessment, where estimated Risk Quotients (RQs) exceed acute and chronic Levels of Concern (LOCs) for avian and small mammal species, the Agency recognizes that these risk calculations are highly conservative and contain a high degree of uncertainty. Because of this conservatism and uncertainty, EPA believes that these risk calculations may overestimate the potential terrestrial risks which may occur. It is possible, for example, that the present calculated RQs may be orders of magnitude lower than determined.

In an attempt to better characterize this terrestrial assessment the Agency wants to point out the two highly conservative and unrealistic assumptions used in this assessment:

- ***Feeding Activity:*** It is assumed that small mammals and birds will selectively feed (all day and every day until mortality or reproductive effects occur) within a 5 cm (or 2 inches) area surrounding a pentachlorophenol-treated telephone pole; and

- ***Diet:*** It is assumed that 100 % of a small mammal's or bird's diet will be contaminated with 2, 3, 7, 8-TCDD, CDDs, and/or CDFs (while feeding within the 2 inches area).

Although the Agency used these assumptions, we acknowledge that both are highly conservative, unrealistic, and unlikely to occur because:

- ***Home ranges:*** The home ranges (where animals roost/rest, nest, breed, feed) for the surrogate species (bobwhite quail and meadow vole), as well as for other species, are considerably larger (in acres) than a 2 inches area around a pentachlorophenol-treated utility pole. This aspect negates the assumption that organisms will selectively feed within 2 inches of a pentachlorophenol-treated utility pole.

- ***Animal food items:*** Considering the home ranges and feeding habits of small mammals and birds, it is highly unlikely that 100 % (or possibly any portion) of these organisms' diets will be contaminated with dioxins. The assessment addresses a 2 inches area around a pentachlorophenol-treated pole and ingestion of only soil and plant matter. However, birds and small mammals will move freely throughout their home ranges and consume dietary items that typically include animal matter as well as plant matter. Further, soil ingestion often occurs incidentally unless (as with birds) the organism is actively seeking grit in its diet.

Additionally, the Agency notes that:

- ***Environmental fate:*** CDD and CDFs are highly lipophilic (fat soluble), neutral organic compounds that are tightly sorbed onto soils and therefore have limited tendencies to move from the point of deposition. They are primarily sorbed to clay and organic matter because of high surface area and chemical reactivity of these soil components. As a result, the characteristics of these compounds and the soil components are expected to negate the assumption that 2, 3, 7, 8-TCDD, CDDs, or CDFs might move significant distances from pentachlorophenol-treated utility poles into large portions of an animal's home range (thus, providing for increased exposure).

- ***Environmental modeling:*** The environmental modeling used to estimate soil EECs for bobwhite quail and meadow voles is based primarily on dioxin levels released via wood erosion as opposed to leaching. Thus, the estimated concentrations in soils immediately adjacent to pentachlorophenol-treated utility poles are based on the accumulation of wood particles which break away from the pole due to wood erosion. This creates additional uncertainty for the terrestrial risk assessment since soil ingestion by small mammals and birds may, or may not include ingestion of such wood particles. Further, these soil EECs were used to estimate the EECs in plant dietary matter. This creates more uncertainty in the assessment as well.

Considering the above, the Agency does not want to discount the highly toxic nature of 2, 3, 7, 8-TCDD, CDDs, or CDFs, which may be released from pentachlorophenol-treated utility poles into the environment. However, the Agency acknowledges the difficulties in estimating terrestrial wildlife exposures since there are no well-established environmental exposure models or methods for determining terrestrial wildlife exposures to 2, 3, 7, 8-TCDD, CDDs, or CDFs released from such utility poles into terrestrial environs. We recognize that the terrestrial risk assessment approach used is conservative and has a high degree of uncertainty. That being said,

we believe the weight of evidence indicates that the terrestrial risks for birds and mammals foraging near pentachlorophenol-treated utility poles is minimal.

Environmental RQs for terrestrial, aquatic, and plant species have been calculated using non-guideline studies for CDDs and CDFs resulting from all potential sources. Avian acute and chronic RQs (63 and 68 respectively), and mammal chronic RQs (4) are of concern. The Agency typically considers RQs above 0.5 data to be of concern. The RQs for aquatic organisms and plants (both terrestrial and aquatic) were calculated and are not of concern. For additional information, please see Chlorinated Dibenzo Dioxins (CDDs) and Chlorinated Dibenzo Furans (CDFs) as Contaminants of Pentachlorophenol Ecological Hazard and Risk Assessment for the Pentachlorophenol Reregistration Eligibility Decision (RED) Document, dated September 18, 2008. This document is located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

c. Hexachlorobenzene

Currently there are no FIFRA guideline studies for the micro-contaminant HCB, since it is not currently registered, and data on the ecological effects of HCB are relatively limited. Scientific literature indicates that HCB has a limited potential to adversely affect aquatic organisms in the short-term, primarily due to its very low solubility in surface water. Release of HCB from pentachlorophenol treated wood into terrestrial or aquatic environments at a concentration of 6 ug/L is not expected to result in adverse acute or chronic effects to non-target or listed species of birds, mammals or aquatic animals. However, reviewed literature indicates that HCB may have potential to adversely affect both aquatic and terrestrial organisms due to its persistence in the environment and its ability to readily accumulate in the aquatic and terrestrial food webs. No honey bee toxicity data are available for HCB.

HCB concentrations in the tissues of aquatic organisms equilibrate very slowly with concentrations in the water. As a result, the chronic toxicity tests for fish species (e.g., rainbow trout and fathead minnows) may not have been of sufficient duration to allow for the full equilibration of HCB in fish tissue with surface water concentrations. Also, due to the tendency of HCB to bioaccumulate in the aquatic food web, there is the potential for adverse effects to higher-trophic level organisms from exposure to HCB in their diet.

Once in birds, HCB is excreted into the eggs, which results in uptake by the embryos. HCB concentrations measured in the eggs of sea birds and raptors from a number of locations around the world approach those associated with reduced embryo weights in herring gulls (1.5 mg/kg), suggesting that HCB has the potential to harm embryos of avian species. For mammals, a sensitive endpoint for chronic HCB exposure is the reduction of birth weight and increased mortality in mink offspring exposed to 1 ppm HCB (0.16 mg/kg BW-day) for 47 weeks. This observation is ecologically significant because field studies have observed HCB concentrations in fish tissue at a number of sites worldwide that are within an order of magnitude of the dietary toxicity level of 1 ppm. This suggests that HCB has the potential to cause adverse effects in mink and perhaps other fish-eating mammals, especially given HCBs tendency to bioaccumulate. The contribution of HCB from pentachlorophenol uses vs. non-pesticidal sources in aquatic and terrestrial environments is a large uncertainty.

3. Risks to Listed Species

Section 7 of the Endangered Species Act (ESA), 16 U.S.C. Section 1536(a)(2), requires that federal agencies consult with the National Marine Fisheries Service (NMFS) for marine and andronomus listed species, or with the United States Fish and Wildlife Services (FWS) for listed wildlife and freshwater organisms, if proposing an "action" that may affect listed species or their designated habitat. Each federal agency is required under the Act to insure that any action they authorize, fund, or carry out is not likely to jeopardize the continued existence of a listed species or result in the destruction or adverse modification of designated critical habitat. To jeopardize the continued existence of a listed species is to "to engage in an action that reasonably would be expected, directly or indirectly, to reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of the species." 50 CFR §402.02.

To comply with subsection (a)(2) of the ESA, EPA's Office of Pesticide Programs has established procedures to evaluate whether a proposed registration action may directly or indirectly appreciably reduce the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of any listed species (U.S. EPA 2004). If any of the Listed Species LOC Criteria are exceeded for either direct or indirect effects in the Agency's screening-level risk assessment, the Agency identifies any listed or candidate species that may occur spatially and temporally in the footprint of the proposed use. Further biological assessment is undertaken to refine the risk. The extent to which any species may be at risk determines the need to develop a more comprehensive consultation package as required by the ESA.

An environmental risk assessment to CDDs and CDFs to listed species has not been conducted at this time; however, there are potential acute and chronic risks to birds and chronic risks to mammals from CDDs and CDFs resulting from pentachlorophenol treated wood. The results of the environmental risk assessment indicate that threatened and endangered species would not be expected to be adversely affected directly by exposure to the micro-contaminant HCB present in pentachlorophenol. However, as discussed above, the strong tendency of CDDs, CDFs, and HCB to persist and bioaccumulate could lead to secondary adverse effects to higher trophic level organisms, or direct effects to organisms exposed to CDDs, CDFs, and HCB from pentachlorophenol use over longer periods of time. Sensitive animals, such as endangered and threatened species may also be at risk; however, it is important to note that pentachlorophenol is not the only source of HCB, CDDs and CDFs in the environment. They are one of many making it difficult to quantify the portion of the environmental risk from HCB, CDDs and CDFs that is attributable to pentachlorophenol wood treatment uses.

Based on the use patterns for pentachlorophenol, there is potential for pentachlorophenol wood treatment uses to overlap with listed species and a more refined assessment may be warranted. This assessment would include direct, indirect and habitat effects, and the refined assessment should involve clear delineation of the action area associated with pentachlorophenol wood treatment uses and best available information on the temporal and spatial co-location of listed species with respect to the action area. This analysis has not been conducted for this assessment. An endangered species effect determination will not be made at this time.

For detailed discussions of all aspects of the environmental risk assessment, see the *Ecological Hazard and Environmental Risk Assessment RED Chapter for Pentachlorophenol*, dated February 26, 2008; *Ecological Hazard and Environmental Risk Assessment RED Chapter for Chlorinated Dibenzo Dioxins and Chlorinated Dibenzo Furans (CDDs and CDFs) – Supplement to the Pentachlorophenol RED*, dated February 26, 2008; and, *Ecological Hazard and Environmental Risk Assessment RED Chapter for Hexachlorobenzene (HCB) – Supplement to the Pentachlorophenol RED*, dated February 26, 2008; located on the Federal Government Public Docket website at www.regulations.gov (Docket ID #EPA-HQ-OPP-2004-0204).

IV. Reregistration Eligibility and Risk Management Decisions

A. Reregistration Eligibility Decision

Section 4(g)(2)(A) of FIFRA calls for EPA to determine, after submission of relevant data concerning an active ingredient, whether or not products containing the active ingredient are eligible for reregistration. EPA has previously identified and required the submission of the generic (i.e., active ingredient-specific) data required to support reregistration of wood preservative products containing pentachlorophenol as an active ingredient. The Agency has reviewed these generic data, and has determined that the data are sufficient to support a reregistration eligibility decision for the wood preservative uses of pentachlorophenol (see Appendix B).

EPA considered the available information and, after a thorough evaluation of the risks and benefits associated with each use, has determined that the wood preservative uses of pentachlorophenol presented in Appendix A will not pose unreasonable risks to humans or the environment provided that (1) all risk mitigation measures are implemented, (2) label amendments are made as described in Section V, and (3) confirmatory data requirements are satisfied. Accordingly, should a registrant fail to implement any of the conditions and requirements for reregistration identified in this document, the Agency may take regulatory action to address the potential risk concerns from the use of pentachlorophenol.

1. Regulatory Rationale

The Agency has determined that wood preservative uses of pentachlorophenol are eligible for reregistration provided that the registrants implement the conditions and requirements in this RED including amended labeling and submission of additional data. With amended labeling, EPA believes that the uses presented in Appendix A will not present risks inconsistent with FIFRA and that the benefits of pentachlorophenol to society outweigh the remaining risks. A summary of EPA's rationale for reregistering and managing risks associated with continued use is presented below.

a. Summary of Risks

As discussed in Section III of this document, EPA acknowledges the complexity and uncertainties associated with assessing potential risk from exposure to pentachlorophenol and its micro-contaminants, dioxin/furans and hexachlorobenzene. Therefore, the risks presented in this document may overestimate actual risk. Notwithstanding, EPA identified the following risk estimates of concern associated with the continued use of wood preservatives containing pentachlorophenol:

- Potential occupational cancer and non-cancer risk from dermal exposure to pentachlorophenol.

- Potential environmental risk from exposure to dioxin/furan resulting from pentachlorophenol use.

- Without the adoption of additional protective measures to reduce exposure to pentachlorophenol and its micro-contaminants continued use would not meet the "no unreasonable adverse effects" criteria of FIFRA.

b. Summary of Benefits and Alternatives

A detailed discussion of pentachlorophenol benefits and alternatives is presented in the document entitled, "A Qualitative Economic Impact Assessment of Alternatives to Pentachlorophenol as a Wood Preservative" dated April 14, 2008.

Chemical alternatives to pentachlorophenol wood preservatives include chromated arsenicals, creosote, copper and zinc naphthenates, ammoniacal/alkaline copper quaternary (ACQ), copper azole (CBA), sodium borates (SBX), and copper HDO (CX-A). Non-chemical alternatives include virgin vinyl, plastic wood composites, high density polyethylene, rubber lumber, concrete, fiberglass, steel, naturally resistant wood poles, and glass.

Although many chemical and non-chemical alternatives exist for wood treated with pentachlorophenol, many are not truly interchangeable due to safety, environmental, efficacy, and/or economic considerations. In the case of utility poles, for example, the material selected can affect the maintenance personnel's safety. Although steel utility poles may result in less human or environmental exposure to pentachlorophenol, they also increase the likelihood of electrocution for workers. For poles treated with chemical alternatives, certain alternatives make poles more slippery and therefore harder to climb which may also affect worker safety. Although the risk of electrocution and slippage cannot be compared quantitatively to potential environmental exposure, the Agency considers direct and indirect safety consequences as a result of its decisions.

Alternatives also vary in their potential effects on the environment. The potential short- and long-term environmental impacts of many chemical and non-chemical alternatives are unknown. Pentachlorophenol, on the other hand, has been the subject of numerous toxicity, exposure, environmental fate, and ecological effects studies. Because there are varying amounts of information on each alternative, it is difficult to quantitatively or qualitatively estimate the potential environmental impacts of alternatives; however, the potential environmental impacts of pentachlorophenol and its micro-contaminants are relatively well understood compared to certain chemical and non-chemical alternatives.

Chemical and non-chemical alternatives also vary in efficacy. In many cases, efficacy is the determining factor for selecting the preservative and/or material used. For example, pentachlorophenol treated crossarms are less likely to warp, crack, twist (causing stress on the wires), or drip then some of the alternatives. In addition, utility and other public works companies require products proven to be capable of withstanding extreme conditions for long periods of time. In the short-term, a product treated with an alternative preservative may offer comparable efficacy compared to a product treated with a pentachlorophenol; however, comparable efficacy may or may not be observed over the entire expected lifespan of the product (e.g., a utility pole may require replacement much sooner than if it had been treated with

pentachlorophenol). Because certain alternatives do not offer the same level of efficacy and because the end products themselves (e.g., utility poles) may not last as long as pentachlorophenol, they also cannot be considered as direct replacements.

Finally, economic considerations almost always impact decisions regarding project materials. Included in economic considerations are initial costs (e.g., cost of wood treatment), lifespan and maintenance costs of the product, and disposal costs. Although many exceptions exist, pentachlorophenol generally offer lower initial costs than many alternatives, offer documented and predictable lifespan, and in many cases can be disposed of in municipal landfills. Because certain alternatives, although lower in initial costs, do not offer the same resistance and/or do not last as long as pentachlorophenol treated products, they also cannot be considered as direct replacements. Economic considerations are particularly relevant to utility and other public works uses because increased costs are frequently passed on to the public.

c. Risk/Benefit Finding

In its risk assessments, EPA identified potential risks of concern for workers exposed to pentachlorophenol at wood treatment plants. Notwithstanding, eliminating these uses could result in reliance on products with greater safety risks, increased adverse effects on the environment, reduced effectiveness, and higher costs that could be passed on to the general public (e.g., public works entities). Therefore, after a thorough evaluation of the risk estimates and benefits, EPA has determined that certain uses of wood preservative uses of pentachlorophenol will not pose unreasonable risks to humans or the environment provided that (1) all risk mitigation measures are implemented, (2) label amendments are made as described in Section V, and (3) current data gaps and confirmatory data requirements are satisfied.

2. Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) “may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other endocrine effects as the Administrator may designate.” Following recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that EPA include evaluations of potential effects in wildlife. For pesticides, EPA will use its authorities under FIFRA and/or the FFDCA to require any necessary data on endocrine-related effects. As the science develops and resources allow, screening for additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

3. Cumulative Risks

Risks summarized in this document are those that result only from the use of pentachlorophenol. The Food Quality Protection Act (FQPA) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information”

concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to pentachlorophenol. EPA has not assumed that the pentachlorophenol share a common mechanism of toxicity with other compounds.

4. Public Comments and Response

Through EPA's public participation process, EPA worked with stakeholders and the public to reach the regulatory decisions for pentachlorophenol. During the 60-day public comment period ending on June 16, 2008, the Agency received comments on the revised risk assessments from several respondents: Parents for a Safer Environment, California Regional Water Quality Control Board, Pentachlorophenol Task Force, Chlorine Chemistry Division of the American Chemistry Council, Beyond Pesticides et al., Utility Solid Waste Activities Group, as well as several concerned consumers. All comments and EPA's comment response documents are available at http://www.regulations.gov in docket number EPA-HQ-OPP-2004-0402.

B. Risk Management Decision

The Agency has concluded that continued use of wood preservatives containing pentachlorophenol would not meet the "no unreasonable adverse effects" criteria of FIFRA unless the mitigation measures and associated label changes presented in Table 5 and Table 7, respectively, are implemented and confirmatory data are submitted. Information is not currently available to quantify the amount of risk reduction; however, implementing these risk reduction measures will reduce potential worker exposure as well as potential environmental exposure to pentachlorophenol and its micro-contaminants. Additional PPE and engineering controls are needed to help reduce potential exposure and risk to workers, and the addition of a final vacuum is needed to help reduce potential environmental exposure and risk. The Agency will require confirmatory monitoring data to ensure that the measures below are protective.

Although the measures below are required at this time, in the future, registrants may request that EPA remove or reduce certain restrictions or mitigation measures based upon submission of acceptable toxicity and exposure studies that demonstrate risk exposure to pentachlorophenol is below EPA's level of concern.

Table 5 discusses the risk mitigation measures for wood preservatives containing pentachlorophenol. Engineering controls are specific to thermal and/or ambient treatments of pentachlorophenol. Additional mitigation measures are being implemented for thermal pentachlorophenol due to the potential for increased inhalation exposure.

Table 5. Risk Mitigation Measures for Wood Preservatives Containing Pentachlorophenol

Risk Estimates of Concern	Mitigation Measure(s)	Required Label Language
Occupational cancer and non-cancer risk estimates from inhalation exposure to pentachlorophenol	After treatment, personnel must not be located within 15 feet of the cylinder opening until the cylinder is ventilated and the door is completely open	"At the conclusion of the treatment, the cylinder must be ventilated by purging the post-treatment cylinder through fresh air exchange. The ventilation process is considered complete after a minimum of 2 volume exchanges based on the empty treatment cylinder volume. The exhaust pipe of the vacuum system or any air moving device utilized in conducting the air purge must terminate into a containment vessel such as a treating solution work tank or water/effluent tank. The ventilation process may be accomplished by one of the following methods: 1) activating an air purge system that operates while the cylinder door remains closed; or 2) using a device to open and hold open the cylinder door (no more than 6 inches) to allow adequate ventilation and activating the vacuum pump. If the second method is utilized, at the conclusion of the treatment, no personnel may be located within 15 feet of the cylinder when open (cracked) until the cylinder has been ventilated. In the event of equipment malfunction, or to place the spacer to hold the door open during venting, only personnel wearing specified PPE are permitted within 15 feet of the cylinder opening prior to ventilation. After ventilation is complete, the cylinder door may be completely opened."
Occupational cancer and non-cancer risk estimates from dermal exposure to pentachlorophenol	The treatment process must include a final vacuum to remove excess preservative from the wood	"The treatment process must include a final vacuum to remove excess preservative from the wood. The final vacuum must attain a vacuum equal to or greater than the initial vacuum. This vacuum must be held for an appropriate time period based on wood species, retention levels, and commodity treated to remove excess preservative from the wood."
	Automatic opening, closing, and locking devices (Elevated Temperature	"As of December 31, 2013, for elevated temperature pressure treatment with pentachlorophenol, automatic, remotely operated devices must be used to open, close, lock, and unlock cylinder doors."

Risk Estimates of Concern	Mitigation Measure(s)	Required Label Language
	Pentachlorophenol)	
	Lock/unlock cylinder doors using automatic locking devices (Ambient Temperature Pentachlorophenol)	"As of December 31, 2013, for ambient temperature pressure treatment with pentachlorophenol, an automatic locking/unlocking device must be used to accomplish locking and unlocking of the cylinder door."
	Allow excess preservative to drain before removing charges from the treatment cylinder and prior to shipment	"After treatment, wood must be moved to a drip pad capable of recovering excess preservative until the wood is drip free."
Occupational cancer and non-cancer risk estimates from dermal exposure to pentachlorophenol	Personnel must wear personal protective equipment when handling treated wood/equipment, when cleaning the cylinder, and approaching cylinder prior to ventilation	"All personnel handling treated wood or handling treating equipment (including poles/hooks used to retrieve charge cables) that has come in contact with preservative must wear the following PPE: * washable or disposable coveralls or long-sleeved shirt and long pants, * chemical resistant gloves, and * socks plus industrial grade safety work boots with chemical resistant soles. All personnel cleaning or maintaining the treatment cylinder gasket/equipment or working with concentrate or wood treatment preservative must wear the following PPE: * washable or disposable coveralls or long-sleeved shirt and long pants, * chemical resistant gloves, * socks plus industrial grade safety work boots with chemical resistant soles, and * a full face shield. In the event of equipment malfunction, or for door spacer placement, all personnel located within 15 feet of the cylinder opening prior to cylinder ventilation must wear the following PPE: * washable or disposable coveralls over long-sleeved shirt and long pants, * chemical resistant gloves, * socks plus industrial grade safety work boots with chemical resistant soles, and * a properly fitting half mask elastomeric respirator with appropriate

Risk Estimates of Concern	Mitigation Measure(s)	Required Label Language
		cartridges and/or filters. Entry to confined spaces is regulated by Federal and/or State Occupational Safety and Health Programs. Compliance is mandated by law. Individuals who enter pressure treatment cylinders or other related equipment that is contaminated with the wood treatment preservative (e.g.,cylinders that are not free of the treatment preservative or preservative storage tanks) must wear protective clothing and/or equipment as required by Federal and/or State Occupational Safety and Health Compliance laws."
Occupational cancer and non-cancer risk estimates from dermal exposure to pentachlorophenol	Cylinder openings and door pits	"Cylinder openings and door pits must use grating and additional measures such as sumps, dams or other devices which prevent or remove spillage of the preservative."
	Personnel must not retrieve charge cables by hand	"Personnel must not directly handle the charge cables, poles or hooks used to retrieve charge cables, or other equipment that has contacted the preservative without wearing chemical resistant gloves."
	Personnel must not place or remove bridge rails by hand	"As of December 31, 2013, mechanical methods must be used to place/remove bridge rails."
	Personnel must not eat, drink, or smoke in work areas	"Eating, drinking, and smoking is prohibited in the treatment cylinder load-out area, drip pad area, and engineering control room of wood treatment facilities. EXCEPTION: Where treating operator control rooms are isolated from the treating cylinders, drip pad, and work tanks, eating, drinking, and smoking (depending on local restrictions) are permitted."
	Work clothing must be left at the treatment facility	"Personnel must leave aprons, protective coveralls, chemical resistant gloves, work footwear, and any other material contaminated with preservative at the treatment facility."
Aquatic organisms acute and chronic risk estimates from exposure to	Double vacuum for wood used in aquatic and other sensitive environments	"For treated wood that will be used in marine or other aquatic or sensitive environments, a double vacuum must be used. Following the pressure period and once the pentachlorophenol has been pumped back to the work tank, a vacuum shall be applied for a minimum of one and a half hours at not less than 22 inches of Hg (560 KPa) (adjusted for elevation) of vacuum to recover excess preservative. Then, depending on plant equipment: 1) vacuum for a minimum of one and a half hours at not less than 22 inches of Hg (560 KPa) (adjusted for elevation); or 2) steam material for one hour minimum and then pull not less than 22 inches of

Risk Estimates of Concern	Mitigation Measure(s)	Required Label Language
		Hg (560 KPa) (adjusted for elevation) vacuum for a minimum of one and a half hours. Maximum temperature during steaming shall not exceed 240 degrees F (115.5 degrees C), as specified in the Best Management Practices (Aug. 2006) issued by the Western Wood Preservers Association, Southern Pressure Treaters' Association, Timber Piling Council, and Wood Preservation Canada."

1. Dioxin/Furan Reduction

Label modifications stipulating use of a final vacuum for all pentachlorophenol treated wood and a double vacuum for wood used in aquatic and other sensitive environments will reduce the amount of pentachlorophenol, CDDs and CDFs on the surface of the treated wood, thus reducing the amount of chemical that can leach into the environment. In addition the Agency is requiring that a terrestrial field dissipation study be submitted to confirm the dioxin levels leaching to the soil, and plant and organisms around pentachlorophenol treated utility poles.

The Pentachlorophenol Task Force has submitted information outlining changes in pentachlorophenol manufacturing process. These changes have been made in an effort to lower the concentrations of CDDs, CDFs as contaminants in pentachlorophenol.

The Agency has conducted a preliminary review of these data and determined that there is potential for a reduction in the amount of CDDs and CDFs in the pentachlorophenol. However, the laboratory data analysis is incomplete, and the data submitted does not detail the methodology, including, the concentrations of each congener (C); fraction of each congener (R); and methods used to calculate TEQ.

Based on incomplete information concerning the manufacturing process, the Agency cannot quantify the reduction in the amount of CDDs and CDFs available for release from pentachlorophenol-treated wood. Therefore, the Agency is requiring additional data regarding the manufacturing process for pentachlorophenol. The data needs are identified in Section V of this document.

2. Management of Pentachlorophenol-treated Materials

The Agency is aware that materials such as utility poles or railroad ties may be sold for reuse after their original intended use has ended. The typical lifespan for a utility pole or railroad tie depends on climate, setting and other factors. These materials are often sold into a secondary market where they may be installed in residential settings for garden borders, etc. Because the lifespan of these treated materials is fairly long, the Agency believes that the pentachlorophenol leaching from the treated material is significantly less than when it was originally placed into service. The Agency has not conducted a risk assessment of these secondary uses of pentachlorophenol treated materials but has begun to evaluate these uses and has found that other options such as disposing of these materials in a landfill, or incinerating these materials for energy generation are also currently practiced. Further evaluation of the potential risks and benefits associated with these secondary uses of pentachlorophenol treated materials will be conducted during the Registration Review process for this active ingredient.

3. Registration Review of Pentachlorophenol

Through this reregistration action, the Agency is implementing mitigation measures discussed above to reduce exposure to workers in wood treatment facilities. In an effort to determine if these mitigation measures are effective in reducing exposure, the Agency is requiring that exposure monitoring studies be conducted at wood treatment facilities. In addition, the Agency may shorten the Registration Review cycle from the current 15 year time-frame. The Agency plans on conducting Registration Review for pentachlorophenol once the submission and review of new data is complete.

V. What Registrants Need to Do

The Agency has determined that wood preservative products containing pentachlorophenol are eligible for reregistration provided that the conditions and requirements for reregistration identified in this RED are implemented (see Section IV). The registrants will also need to amend product labeling for each product.

The database supporting the reregistration of pentachlorophenol wood preservatives has been reviewed and determined to be adequate to support a reregistration eligibility decision. However, additional confirmatory data are required to support continued registration.

A. Manufacturing Use Products

1. Generic Data Requirements

The generic databases supporting the reregistration of pentachlorophenol for currently registered wood preservative uses has been reviewed and determined to be adequate to support a reregistration eligibility decision. However, the confirmatory data presented in Table 9 are required. Generally, registrants will have 90 days from receipt of a generic data call-in (GDCI) to complete and submit response forms or request time extensions and/or waivers with a full written justification. Timeframes for submitting generic data will be presented in the GDCI.

Table 6. Generic Data Required to Support Pentachlorophenol Wood Preservative Registrations

EPA Guideline Number	Requirement Name
GLN 830.1550	Product Identity and Composition
GLN 830.1600	Description of Materials Used to Produce the Products
GLN 830.1620	Description of Production Process
GLN 830.1650	Description of Formulation Process
GLN 830.1670	Discussion of Formation of Impurities
GLN 835.6100	Terrestrial Field Dissipation (potential dioxin exposure in substrate and organism sampling around treated utility poles)
GLN 875.1100	Dermal Outdoor Exposure
GLN 875.1200	Dermal Indoor Exposure
GLN 875.1300	Inhalation Outdoor Exposure
GLN 875.1400	Inhalation Indoor Exposure
GLN 875.1600	Applicator Exposure Monitoring Data Reporting
GLN 875.1700	Product Use Information

For pentachlorophenol technical grade active ingredient products, the registrant needs to submit the following items:

Within 90 days from receipt of the generic data call-in (DCI):

1. Completed response forms to the generic DCI (i.e., DCI response form and requirements status and registrant's response form); and

2. Submit any time extension and/or waiver requests with a full written justification.

Within the time limit specified in the generic DCI:

1. Cite any existing generic data which address data requirements or submit new generic data responding to the DCI.

Please contact Diane Isbell at (703) 308-8154 with questions regarding generic reregistration.

By US mail:
Document Processing Desk
Diane Isbell
Office of Pesticide Programs (7510P)
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

By express or courier service:
Document Processing Desk
Diane Isbell
Office of Pesticide Programs (7510P)
U.S. Environmental Protection Agency
One Potomac Yard, Room S-4900
2777 South Crystal Drive
Arlington, VA 22202

B. End-Use Products

1. Product Specific Data Requirements

Section 4(g)(2)(B) of FIFRA calls for the Agency to obtain any needed product-specific data regarding the pesticide after a determination of eligibility has been made. The registrant must review previous data submissions to ensure that they meet current EPA acceptance criteria and if not, commit to conduct new studies. If a registrant believes that previously submitted data meet current testing standards, then the study MRID numbers should be cited according to the instructions in the Requirement Status and Registrants Response Form provided for each product. The Agency intends to issue a separate product-specific data call-in (PDCI) outlining specific data requirements.

Generally, registrants will have 90 days from receipt of a PDCI to complete and submit response forms or request time extensions and/or waivers with a full written justification. Registrants will have eight months to submit product-specific data.

For wood preservative end-use products containing the active ingredient pentachlorophenol, the registrants need to submit the following items for each product.

Within 90 days from the receipt of the product-specific data call-in (PDCI):

1. Completed response forms to the PDCI (i.e., PDCI response form and requirements status and registrant's response form); and

2. Submit any time extension or waiver requests with a full written justification.

Within eight months from the receipt of the PDCI:

1. Two copies of the confidential statement of formula (EPA Form 8570-4);

2. A completed original application for reregistration (EPA Form 8570-1). Indicate on the form that it is an "application for reregistration";

3. Five copies of the draft label incorporating all label amendments outlined in Table 10 of this document;

4. A completed form certifying compliance with data compensation requirements (EPA Form 8570-34);

5. If applicable, a completed form certifying compliance with cost share offer requirements (EPA Form 8570-32); and

6. The product-specific data responding to the PDCI.

Please contact Adam Heyward at (703) 308-6422 with questions regarding product reregistration and/or the PDCI. All materials submitted in response to the PDCI should be addressed as follows:

By US mail:
Document Processing Desk
Adam Heyward
Office of Pesticide Programs (7510P)
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

By express or courier service:
Document Processing Desk
Adam Heyward
Office of Pesticide Programs (7510P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

2. Labeling for End-Use Products

To be eligible for reregistration, labeling changes are necessary to implement measures outlined in Section IV. Specific language to incorporate these changes is presented in Table 10. Generally, conditions for the distribution and sale of products bearing old labels/labeling will be established when the label changes are approved. However, specific existing stocks time frames will be established case-by-case, depending on the number of products involved, the number of label changes, and other factors.

Amended product labeling must be submitted no later than March 31, 2009. Registrants may generally distribute and sell products bearing old labels/labeling for 26 months from the date of the issuance of this Reregistration Eligibility Decision document. Persons other than the registrant may generally distribute or sell such products for 52 months from the approval of labels reflecting the mitigation described in this RED. However, existing stocks time frames will be established case-by-case, depending on the number of products involved, the number of label changes, and other factors. Refer to "Existing Stocks of Pesticide Products; Statement of Policy," *Federal Register*, Volume 56, No. 123, June 26, 1991.

Table 7. Required Label Changes for Manufacturing and End-Use Wood Preservative Products Containing Pentachlorophenol

Description	Pentachlorophenol: Required Labeling Language	Placement on Label
	Manufacturing-Use Products	
For all Manufacturing Use Products	"Only for formulation as a preservative for the following use(s) [fill blank only with those uses that are being supported by MP registrant]."	Directions for Use
One of these statements may be added to a label to allow reformulation of the product for a specific use or all additional uses supported by a formulator or user group.	"This product may be used to formulate products for specific use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s)." "This product may be used to formulate products for any additional use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s)."	Directions for Use
Environmental Hazards Statements Required by the RED and PR Notice 93-10 and 95-1	"Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollution Discharge Elimination System (NPDES) permit and the permitting authority have been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA."	Precautionary Statements

Description	Pentachlorophenol: Required Labeling Language	Placement on Label
	End-Use Products	
PPE Requirements Established by the RED	"Personal Protective Equipment (PPE)" "All personnel handling treated wood or handling treating equipment (including poles/hooks used to retrieve charge cables) that has come in contact with preservative must wear the following PPE: * washable or disposable coveralls or long-sleeved shirt and long pants, * chemical resistant gloves, and * socks plus industrial grade safety work boots with chemical resistant soles. All personnel cleaning or maintaining the treatment cylinder gasket/equipment or working with concentrate or wood treatment preservative must wear the following PPE: * washable or disposable coveralls or long-sleeved shirt and long pants, * chemical resistant gloves, * socks plus industrial grade safety work boots with chemical resistant soles, and * a full face shield. In the event of equipment malfunction, or for door spacer placement, all personnel located within 15 feet of the cylinder opening prior to cylinder ventilation must wear the following PPE: * washable or disposable coveralls over long-sleeved shirt and long pants, * chemical resistant gloves, * socks plus industrial grade safety work boots with chemical resistant soles, and * a properly fitting half mask elastomeric respirator with appropriate cartridges and/or filters. Entry to confined spaces is regulated by Federal and/or State Occupational Safety and Health Programs. Compliance is mandated by law. Individuals who enter pressure treatment cylinders or other related equipment that is contaminated with the wood treatment preservative (e.g.,cylinders that are not free of the treatment preservative or preservative storage tanks) must wear protective clothing and/or equipment as required by Federal and/or State Occupational Safety and Health Compliance laws."	Immediately following/below Precautionary Statements: Hazards to Humans and Domestic Animals

Description	Pentachlorophenol: Required Labeling Language	Placement on Label
User Safety Requirement	"Personnel must leave aprons, protective coveralls, chemical resistant gloves, work footwear, and any other material contaminated with preservative at the treatment facility." "Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables exist, use detergent and hot water. Keep and wash PPE separately from other laundry." "Discard clothing and other absorbent material that have been drenched or heavily contaminated with the product's concentrate. Do not reuse them." "Eating, drinking, and smoking are prohibited in the treatment cylinder load-out area, drip pad area, and engineering control room of the wood treatment facilities." EXCEPTION: Where treating operator control rooms are isolated from the treating cylinders, drip pad, and work tanks, eating, drinking, and smoking (depending on local restrictions) are permitted."	Precautionary Statements: Hazards to Humans and Domestic Animals Immediately following the PPE requirements
User Safety Recommendations	"USER SAFETY RECOMMENDATIONS" "Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet." "Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing." "Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."	Precautionary Statements: Hazards to Humans and Domestic Animals immediately following Engineering Controls (Must be placed in a box.)

Description	Pentachlorophenol: Required Labeling Language	Placement on Label
Other Application Restrictions (Risk Mitigation)	"At the conclusion of the treatment, the cylinder must be ventilated by purging the post-treatment cylinder through fresh air exchange. The ventilation process is considered complete after a minimum of 2 volume exchanges based on the empty treatment cylinder volume. The exhaust pipe of the vacuum system or any air moving device utilized in conducting the air purge must terminate into a containment vessel such as a treating solution work tank or water/effluent tank. The ventilation process may be accomplished by one of the following methods: 1) activating an air purge system that operates while the cylinder door remains closed; or 2) using a device to open and hold open the cylinder door (no more than 6 inches) to allow adequate ventilation and activating the vacuum pump. If the second method is utilized, at the conclusion of the treatment, no personnel may be located within 15 feet of the cylinder when open (cracked) until the cylinder has been ventilated. In the event of equipment malfunction, or to place the spacer to hold the door open during venting, only personnel wearing specified PPE are permitted within 15 feet of the cylinder opening prior to ventilation. After ventilation is complete, the cylinder door may be completely opened."	Directions for Use
Other Application Restrictions (Risk Mitigation)	"After treatment, wood must be moved to a drip pad capable of recovering excess preservative until the wood is drip free."	Directions for Use
Other Application Restrictions (Risk Mitigation)	"The treatment process must include a final vacuum to remove excess preservative from the wood. The final vacuum must attain a vacuum equal to or greater than the initial vacuum. This vacuum must be held for an appropriate time period based on wood species, retention levels, and commodity treated to remove excess preservative from the wood."	Directions for Use

Description	Pentachlorophenol: Required Labeling Language	Placement on Label
Other Application Restrictions (Risk Mitigation)	"For treated wood that will be used in marine or other aquatic or sensitive environments, a double vacuum must be used. Following the pressure period and once the pentachlorophenol has been pumped back to the work tank, a vacuum shall be applied for a minimum of one and a half hours at not less than 22 inches of Hg (560 KPa) (adjusted for elevation) of vacuum to recover excess preservative. Then, depending on plant equipment: 1) vacuum for a minimum of one and a half hours at not less than 22 inches of Hg (560 KPa) (adjusted for elevation); or 2) steam material for one hour minimum and then pull not less than 22 inches of Hg (560 KPa) (adjusted for elevation) vacuum for a minimum of one and a half hours. Maximum temperature during steaming shall not exceed 240 degrees F (115.5 degrees C), as specified in the Best Management Practices (Aug. 2006) issued by the Western Wood Preservers Association, Southern Pressure Treaters' Association, Timber Piling Council, and Wood Preservation Canada."	Directions for Use
Other Application Restrictions (Risk Mitigation)	"As of December 31, 2013, for elevated temperature pressure treatment with pentachlorophenol, automatic, remotely operated devices must be used to open, close, lock, and unlock cylinder doors."	Directions for Use
Other Application Restrictions (Risk Mitigation)	"As of December 31, 2013, for ambient pentachlorophenol treatments, an automatic locking/unlocking device must be used to accomplish locking and unlocking of the cylinder door."	Directions for Use
Other Application Restrictions (Risk Mitigation)	"Cylinder openings and door pits must use grating and additional measures such as sumps, dams or other devices which prevent or remove spillage of the preservative."	Directions for Use
Other Application Restrictions (Risk Mitigation)	"Personnel must not directly handle the charge cables, poles or hooks used to retrieve charge cables, or other equipment that has contacted the preservative without wearing chemical resistant gloves."	Directions for Use
Other Application Restrictions (Risk Mitigation)	"As of December 31, 2013, mechanical methods must be used to place/remove bridge rails."	Directions for Use

Appendix A: Use patterns Eligible for Reregistration
Pentachlorophenol

Use Site	Formulation	Method of Application	Application Rate/ No. of applications	Use Limitations
(10) **Wood preservatives**				
(Exterior use only) Lumber, timber's, posts, poles, and other wooden members	Ready to use Reg: 61483-1 Reg: 61483-58 Reg: 61483-59	Pressure treatment In a commercial vessel capable of physically impregnating the wood and providing adequate penetration and retention	If temperature or time is used as the treating parameter, treat for 12 to 48 hours or until effective penetration is achieved	**Restricted use pesticide** *Due to fetotoxicity and oncogenicity in laboratory animals* For retail sale and use only by certified applicators or by persons under their direct supervision and only for those uses covered by certified applicator's certification This product is intended for exterior use. Is not intended for home and farm use, must not be used for pressure or thermal treated logs used in the construction of log homes except laminated beams or building components which are in ground contact and are subject to decay or insect infestation and where two coats of an appropriate sealer are applied. Urethane,
(Exterior use only) Lumber, timber's, posts, poles, and other wooden members	Soluble Concentrate Reg: 61483-62 Reg: 61483-2 Reg: 61483-3	Pressure treatment In a commercial vessel capable of physically impregnating the wood and providing adequate penetration and retention	Add one part of product to nine parts of fuel oil, kerosene, or other hydrocarbon with the desired volatility, and mix well If temperature or time is used as the treating parameter, treat for 12 to 48 hours or until effective penetration is achieved	**Restricted use pesticide** *Due to fetotoxicity and oncogenicity in laboratory animals* For retail sale and use only by certified applicators or by persons under their direct supervision and only for those uses covered by certified applicator's certification This product is intended for exterior use. Is not intended for home and farm use, must not be used for pressure or thermal treated logs used in the construction of log homes except laminated beams or building components which are in ground contact andare subject to decay or insect infestation and where two coats of an appropriate sealer are applied. Urethane, shellac, latex, epoxy, enamel and varnish are acceptable sealers for pentachlorophenol treated wood

APPENDIX B: Pentachlorophenol Case (2505)

Appendix B lists the **generic** (not product specific) data requirements which support the re-registration of Pentachlorophenol. These requirements apply to Pentachlorophenol in all products, including data requirements for which a technical grade active ingredient is the test substance. The data table is organized in the following formats:

1. **Data Requirement** (Columns 1 and 2). The data requirements are listed by Guideline Number. The first column lists the new Part 158 Guideline numbers, and the second column lists the old Part 158 Guideline numbers. Each Guideline Number has an associated test protocol set forth in the Pesticide Assessment Guidance, which are available on the EPA website.

2. **Guideline Description** (Column 3). Identifies the guideline type.

3. **Use Pattern** (Column 4). This column indicates the standard Antimicrobial Division use patterns categories for which the generic (not product specific) data requirements apply. The number designations are used in Appendix B.

   (1) Agricultural premises and equipment
   (2) Food handling/ storage establishment premises and equipment
   (3) Commercial, institutional and industrial premises and equipment
   (4) Residential and public access premises
   (5) Medical premises and equipment
   (6) Human water systems
   (7) Materials preservatives
   (8) Industrial processes and water systems
   (9) Antifouling coatings
   (10) Wood preservatives
   (11) Swimming pools
   (12) Aquatic areas

3. **Bibliographic Citation** (Column 5). If the Agency has data in its files to support a specific generic Guideline requirement, this column will identity each study by a "Master Record Identification (MRID) number. The listed studies are considered "valid" and acceptable for satisfying the Guideline requirement. Refer to the Bibliography appendix for a complete citation of each study.

DATA REQUIREMENT				CITATION(S)
New Guideline Number	**Old Guideline Number**	**Study Title**	**Use Pattern**	**MRID Number**
PRODUCT CHEMISTRY				
830.1550	61-1	Product Identity and Composition		Open Literature
830.1600	61-2	Description of Beginning Materials and Manufacturing Process		41002701
830.1670	61-3	Discussion of Formation of Impurities		41002701
830.1600 830.1620 830.1650	61-2a	Starting Materials and Manufacturing Process		Open Literature
830.1670	61-2b	Formation of Impurities		Open Literature
830.1700	62-1	Preliminary Analysis		40999402, 41002702
830.1750	62-2	Certification of Limits		40999402, 41002702
830.1800	62-3	Analytical Method		41002702
830.6300	63-0	Reports of Multiple phys/chem Characteristics		40999403, 41002703
830.6302	63-2	Color		Open Literature
830.6303	63-3	Physical State		Open Literature
830.6304	63-4	Odor		Open Literature
830.7200	63-5	Melting Point		Open Literature
830.7220	63-6	Boiling Point		Open Literature
830.7300	63-7	Density		Open Literature
830.7840 830.7860	63-8	Solubility		Open Literature
830.7950	63-9	Vapor Pressure		Open Literature

DATA REQUIREMENT				CITATION(S)
New Guideline Number	**Old Guideline Number**	**Study Title**	**Use Pattern**	**MRID Number**
830.7550 830.7560 830.7570	63-11	Partition Coefficient (Octanol/Water)		Open Literature
830.7000	63-12	pH		Open Literature
830.6313	63-13	Stability		Open Literature
830.6314	63-14	Oxidizing/Reducing Action		Open Literature
830.6315	63-15	Flammability		Open Literature
830.6316	63-16	Explodability		Open Literature
830.6317	63-17	Storage Stability		Open Literature
830.6319	63-19	Miscibility		Open Literature
ECOLOGICAL EFFECTS				
850.4400	122-2	Aquatic plant growth		42633704, 42633705, 42633706
850.4400	123-2	Aquatic vascular plant dose-response toxicity- *Lemna* sp.		42633704, 42633705, 42633706
850.220	71-2	Avian Dietary Toxicity		42633702
TOXICOLOGY				
870.1100	81-1	Acute Oral - Rat		00101715
870.1200	81-2	Acute Dermal - Rabbit		00101715
870.1300	81-3	Acute Inhalation - Rat		waiver
870.2400	81-4	Primary Eye Irritation - Rabbit		00101715
870.2500	81-5	Primary Dermal Irritation - Rabbit		00101715
870.2600	81-6	Dermal Sensitization		42594301
870.3250	82-3	Sub chronic Dermal Toxicity		43091702

DATA REQUIREMENT				CITATION(S)
New Guideline Number	**Old Guideline Number**	**Study Title**	**Use Pattern**	**MRID Number**
870.4100	83-1 (a)	Chronic Toxicity		43982701
870.4200	83-2(a)	Carcinogenicity in Mice		NTP, 1989
870.4300		Combined Chronic Toxicity / Carcinogencity in Rats		NTP, 1999
870.3700	83-3	Developmental Toxicity in Rabbits		43091701, 43091702
870.3700	83-3	Developmental Toxicity -Rat		43091702
870.3800		2-Genaration Reproduction Toxicity in Rats		44464101
870.5265		Salmonella thyphimurium reverse mutation assay		NTP study
870.5395		Erythrocyte micronucleus assay		43911301
870.6200		Neurotoxicity screening battery		Open literature
870.8700		Immunotoxicity		Open literature

Appendix C. Technical Support Documents

Additional documentation in support of this RED is maintained in the OPP docket, located in Room 119, Crystal Mall #2, 1801 Bell Street, Arlington, VA. It is open Monday through Friday, excluding legal holidays, from 8:30 am to 4 pm.

OPP public docket is located in Room S-4400, One Potomac Yard (South Building), 2777 South Crystal Drive, Arlington, VA, 22202 and is open Monday through Friday, excluding Federal holidays, from 8:30 a.m. to 4:00 p.m.

The docket initially contained the August 26, 2004 preliminary risk assessment and the related documents. EPA then considered comments on these risk assessments (which are posted to the e-docket) and revised the risk assessments. The revised risk assessments will be posted in the docket at the same time as the RED.

All documents, in hard copy form, may be viewed in the OPP docket room or downloaded or viewed via the Internet at www.regulations.gov

These documents include:

- Pentachlorophneol Preliminary Risk Assessment; Notice of Availability, 11/30/2004

Preliminary Risk Assessment and Supporting Science Documents:

- Pentachlorophenol: Preliminary Risk Assessment for the Reregistration Eligibility Decision, PC Code 063001, Case 2505, Antimicrobials Division, 11/19/2004
- Product Chemistry Science Chapter on Pentachlorophenol PC Code 063001, Case 2505, Antimicrobials Division, 11/19/2004.
- Pentachlorophenol Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document, PC Code 063001, Case 2505, Antimicrobials Division, 11/19/2004, Timothy F. McMahon, Ph.D.
- Pentachlorophenol Dietary Exposure Assessments for the Reregistration Eligibility Decision. PC Code 063001, Case 2505, Antimicrobials Division 11/19/2004
- Pentachlorolphenol Occupational/Residential Exposure Assessment. PC Code 063001, Case 2505, Antimicrobials Division, 11/19/2004, Siroos Mostaghini, PhD. Senior Scientist
- Environmental Fate Assessment of Pentachlorlophenol for the Reregistration Eligibility Decision (RED). PC Code 063001, Case 2505, Antimicrobials Division, 11/19/2004
- Ecological Hazard and Environmental Risk Assessment:Pentachlorophenol PC Code 063001, Case2505, Antimicrobials Division, 11/19/2004, Richard C. Petrie Argonomist, Team Leader 3

Revised Risk Assessment and Supporting Science Documents (RED Supporting Documents):

- Pentachlorophenol: Revised Risk Assessment for the Reregistration Eligibility Decision, PC Code 063001, Case 2505, Antimicrobials Division 8/29/2008 Timothy F. McMahon, Ph.D. Senior Toxicologist/Risk Assessor
- Product Chemistry Science Chapter on Pentachlorophenol PC Code 063001, Case 2505, Antimicrobials Division, 11/19/2004.
- Pentachlorophenol Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document, PC Code 063001, Case 2505, Antimicrobials Division, 3/16/2008, Timothy F. McMahon, Ph.D.
- Pentachlorophenol Dietary Exposure Assessments for the Reregistration Eligibility Decision. PC Code 063001, Case 2505, Antimicrobials Division 11/19/2004
- Pentachlorolphenol Occupational/Residential Exposure Assessment. PC Code 063001, Case 2505, Antimicrobials Division, 11/19/2004, Siroos Mostaghini, PhD. Senior Scientist
- Environmental Fate Assessment of Pentachlorlophenol for the Reregistration Eligibility Decision (RED). PC Code 063001, Case 2505, Antimicrobials Division, 11/19/2004.
- Ecological Hazard and Environmental Risk Assessment:Pentachlorophenol PC Code 063001, Case2505, Antimicrobials Division, 11/19/2004, Richard C. Petrie Argonomist, Team Leader 3.

Appendix D. Citations Supporting the Reregistration Eligibility Decision (Bibliography)

GUIDE TO APPENDIX D

1. CONTENTS OF BIBLIOGRAPHY. This bibliography contains citations of all studies considered relevant by EPA in arriving at the positions and conclusions stated elsewhere in the Pentachlorophenol Reregistration Eligibility Decision Document. Primary sources for studies in this bibliography have been the body of data submitted to EPA and its predecessor agencies in support of past regulatory decisions. Selections from other sources including the published literature, in those instances where they have been considered, are included.

2. UNITS OF ENTRY. The unit of entry in this bibliography is called a "study." In the case of published materials, this corresponds closely to an article. In the case of unpublished materials submitted to the Agency, the Agency has sought to identify documents at a level parallel to the published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes of review and can be described with a conventional bibliographic citation. The Agency has also attempted to unite basic documents and commentaries upon them, treating them as a single study.

3. IDENTIFICATION OF ENTRIES. The entries in this bibliography are sorted numerically by Master Record Identifier, or "MRID" number. This number is unique to the citation, and should be used whenever a specific reference is required. It is not related to the six-digit "Accession Number" which has been used to identify volumes of submitted studies (see paragraph 4(d)(4) below for further explanation). In a few cases, entries added to the bibliography late in the review may be preceded by a nine character temporary identifier. These entries are listed after all MRID entries. This temporary identifying number is also to be used whenever specific reference is needed.

4. FORM OF ENTRY. In addition to the Master Record Identifier (MRID), each entry consists of a citation containing standard elements followed, in the case of material submitted to EPA, by a description of the earliest known submission. Bibliographic conventions used reflect the standard of the American National Standards Institute (ANSI), expanded to provide for certain special needs.

a. Author. Whenever the author could confidently be identified, the Agency has chosen to show a personal author. When no individual was identified, the Agency has shown an identifiable laboratory or testing facility as the author. When no author or laboratory could be identified, the Agency has shown the first submitter as the author.

b. Document date. The date of the study is taken directly from the document. When the date is followed by a question mark, the bibliographer has deduced the date from the evidence contained in the document. When the date appears as (1999), the Agency was unable to determine or estimate the date of the document.

c. Title. In some cases, it has been necessary for the Agency bibliographers to create or enhance a document title. Any such editorial insertions are contained between square brackets.

d. Trailing parentheses. For studies submitted to the Agency in the past, the trailing parentheses include (in addition to any self-explanatory text) the following elements describing the earliest known submission:

(1) Submission date. The date of the earliest known submission appears immediately following the word "received."

(2) Administrative number. The next element immediately following the word "under" is the registration number, experimental use permit number, petition number, or other administrative number associated with the earliest known submission.

(3) Submitter. The third element is the submitter. When authorship is defaulted to the submitter, this element is omitted.

(4) Volume Identification (Accession Numbers). The final element in the trailing parentheses identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol "CDL," which stands for "Company Data Library." This accession number is in turn followed by an alphabetic suffix which shows the relative position of the study within the volume.

1. MRID Studies

<u>Citation</u>

None Electric Power Research Institute (EPRI). 1993. Biodegradability of pentachlorophenol in the environment: a literature review. Document EPRI TR-102172s. Final Draft/April 1993.

None Malecki, R.1992. Regulations regarding the disposal of treated wood. Proceedings of wood pole seminar. Sept. 17-18, Syracuse, NY.

None NTP Technical Report TR 349 on the Toxicology and Carcinogenesis Studies of Pentachlorophenol in B6C3F1 Mice. March, 1989.

None NTP Technical Report TR 483 on the Toxicology and Carcinogenesis Studies of Pentachloropehnol in Fisher 344 Rats April, 1999.

None Schwetz, B.A., Keeler, P.A., and Gehring, P.J. (1974): The Effect of Purified and Commercial Grade Pentachlorophenol on Rat Embryonal and Fetal Development. Toxicol. Appl. Pharmacol 28: 151-161.

None Welsh, J.J. et al. (1987): Teratogenic Potential of Purified Pentachlorophenol and Pentachloroanisole in Subchronically Exposed Sprague-Dawley Rats. Fd. Chem. Toxic. 25(2): 163-172.

None Jekat, F.W., Meisel, M.L., Eckard, R., and Winterhoff, H. 1994. Effects of pentachlorophenol (PCP) on the pituitary and thyroidal hormone regulation in the rat. Toxicol. Lett. 71:9-25.

None McConnell, E.E., Moore, J.A., Gupta, B.N., et al. 1980. The chronic toxicity of technical and analytical pentachlorophenol in cattle. I. Clinicopathology. Toxicol. Appl. Pharmacol. 52:468-490.

None Beard, A.P. and Rawlings, N.C. 1999. Thyroid function and effects on reproduction in ewes exposed to the organochlorine pesticides lindane or pentachlorophenol (PCP) from conception. J. Toxicol. Environ. Health, Part A, 58:509-530.

None Beard, A.P., Bartlewski, P.M., Rawlings, N.C. 1999a. Endocrine and reproductive function in ewes exposed to the organochlorine pesticides lindane or pentachlorophenol. J. Toxicol. Environ.Health (Part A) 56:23-46.

None Beard, A.P., Bartlewski, P.M., and Chandolia, R.K., Honaramooz, A., Rawlings, N.C. 1997. Pituitary, thyroid and testis function in rams exposed to organochlorine pesticides from conception. Biol. Reprod. 56 (Suppl. 1): 200.

None Beard, A.P. and Rawlings, N.C. 1999. Thyroid function and effects on reproduction in ewes exposed to the organochlorine pesticides lindane or pentachlorophenol (PCP) from conception. J. Toxicol. Environ. Health, Part A, 58:509-530.

None Rawlings, N.C., Cook, S.J., and Waldbillig, D. 1998. Effects of the pesticides carbofuran, chlorpyrifos, dimethoate, lindane, triallate, trifluralin, 2,4-D, and pentachlorophenol on the metabolic endocrine and reproductive endocrine system in ewes. J. Toxicol. Environ. Health (Part A) 54:21-36.

None United States Environmental Protection Agency (U.S. EPA). 1984. Wood Preservative Pesticides: Creosote, Pentachlorophenol, Inorganic Arsenicals. Position Document 4. U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances.

00101715 Norris, J. (1972) Acute Toxicological Properties of XD-8108.00L Antimicrobial. (Unpublished study received Apr 18, 1972 under 464-431; submitted by Dow Chemical U.S.A., Midland, MI; CDL: 003666-F).

00259257 Selim, S. 1985. Evaluation of the Dermal Absorption Characteristics of Pentachlorophenol. Unpublished study prepared by Biological Test Center. 18p. also listed under MRID 00148495.

40999402 Hildebrand, D. (1989) (Vulcan Pentachlorophenol) - Analysis of Product Ingredients. Unpublished study prepared by Vulcan Chemicals. 104 p.

40999403 Hildebrand, D. (1989) (Vulcan Pentachlorophenol) - Physical and Chemical Characteristics. Unpublished study prepared by Vulcan Chemicals. 82 p.

41002701 Martin, M. (1989) (Idacon Pentachlorophenol) - Product Identity and Composition. Unpublished study prepared by Idacon, Inc. 33 p.

41002702 Martin, M. (1989) (Idacon Pentachlorophenol) - Analysis of Product Ingredients. Unpublished study prepared by Idacon, Inc. 65 p.

41002703 Martin, M. (1989) (Idacon Pentachlorophenol) - Physical and Chemical Characteristics. Unpublished study prepared by Idacon, Inc. 7 p.

42594301 Johnson, W.D. (1992): Dermal Sensitization Study of Pentachlorophenol in Guinea Pigs using the Modified Buehler Method. Study conducted by IIT Research Institute for the Pentachlorophenol Task Force. (unpublished).

42633702 Campbell, S.M. and Jaber, M. 1993. Pentachlorophenol: A Dietary LC50 Study with the Northern Bobwhite. Project No. 345-101. Performed by Wildlife International Ltd.,Easton, MD. Submitted by Pentachlorophenol Task Force, c/o SRA International,Inc., Washington, DC. EPA

42633704 Hoberg, J.R. 1993. Pentachlorophenol Technical - Toxicity to the Marine Diatom, Skeletonema *costatum*. Report No. 92-12-4540. Conducted by Springborn Laboratories, Inc., Wareham, MA. Submitted by Pentachlorophenol Task Force, c/o SRA International, Inc., Washington, DC. EPA

42633705 Hoberg, J.R. 1993. Pentachlorophenol Technical - Toxicity ot the Freshwater Diatom, *Navicula pelliculosa*. Report No. 92-12-4521. Conducted by Springborn Laboratories, Inc., Wareham, MA. Submitted by Pentachlorophenol Task Force, c/o SRA International, Inc., Washington, DC. EPA.

42633706 Hoberg, J.R. 1993. Pentachlorophenol Technical - Toxicity to the Freshwater Green Algae, *Slenastrum capricornutum*. Report No. 92-10-4481. Conducted by Springborn Laboratories, Inc., Wareham, MA. Submitted by Pentachlorophenol Task Force, c/o SRA International, Inc., Washington, DC. EPA.

43091701 Hoberman, A.M. 1994. Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Pentachlorophenol Administered Orally Via Stomach Tube to New Zealand White Rabbits. Study conducted by Argus Research Laboratories for the Pentachlorophenol Task Force.

43091702 Hoberman, A.M. 1994. Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Pentachlorophenol Administered Orally Via Gavage to Crl:CD7BR VAF/Plus7 Presumed Pregnant Rats. Study conducted by Argus Research Laboratories for the Pentachlorophenol Task Force.

43182301 Osheroff, M.R. et al. 1994. Ninety-one Day Repeated Dose Dermal Toxicity Study of Pentachlorophenol in Sprague-Dawley Rats. Study conducted by TSI Mason Labs for the Pentachlorophenol Task Force (Study No. 2-J27).

43911301 Xu, J (1996): In vivo test for chemical induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells. Study conducted by SITEK Research Laboratories for the Pentachlorophenol Task Force. (unpublished).

43982701 Mecler, F.C. 1996. Pentachlorophenol: Fifty-two Week Repeated Dose Chronic Oral Study of Pentachlorophenol Administered via capsule to Dogs. Study conducted by TSI Mason Labs for the Pentachlorophenol Task Force (study no. 2-J31).

44464101 Hoberman, A.M. (1997): Oral (Gavage) Two-Generation (One Litter Per Generation) Reproduction Study of Pentachlorophenol in Rats. Study performed by Argus Research Laboratories for the Pentachlorophenol Task Force. (unpublished).

44813701 Bookbinder, M. (1999) Inhalation Dosimetry and Biomonitoring Assessment of Worker Exposure to Pentachlorophenol During Pressure-Treatment of Lumber: Final Report: Lab Project Number: AA980307: ML98-0734-PTF: PENTA-90. Unpublished study prepared by American Agricultural Services, Inc. 321 p. {OPPTS 875.1300, 875.1500}

2. Open Literature

Citation

Arsenault RD. 1976. Pentachlorophenol and Contained Chlorinated Dibenzodioxins in the Environment. Alexandria, VA: American Wood Preservers Association (AWPA), 122-147.

Agency for Toxic Substances and Disease Registry (ATSDR). 1994. Toxicological Profile for Pentachlorophenol. Prepared by Clement International Corporation Contract No. 205-88-0608. Prepared for U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. May 1994.

Braun, W.H.; Blau, G.E.; Chenoweth, M.B. 1979. The Metabolism/Pharmacokinetics of Pentachlorophenol in Man, and a Comparison with Rat and Monkey. In: Toxicology and Occupational Medicine (Deichmann, W.E., ed.). Elsevier/North Holland, New York, Amsterdam, Oxford. Pp. 289-296.

Brodberg, R.K. and Thonginthusak, T. 1995. Estimation of Exposure of Persons in California to Pesticide Products Containing Pentachlorophenol. Worker Health and Safety Branch. California Department of Pesticide Regulation. Sacramento, CA. March 1995.

CDPR. 1999. Comments on the Pentachlorophenol (PCP) Task Force's Biomonitoring Study. Memorandum from Michael H. Dong, Staff Toxicologist to John H. Ross, Senior Toxicologist. California Environmental Protection Agency. Department of Pesticide Regulation. August 13, 1999.

Coad, C. and Newhook, R, 1992. APCP Exposure for the Canadian General Population: A Multimedia Analysis. Journal of Exposure Analysis and Environmental Epidemiology, Vol 2, No. 4.

Cohen J. 2008. Computations of Human Pentachlorophenol Dose Based On NHANES Urine Concentrations. Memorandum from Dr. Jonathan Cohen, ICF International to Tim Leighton and David Miller, USEPA, dated July 31, 2008. Contract EP-W-06-091, WA 0-02, TAF CM 28.

Dahlgren et al. 2007. Residential and biological exposure assessment of chemicals from a wood treatment plant. Chemosphere 67 (2007) S279-S285.

Electric Power Research Institute (EPRI) 1995. Pentachlorophenol (PCP) in Soils Adjacent to In-Service Utility Poles in New York State. March 1995. EPRI TR-104893.

Geigy. 1981. *Geigy Scientific Tables, Volume 1. Units of measurement, body fluids, composition of the body, nutrition.* Eighth edition. (Edited by C. Lentner). CIBA-GEIGY.

IBC, 1999. Pentachlorophenol Uses for the following products. Memorandum from Gail Early, Registrations Representative, IBC Manufacturing Company to Connie B. Welch, Chief, Regulatory Branch II, Antimicrobial Division, U.S EPA Office of Pesticide Programs. September 10, 1999.

Mage D.T., Allen R., Gondy G., Smith W., Barr D.B., Needham L.L. 2004. Estimating Pesticide Dose from Pesticide Exposure Data by Creatinine Correction in the Third National Health and Nutrition Examination Survey (NHANES-III). *J Exposure Anal Environ Epidemiol* 14:457-465.

Mage D.T., Allen, R.H., Kodali, A. 2007. Creatinine corrections for estimating children's and adult's pesticide intake doses in equilibrium with urinary pesticide and creatinine concentrations. *J Exposure Sci Environ Epidemiol* 1-9.

Pekari, K.; Liotamo, M.; Jarvisalo, J.; Lindroos, L.; Aito, A. 1991. Urinary Excretion of Chlorinated Phenols in Saw-Mill Workers. Int. Arch. Occup. Environ. Health. 63(1): 57-62.

Pentachlorophenol Task Force. 1999. Re: Response to Comments on Penta Biomonitoring Study. Memorandum from E. John Wilkinson to Michael H. Dong. Vulcan Chemicals. October 22, 1999.

Personal Communication, 1998. Personal Communication with Dr. Timothy McMahon, Toxicologist. U.S. EPA. Risk Assessment Science Support Branch. Antimicrobial Division. July 1998.

Schafer, K.S,, Reeves, M., Spitzer, S., Kegley, S. E. 2004. Chemical Trespass: Pesticides in Our Bodies and Corporate Accountability. Pesticide Action Network North America. May 2004.

The Merk Manual of Diagnosis and Therapy. 1977. Eds: Berkonw, R. and Talbott, J.H. Rahway, NJ: Merck, Sharp and Dohme Research Laboratories.

Thind, K.S., Karmali, S., and House, R.A., 1991. Occupational Exposure of Electrical Utility Linemen to Pentachlorophenol. American Industrial Hygiene Association Journal 52:547-552.

Treble, R.G. and Thompson, T.S. 1996. Normal Values for Pentachlorophenol in Urine Samples Collected from a General Population. J. Anal. Toxicol. 20(5):313-317.

Van den Berg et al, 2006. Review, The 2005 World Health Organization Reevaluation of Human and Mammalian Toxic Factors for Dioxins and Dioxin -Like Compounds. Toxicological Sciences 93 (2), 223-241.

Wilson et al 2004. Design and sampling methodology for a large study of preschool children's aggregate exposures to persistent organic pollutants in their everyday environments. Journal of Exposure Analysis and Environmental Epidemiology (2004) 14, 260-274.

Wilson et al. 2007. An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare. Environmental Research 103 (2007) 9-20.

Baker, M.D., C.I. Mayfield, and W.E. Inniss. 1980. Degradation of chlorophenols in soil, sediment and water at low temperature. Water Research Vol.14:1765-1771.

Boyle, T.P., E.F. Robinson-Wilson, J.D. Petty and W. Weber. 1980. Degradation of pentachlorophenol in simulated lentic environment. Bull. Environm. Contam. Toxicol. 24:177-184.

Bryant, F.O., D.D. Hale and J.E. Rogers. 1991. Regiospecific dechlorination of pentachlorophenol by dichlorophenol-adapted microorganisms in freshwater, anaerobic sediment slurries. Appl. and Environ. Microbiol. pp. 2293-2301.

Christdoulatos, C., G.P. Korfiatis, N.M. Talimcioglu and M. Mohiuddin. 1994. Adsorption of pentachlorophenol by natural soils. J. Environ. Sci. Health A29(5):883-898.

Cooper, P.A. 1991. Leaching of wood preservatives from wood poles in service. Public Works Canada, Ottawa, Ontario, p 79.

Cserjesi, A.J. 1976. Permanence of preservatives in treated experimental shake roofs. Forest Prod. J. 26: 34-39.

Crossland, N.O. and C.J.M. Wolff. 1985. Fate and biological effects of pentachlorophenol in outdoor ponds. Environ. Toxic. and Chem. 4:73-86.

Davis, A., J. Campbell, C. Gilbert, M.V. Ruby, M. Bennett and S. Tobin. 1994. Attenuation and biodegradation of chlorophenols in ground water at a former wood treating facility. Groundwater Vol. 32, No. 2:248-257.

DeLaune, R.D., R.P. Gambrell and K.S. Reddy. 1983. Fate of pentachlorophenol in estuarine sediment. Environ. Pollut. Ser. B 6:297-308.

Donaldson, S. and G. Miller. 1997. Transport and photolysis of pentachlorophenol in soils subject to evaporating water. J. Envir. Qual. 26:402-409.

Englehardt, G., P.R. Wallnöfer, W. Mücke and G. Renner. 1986. Transformations of pentachlorophenol. Part II: Transformations under environmental conditions. Tox. and Envir. Chem. 11:233-252.

Electric Power Research Institute (EPRI). 1993. Biodegradability of pentachlorophenol in the environment: a literature review. Document EPRI TR-102172s. Final Draft/April 1993.

Electric Power Research Institute (EPRI). 1995a. Pentachlorophenol (PCP) in soils adjacent to in-service utility poles in New York State. Document EPRI TR-104893. Final Report/March 1995.

Electric Power Research Institute (EPRI). 1995b. Interim report on the fate of wood preservatives in soils adjacent to in-service utility poles in the United States. Document EPRI TR-104968. Interim Report/June 1995.

Galil, N.I. and J.T. Novak. 1995. Pentachlorophenol-induced release of soil organics and colloids. Wat. Res. 29:1533-1544.

Gile, J.D., J.C. Collins and J.W. Gillett. 1982. Fate and impact of wood preservatives in a terrestrial microcosm. J. Agric. Food Chem. 30:295-301.

Gile, J.D. and J.W. Gillett. 1979. Fate of selected herbicides in a terrestrial laboratory ecosystem. J. Agric. Food Chem. 27:1159-1164.

Hendriksen, H.V., S. Larsen and B.K. Ahring. 1991. Anaerobic degradation of PCP and phenol in fixed-film reactors: The influence of an additional substrate. Water Sci. Technol. 24:431-436.

Howard, P.H. 1993. Handbook of environmental fate and exposure data for organic chemicals. Vol. 3. Chelsea, MI: Lewis Publishers, Inc. pp.559-569.

Ingerslev, F., A. Baun and N. Nyholm. 1998. Aquatic biodegradation behavior of pentachlorophenol assessed through a battery of shake flask die-away tests. Envir. Chem. Tox. 17:1712-1719.

Jackson, D.R. and D.L. Bisson. 1990. Mobility of polychlorinated aromatic compounds in soils contaminated with wood-preserving oil. J. Air Waste Manage. Assoc. 40:1129-1133.

Jensen, J. 1996. Chlorophenols in the terrestrial environment. In: Reviews of Environmental Contamination and Toxicology. Vol. 46, pp. 25-51.

Larsson, P., G. Bremle and L. Okla. 1993. Uptake of pentachlorophenol in fish of acidified and nonacidified lakes. Bull. Environ. Contam. Toxicol. 50:653-658.

Malecki, R. 1992. Regulations regarding the disposal of treated wood. Proceedings of wood pole seminar. Sept. 17-18, Syracuse, NY.

Mikesell, M.D. and S.A. Boyd. 1986. Complete reductive dechlorination and mineralization of pentachlorophenol by anaerobic microorganisms. Appl. and Environ. Microbiol. pp. 861- 865.

Mohammed, S.A., D.L. Sorensen, R.C. Sims, and J.L. Sims. 1998. Pentachlorophenol and phenanthrene biodegradation in creosote contaminated aquifer material. Chemosphere Vol. 37, No. 1:103-111.

Mueller, J.G., D.P. Middaugh, S.E. Lantz and P.J. Chapman. 1991. Biodegradation of creosote and pentachlorophenol in contaminated groundwater: chemical and biological assessment. Appl. and Environ. Microbiol. Vol. 57, No. 3::1277-1285.

Murthy, N.B.K., D.D. Kaufman and G.F. Fries. 1979. Degradation of pentachlorophenol (PCP) in aerobic and anaerobic soil. J. Environ. Sci. Health B14(1):1-14.

Niimi, A.J. and C.Y. Cho. 1983. Laboratory and field analysis of pentachlorophenol (PCP) accumulation by salmonids. Water Res. 17:1791-1795.

Pignatello, J.J., M.M. Martinson, J.G. Steiert, R.E. Carlson, and R.L. Crawford. 1983. Biodegradation and photolysis of pentachlorophenol in artificial freshwater streams. Appl. Environ. Microbiol. 1024-1031.

Weinburg Group Inc, The. 1997. (Draft) Preliminary risk assessment of mircocontaminant leaching from pentachlorophenol-treated wood poles in Canada. Washington, D.C.: Prepared for the Penta Task Force.

Weiss, U.M., I. Scheunert, W. Klein and F. Korte. 1982. Fate of pentachlorophenol-^{14}C in soil under controlled conditions. J. Agric. Food Chem. 30:1191-1194.

Whiticar, D.M. et al. (1994). Evaluation of leachate quality from pentachlorophenol, creosote and ACA preserved wood products. Environment Canada DOE FRAP 1993-36.

Wong, A.S. and D.G. Crosby. 1978. Photolysis of pentachlorophenol in water. Environ. Sci. Res. 12:19-25.

Wong, A.S. and D.G. Crosby. 1981. Photodecomposition of pentachlorophenol in water. J. Agric. Food Chem. 29:125-130.

You, C.N. and J.C. Liu. 1996. Desorptive behavior of chlorophenols in contaminated soils. Wat. Sci. Tech. Vol. 33, No. 6:263-270.

Bentley, R.E. Citation: Acute Toxicity of Pentachlorophenol to Bluegill (*Leopomis macrochirus)*, Rainbow Trout (*Salmo gairdneri*), and Pink Shrimp (*Penaeus duorarum*). Prepared by Bionomics, Wareham, MA for USEPA. Order No. WA-6-99-1414-B.

Eisler, R. 1989. Pentachlorophenol Hazards to Fish, Wildlife, and Invertebrates: A Synoptic Review. U.S. Fish and Wildlife Service, Department of the Interior. Biological Report 85 (1.17). 72 pp.

EPA Document: (Science Chapter) Pentachlorophenol Registration Standard.

EPA Document: Oct. 1980. An Exposure and Risk Assessment for Pentachlorophenol. PB85-211944.

EPA Document: Sept. 1986. Ambient Water Quality Criteria for Pentachlorophenol. Prepared by Stephan, C., ORD, USEPA. EPA-440/5-86-009.

CDL:232112-A McCarty, W.M. 1977. Toxicity of Dowicide - (TM) #EC-7 to Daphnids. Unpublished study received October 28, 1977 under 464-31; submitted by Dow Chemical U.S.A. Midland, Michigan.

Armstrong RW, Eichner ER, Klein DE, Barthel WF, Bennett JV, Jonsson V, Bruce H, Loveless LE. 1969. Pentachlorophenol poisoning in a nursery for newborn infants. II. Epidemiologic and toxicologic studies. The Journal of PEDIATRICS 75(2):317-325.

Bauchinger M., Dresp J, Schmid E, and Hauf R: 1982. Chromosome changes in lymphocytes after occupational exposure to pentachlorophenol (PCP). Mutat. Res., 102, 83-88.

Bevenue A, Haley TJ, Klemmer HW. 1967. A note on the effects of a temporary exposure of an individual to pentachlorophenol. Bulletin of Environmental Contamination and Toxicology 2:293-296.

Bishop CM, Jones AH: Non-Hodgkin's lymphoma of the scalp in workers exposed to dioxins. Lancet. 1981; 2:369.

Cheng WN, Coenraads PJ, Hao ZH, Liu GF. 1993. A health survey of workers in the pentachlorophenol section of a chemical manufacturing plant. American Journal of Industrial Medicine 24(1):81-92.

Cole GW, Stone O, Gates D, Culver D. 1986. Chloracne from pentachlorophenol-preserved wood. Contact Dermatitis 15:164-168.

Cooper RG, Macaulay MB. 1982. Pentachlorophenol pancreatitis. Lancet 1(5805):517. Feb. 27, 1982.

Dimich-Ward H, Hertzman C, Teschke K, Hershler R, Marion SA, Ostry A, Kelly S. 1996. Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry. Scand Journal of Work Environ Health 22(4):267B273.

Eriksson M, Hardell L, Adami HO. 1990. Exposure to dioxins as a risk factor for soft tissue sarcoma: a population-based caseBcontrol study. Journal of the National Cancer Institute 82(6):486B490.

Gerhard I, Frick A, Monga B, Runnebaum B. 1999. Pentachlorophenol exposure in women with gynecological and endocrine dysfunction. Environmental Research Section 80(4):383-388.

Gilbert FI Jr, Minn CE, Duncan RC, Wilkinson J. 1990. Effects of pentachlorophenol and other chemical preservatives on the health of wood-treating workers in Hawaii. Archives of Environmental Contamination and Toxicology 19(4):603-609.

Gray RE, Gilliland RD, Smith EE, Lockard VG, Hume AS. 1985. Pentachlorophenol intoxication: Report of a fatal case, with comments on the clinical course and pathologic anatomy. Archives of Environmental Health 40:161-164.

Hardell L, Eriksson M, Degerman A. 1994. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. Cancer Research 54(9): 2386-2389.

Hardell L, Eriksson M, Degerman A. 1995. Meta-analysis of four Swedish case-control studies on exposure to pesticides as risk-factor for soft-tissue sarcoma including the relation to tumour localization and histopathological type. International Journal of Oncology 6(4):847-851.

Hertzman C, Teschke K, Ostry A, Hershler R, Dimich-Ward H, Kelly S, Spinelli JJ, Gallagher RP, McBride M, Marion SA. 1997. Mortality and cancer incidence among sawmill workers exposed to chlorophenate wood preservatives. American Journal of Public Health 87(1):71-79.

Hoffmann W. 1996. Organochlorine compounds: risk of non-Hodgkin's lymphoma and breast cancer? Archives of Environmental Health 51(3):189-192.

Hogstedt C. 1990. Cancer epidemiology in the paper and pulp industry. In: Vainio H, M Sorsa and A.J. McMichael (eds.) International Agency for Research on Cancer, Complex Mixture and Cancer Risk. Lyon,. 104:382-389.

Hosenfeld JM. 1986. Pentachlorophenol in log homes: A study of environmental and clinical aspects. Executive summary. U.S. Environmental Protection Agency (EPA 560/5-87-001A), Washington, D.C.

Hryhorczuk DO, Wallace W H, Persky V, Furner S, Webster JR Jr, Oleske D, Haselhorst B, Ellefson R, Zugerman C. 1998. A morbidity study of former pentachlorophenol-production workers. Environmental Health Perspectives. 106(7):401-408.

International Agency for Research on Cancer. 1986. Occupational exposures to chlorophenols. In IARC Monographs of the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some Halogenated Hydrocarbons and Pesticide Exposures. Volume 41. International Agency for Research on Cancer, Lyon, France, 319-356.

International Agency for Research on Cancer. 1987. Chlorophenols (Group 2B). In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, Supplement 7, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. IARC, Lyon, France, 154-156.

International Agency for Research on Cancer. 1991. Pentachlorophenol. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Occupational Exposures in Insecticide Application, and some Pesticides. Volume 53. International Agency for Research on Cancer, Lyon, France, 371-402.

Johnson ES. 1990. Association between soft tissue sarcomas, malignant lymphomas, and phenoxy herbicides/chlorophenols: evidence from occupational cohort studies. Fundamental and Applied Toxicology 14(2):219-234.

Jorens PG, Schepens PJC. 1993. Human pentachlorophenol poisoning. Human & Experimental Toxicology 12:479-495.

Karmaus W, Wolf N. 1995. Reduced birthweight and length in the offspring of females exposed to PCDFs, PCP, and lindane. Environmental Health Perspectives 103(13):1120-1125.

Klemmer HW, Wong L, Sato MM, Reichert EL, Korsak RJ, Rashad MN. 1980. Clinical findings in workers exposed to pentachlorophenol. Archives of Environmental Contamination and Toxicology 9(6):715-725.

Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-De-Mesquita HB; Coggon D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Saracci R. 1997. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An Expanded and Updated International Cohort Study. American Journal of Epidemiology 145(12):1061-1075.

Kogevinas M, Kauppinen T, Winkelmann R, Becher H, Bertazzi PA, Bueno de Mesquita HB, Coggon D, Green L, Johnson E, Littorin M, Lynge E, Marlow DA, Mathews JD, Neuberger M, Benn T, Pannett B, Pearce N, Saracci R. 1995. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. Epidemiology 6(4):396-402.

Kogevinas M, Saracci R, Bertazzi PA, Bueno de Mesquita BH, Coggon D, Green LM, Kauppinen T, Littorin M, Lynge E, Mathews JD, Osman J, Pearce N, Winkelmann R. 1992. Cancer mortality from soft-tissue sarcoma and malignant lymphomas in an International cohort of workers exposed to chlorophenoxy herbicides and chlorophenols. Chemosphere 25 (7-10):1071-1076.

Lambert J, Schepens P, Janssens J, Dockx P. 1986. Skin lesions as a sign of subacute pentachlorophenol intoxication. Acta Dermato-Venereol 66(2):170-172.

National Research Council. 1985. Assessment of the health risks of seven pesticides used for termite control. National Academy of Sciences, Washington, D.C.

O'Malley MA, Carpenter AV, Sweeney MH, Fingerhut MA, Marlow DA, Halperin WE, Mathias CG. 1990. Chloracne associated with employment in the production of pentachlorophenol. American Journal of Industrial Medicine 17:411-421.

Pearce NE, Smith AH, Fisher DO. 1985. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. American Journal of Epidemiology 121(2):225-237.

Ramlow JM, Spadacene NW, Hoag SR, Stafford BA., Cartmill JB, Lerner PJ. 1996. Mortality in a cohort of pentachlorophenol manufacturing workers, 1940-1989. American Journal of Industrial Medicine 30(2):180-194

Reigart JR, Roberts JR. 1999. Recognition and Management of Pesticide Poisonings, Fifth Edition. U.S. Environmental Protection Agency (EPA 735-R-98-003), Washington, D.C.

Robinson CF, Fowler D, Brown DP, Lemen RA. 1987. Plywood mill workers' mortality patterns 1945-1977 (revised). NIOSH, U.S. Department of Health and Human Services, Cincinnati, Ohio, 34 pages, 18 references. Report No. NTIS-PB90-147-075.

Saracci R, Kogevinas M, Bertazzi P, Bueno de Mesquita BH, Coggon D, Green LM, Kauppinen T, L'Abbe K A, Littorin M, Lynge E, Mathews JD, Neuberger M, Osman J, Pearce N, Winkelmann R. 1991. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. Lancet 338(8774):1027-1032.

Scow K, Goyer M, Payne E, Perwak J, Thomas R, Wallace D, Walker P, Wood M, Delpire L. 1980. An exposure and risk assessment for pehtachlorophenol. Final Report. U.S. Environmental Protection Agency (EPA-440/4-81/021, Washington, D.C.

Seidler A, Hellenbrand W, Robra B-P, Vieregge P, Nischan P, Joerg J, Oertel WH, Ulm G, Schneider E. 1996. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: A case-control study in Germany. Neurology 46(5):1275-1284.

Smith JE, Loveless LE, Belden EA et al. Pentachlorophenol poisoning in newborn infants -- St. Louis, Missouri, April-August 1967. Morbidity and Mortality Weekly Report 45(25):545-5549. Reprinted from October 7, 1967, MMWR.

Smith JG, Christophers A.J. 1992. Phenoxy herbicides and chlorophenols: a case control study on soft tissue sarcoma and malignant lymphoma. British Journal Cancer 65(3):442-446.

Triebig G, Csuzda I, Krekeler HJ, Schaller KH. 1987. Pentachlorophenol and the peripheral nervous system: a longitudinal study in exposed workers. British Journal of Industrial Medicine 44(9):638-641.

Truhaut R, L'Epee P, Boussemart E: Recherches sur la toxicologie due pentachlorophenol. II. Intoxications professionelles dans l'industrie du bois. Observations de deux cas mortels. Arch. Mal. Profess. 13:567, 1952.

U.S. Environmental Protection Agency. 1984. Health effects assessment for pentachlorophenol. U.S. Environmental Protection Agency (EPA/540/1-86-043) Washington, D.C.

U.S. Department of Health and Human Services. Agency for Toxic Substances and Disease Registry. 1989. Toxicological Profile for Pentachlorophenol. Murray HE, Henriques W, Segal SA. ATSDR TP-89/2310-9.

U.S. Department of Health and Human Services. Agency for Toxic Substances and Disease Registry. 1993. Pentachlorophenol Toxicity. Case studies in Environmental Medicine. Nadig RJ, Leonard RB. ATSDR TP-CSEM93/16190.

U.S. Department of Health and Human Services. Agency for Toxic Substances and Disease Registry. 1994. Toxicological Profile for Pentachlorophenol. Update. Murray HE, Henriques W, Segal SA. ATSDR TP-93/13.

Vena J, Boffetta P, Becher H, Benn T, Bueno-De Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Pesatori AC, Saracci R, Steenland K, Kogevinas M. 1998. Exposure to dioxin and nonneoplastic mortality in the expanded IARC International cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. Environmental Health Perspectives 106(Suppl. 2):645-653.

Walls CB, Glass WI, Pearce NE . 1998. Health effects of occupational pentachlorophenol exposure in timber sawmill employees: a preliminary study. New Zealand Medical Journal. 111(1074):362-364.

Wood S, Rom WN, White GL, Logan DC. 1983. Pentachlorophenol Poisoning. Journal of Occupational Medicine 25:527-530.

World Health Organization Working Group, 1987. Pentachlorophenol. Environmental Health Criteria 71:1-236. WHO, Geneva, Switzerland.

NTP Technical Report TR 349 on the Toxicology and Carcinogenesis Studies of Pentachlorophenol in B6C3F1 Mice. March, 1989.

NTP Technical Report TR 483 on the Toxicology and Carcinogenesis Studies of Pentachloropehnol in Fisher 344 Rats April, 1999.

Schwetz, B.A., Keeler, P.A., and Gehring, P.J. (1974): The Effect of Purified and Commercial Grade Pentachlorophenol on Rat Embryonal and Fetal Development. Toxicol. Appl. Pharmacol 28: 151-161.

Welsh, J.J. et al. (1987): Teratogenic Potential of Purified Pentachlorophenol and Pentachloroanisole in Subchronically Exposed Sprague-Dawley Rats. Fd. Chem. Toxic. 25(2): 163-172.

USEPA (1984): Wood Preservative Pesticides: Creosote, Pentachlorophenol, Inorganic Arsenicals: Position Document 4.

Yuan, J.H. et al. (1994): Toxicokinetics of pentachlorophenol in the F344 Rat. Gavage and Dosed Feed Studies. Xenobiotica 24(6): 553-560.

Reigner, B.G. et al. (1991): Pentachlorophenol Toxicokinetics after Intravenous and Oral Administration to Rat. Xenobiotica 21(12): 1547-1558.

Wester, R.C. et al. (1993): Percutaneous Absorption of Pentachlorophenol from Soil. Fundam. Appl. Toxicol. 20: 68-71.

Igisu, H., Hamasaki, N. and Ikeda, M. (1993): Highly Cooperative Inhibition of Acetylcholinesterase by Pentachlorophenol in Human Erythrocytes. Biochem. Pharmacol. 46: 175-177.

Montoya, G.A. and Quevedo, L. (1990): The Effects of Pentachlorophenol at the Toad Neuromuscular Junction. Comp. Biochem. Physiol. 96C: 193-197.

Montoya et al. (1988): The Actions of Phenol and Pentachlorophenol on Axonal Conduction, Ganglionic Synaptic Transmission, and the Effect of pH Changes. Comp. Biochem. Physiol. 89C: 377-382.

Jorens, P.G. et al. (1991): Pentachlorophenol concentrations in human cerebrospinal fluid. Neurotoxicology 12: 1-8.

Forsell, J., Shull, L., and Kately, J. (1981): Subchronic administration of technical pentachlorophenol to lactating dairy cattle: immunotoxicologic evaluation. J. Tox. Environ. Health 8: 543-558.

Kerkvliet, N.I. Baecher-Steppan, L. and Scmitz, J.A. (1982b): Immunotoxicity of pentachlorophenol (PCP): Increased susceptibility to tumor growth in adult mice fed technical PCP-contaminated diets. Toxicol. Appl. Pharmacol. 62: 55-64.

White, K. and Anderson, A. (1985): Suppression of mouse complement activity by contaminants of technical grade pentachlorophenol. Agents and Actions 16: 387-392.

McConnachie, P.R. and Zahalsky, A.C. (1991): Immunological consequences of exposure to pentachlorophenol. Arch. Environ. Health 46: 249-253.

Daniel, V., Huber, W., Bauer, K., and Opelz, G. (1995): Impaired in vitro lymphocyte responses in patients with elevated pentachlorophenol blood levels. Arch. Environ. Health 50: 287-292.

Colosio, C., et al. (1993): Toxicological and immune findings in workers exposed to pentachlorophenol. Arch. Environ. Health 48: 81-88.

Pentachlorophenol: Report of the Hazard Identification Assessment Review Committee. Document No. 012410. December 8, 1997.

Suzuki, T., Komatsu, M., and Isono, H.: (1996): Cytotoxicity of Organochlorine Pesticides and Lipid Peroxidation in isolated Rat Hepatocytes. Biol. Pharm. Bull 20(3): 271-274.

Lin, Po-Hsiung, et al. (1997): Dosimetry of Chlorinated Quinone Metabolites of Pentachlorophenol in the Livers of Rats and Mice Based upon Measurement of Protein Adducts. Toxicol. Appl. Pharmacol. 145: 399-408.

Umemura, T., et al. (1996): Oxidative DNA Damage and Cell Proliferation in the Li808032vers of B6C3F1 Mice Exposed to Pentachlorophenol in Their Diet. Fundam. Appl. Toxicol. 30: 285-289.

Lin, P.H., La, D.K., Upton, P.B., Swenberg, J.A. (2002): Analysis of DNA adducts in rats exposed to pentachlorophenol. Carcinogenesis 23(2): 365-369.

Adams, W.J.; Blain, K.M. (1986) A water solubility determination of 2,3,7,8-TCDD. Chemosphere. 15:1397-1400.

Adams, W.J.; DeGraeve, G.M.; Sanbourin, T.D.; Cooney, J.D.; Mosher, G.M. (1986) Toxicity and bioconcentration of 2,3,7,8-TCDD to fathead minnows (*Pimephales promelas*). Chemosphere. 15:1503-1511.

Adams, W.J.; Degraeve, G.M.; Sanbourin, T.D.; Cooney, J.D.; Mosher, G.M. (1986) Toxicity and bioconcentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin to fathead minnows (*Pimephales promelas*). Chemosphere. 15:1503-1511.

Allen, J.R.; Barsotti, D.A.; Lambrecht, L.K.; and Van Miller, J.P. (1979) Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates. Ann. NY Aca. Sci, 320:419-425.

Aulerich, R.J.; Bursian, S.J.; Napolitano, A.C. (1988) Biological effects of epidermal growth factor and 2,3,7,8-tetrachlorodibenzo-p-dioxin on developmental parameters of neonatal mink. Arch. Environ. Contam. Toxicol. 17:27-31.

Beatty, P.W.; Holscher, M.A.; Neal, R.A. (1976) Toxicity of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in larval and adult forms of *Rana catesbeiana.* Bull. Environ. Contam. Toxicol. 16:578-581.

Bend, J.R.; Pohl, R.J.; Davidson, N.P.; Fouts, J.R. (1974) Response of hepatic and renal microsomal mixed-function oxidases in the little skate, *Raja erinacea*, to pretreatment with 3-methylchlolanthrene or TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin). Bull. Mt. Desert Biol. Lab. 14:7-12.

Berends, A.G., Boelhouwers, E.J.; Thus, J.L.G.; Gerlache, J. De; Rooij, C.G. De. (1997) Bioaccumulation and lack of toxicity of octachlorodibenzofuran (OCDF) and octachlorodibenzo-p-dioxin (OCDD) to early-life stages of zebra fish. Chemosphere 35(4):853-865.

Besselink, H.T.; Van Santen, E.; Vorstman, W.; Vethaak, A.D.; Koeman, J.H.; Brouwer, A. (1997) High induction of cytochrome P4501A activity without changes in retinoid and thyroid hormone levels in flounder (*Platichthys flesus)* exposed to TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin). Environ. Toxicol. Chem. 16(4):816-823.

Beyer, W.; Conner, E. and S. Gerould. 1994. Estimates of Soil Ingestion by Wildlife. Journal of Wildlife Management, 58: 375-382.

Bol, J.; van den Berg, M.; Seinen, W. (1989) Interactive effects of PCDD's and PCB's as assessed by the E.L.S.-Bioassay. Chemosphere. 19:899-906.

Bowman, R.E.; Schantz, S.L.; Weerasinghe, N.C.A.; Gross, M.L.; and Barsotti, D.A. 1989. Chronic dietary intake of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at 5 and 25 parts per trillion in the monkey: TCDD kinetics and dose-effect estimate of reproductive toxicity. Chemosphere 18:243-252.

Boyer, I. (1989) Bioavailability of ingested 2,3,7,8-TCDD and related substances. U.S. Food and Drug Administration (Draft report submitted to U.S. EPA/OTS).

Branson, D.R.; Takahashi, I.T.; Parker, W.M.; Blau, G.E. (1985) Bioconcentration kinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rainbow trout. Environ. Toxicol. Chem. 4:779-788.

Brooke, L.T. (1991) Results of freshwater exposures with the chemicals atrazine, biphenyl, butachlor, carbaryl, carbazole, dibenzofuran, 3,3-dichlorobenzidine, dichlorvos. WI:110 p. (Memo to R.L. Spehar, U.S. EPA, Duluth, MN).

Chiao, F.F., C, Richard, B.S. Currie and T. E. McKone. 1994. Intermedia Transfer Factors for Contaminants Found at Hazardous Waste Sites: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). California Environmental Protection Agency, The Department of Toxic Substances Control, and The Office of Scientific Affairs.

Cook, P.M.; Kuehl, D.W.; Walker, M.K.; Peterson, R.E. (1991) Bioaccumulation and toxicity of TCDD and related compounds in aquatic ecosystems. Banbury Report 35: Biological Basis for Risk Assessment of Dioxins and Related Compounds, Cold Spring Harbor Laboratory Press, Plainview, NY, pp. 143-167.

Davies, D.E. and F.B. and Golly. (1963). Principles of Mammalogy. Reinhold Publ. Corp., New York, NY.

Eisler, R. (1986) Dioxin hazards to fish, wildlife, and invertebrates: a synoptic review. U.S. Department of the Interior, Fish and Wildlife Service, Biological Report 85 (1.8).

Geiger, D.L.; Call, D.J.; Brooke, L.T. (1988) Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas)*, Vol. 4. WI:355 p. (Contains data also found in 10183, 15823).

Greg, J.B.; Jones, G.; Butler, W.H.; and Barnes, J.M. (1973) Toxicity of effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fd. Cosmet. Toxicol. 11:585-595.

Harris, G.E.; Kiparissis, Y.; Metcalfe, C.D. (1994) Assessment of the toxic potential of PCB congener 81 (3,4,4',5'-tetrachlorobiphenyl) to fish in relation to other non-ortho-substituted PCB congeners. Environ. Toxicol. Chem. 13(9):1405-1413.

Hawkes, C.L.; Norris, L.A. (1977) Chronic oral toxicity of 2,3,7,8-tetrachlordibenzo-p-dioxin (TCDD) to rainbow trout. Trans. Amer. Fish. Soc. 106:641-645.

Heitmuller, P.T.; Hollister, T.A.; Parrish, P.R. (1981) Acute toxicity of 54 industrial chemicals to sheepshead minnows (*Cyprinodon variegatus)*. Bull. Environ. Contam. Toxicol. 27(5):596-604.

Helder, T. (1980) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the early life stages of the pike (*Esox lucius L.*) Sci. Total Environ. 14:225-264.

Helder, T.; Seinen. W. (1985) Standardization and application of an E.L.S.-bioassay for PCDDs and PCDFs. Chemosphere. 14:183-193.

Helder, T.; Seinen, W. (1986) Relative toxicities of some CDDs and CDFs and toxic potentials of incineration products assessed by E.L.S.-bioassay. Chemosphere. 15(19-12):1165-1172.

Helder, T. (1982a) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on early life stages of two fresh-water fish species. In: Chlorinated Dioxins and Related Compounds. Hutzinger, O.; Frei, R.W.; Merian, E.; Pocchiari, F. (Eds.). Pergamon Press, NY. pp. 455-462.

Helder, T. (1982b) Effects of TCDD on early life stages of fresh water fish. In: Principles for the Interpretation of the Results of Testing Procedures in Ecotoxicology. EUR 7549. Commission of the European Communities on Environment and Quality of Life, Luxembourg, Belgium. pp. 465-5471.

Helder, T. (1981) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on early life stages of rainbow trout (*Salmo gairdneri,* Richardson). Toxicology 19:101-112.

Helder, T. (1980) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on early life stages of the pike (*Esox lucius L.)*. Sci. Total Environ. 14:255-264.

Hochstein, J.R.; Aulerich, R.J.; Bursian, S.J. (1988) Acute toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin to mink. Arch. Environ. Contam. Toxicol. 17:33-37.

Hudson, R., Tucker, R., and Haegele, M. (1984) Handbook of toxicity of pesticides to wildlife. Second Edition. U.S. Fish and Wildlife Service, Resources Publication No. 153, Washington, D.C.

Isensee, A.R.; Jones, G.E. (1975) Distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in aquatic model ecosystem. Environ. Sci. Technol. 9:668-672.

Isensee, A.R. (1978) Bioaccumulation of 2,3,7,8-tetrachlorodibenzo-para-dioxin. Ecol. Bull. (Stockholm) 27:255-262.

Janz, D.M.; Metcalfe, C.D. (1991) Nonadditive interactions of mixtures of 2,3,7,8-TCDD and 3,3',4,4'-tetrachlorobiphenyl on aryl hydrocarbon hydroxylase induction in rainbow trout (*Oncorhynchus mykiss)*. Chemosphere 23:467-472.

Jung, R.E.; Walker, M.K. (1997) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on development of anuran amphibians. Environ. Toxicol. Chem. 16(2):230-240.

Kenaga, E.D.; Norris, L.A. (1983) Environmental toxicity of TCDD. In: Human and environmental risks of chlorinated dioxins and related compounds. Tucher, R.E.; Young, A.L.; Gray, A.G. (eds.). New York: Plenum Press.

Khera, K.S.; and Ruddick, J.A. (1973) Polychlorodibenzo-p-dioxins: Perinatal effects and the dominant lethal test in Wistar rats. In: E.H. Blair, ed., Chlorodioxins - Origin and Fate. Advances in Chemistry Series 120. Amer. Chem. Soc., Washington, DC.

Kleeman, J.M.; Olson, J.R.; Peterson, R.E. (1988) Species differences in 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity and biotransformation in fish. Fund. Appl. Toxicol. 10:206-213.

Kleeman, J.M.; Olson, J.R.; Chen, S.M.; Peterson, R.E. (1986a) Metabolism and disposition of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rainbow trout. Toxicol. Appl. Pharmacol. 83:391-401.

Kociba, R.J.; Keyes, D.G.; Beyer, J.E.; Carreon, R.M; Wade, C.E.; Dittenber, D.A.; Kalnins, R.P.; Frauson, L.E.; Park, C.N.; Barnard, S.D.; Hummel, R.A.; and Humiston, C.G. (1978) Results of a two year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol. Appl. Pharmacol. 46:279-303.

Kociba, R.J.; Schwetz, B.A. (1982) Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Drug Metabolism Reviews. 13(3):387-406.

LeBlanc, G.A. (1980) Acute toxicity of priority pollutants to water flea (*Daphnia magna*). Bull. Environ. Contam. Toxicol. 24(5):684-691.

Kleeman, J.M.; Olson, J.R.; Chen, S.M.; Peterson, R.E. (1986b) 2,3,7,8-tetrachlorodibenzo-p-dioxin metabolism and disposition in yellow perch. Toxicol. Appl. Pharmacol. 83:402-411.

Maas, J.L. (1990) Toxicity research with thiourea. Water Treatment, Report No. AOCE:4 p. (DUT).

Merhle, P.M.; Buckler, D.R.; Little, E.E.; Smith L.M.; Petty, J.D.; Peterson, P.H.; Stalling, D.L.; DeGaeve, G.M.; Goyle, J.J.; Adams, W.L. (1988) Toxicity and bioconcentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzofuran in rainbow trout. Environ. Toxicol. Chem. 7:47-62.

Metcalfe, C.D.; Niimi, A.J. (1993) AHH induction in rainbow trout by chlorinated diphenyl ethers. In: Baddaloo, E.G.; Ramamoorthy, S.; Moore, J.W. (Eds.), Proc. 19th Annual Aquatic Toxicity Workshop, Oct. 4-7, 1993, Edmonton, Alberta; Can. Tech. Rep. Fish. Aquat. Sci. No. 1942:359 (ABS).

Metcalfe, C.D.; Metcalfe, T.L.; Cormier, J.A.; Huestis, S.Y.; Niimi, A.J. (1997) Early life-stage mortalities of Japanese medaka (*Oryziaws latipes*) exposed to polychlorinated diphenyl ethers. Environ. Toxicol. Chem. 16(8):1749-1754.

Mehrle, P.M.; Buckler, D.R.; Little, E.E.; Smith, L.M.; Petty, J.D.; Peterman, P.H.; Stalling, D.L. (1988) Toxicity and bioconcentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzofuran in rainbow trout. Environ. Toxicol. Chem. 7(1):47-62.

Miller, R.A.; Norris, L.A.; Hawes, C.L. (1973) Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in aquatic organisms. Environ. Health Perspect. 5:177-186.

Miller, R.A.; Norris, L.A.; Loper, B.R. (1979) The response of coho salmon and guppies to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in water. Trans. Am. Fish. Soc. 108:401-407.

Miller, R.A.; Norris, L.A.; Hawkes, C.L. (1973) Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in aquatic organisms. Environ. H. Per. 5:177-186.

Murray, F.J.; Smith, F.A.; Nitschke, K.O.; Huniston, C.G.; Kociba, R.J.; Schwetz, B.A. (1979) Three-generation reproduction study of rats given 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the diet. Toxicol. App. Pharmacol. 50:241-252.

Newsted, J.L.; Giesy, J.P. (1993) Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the epidermal growth factor receptor in hepatic plasma membranes of rainbow trout. Toxicol. Appl. Pharmacol. 119(1):41-51.

Newsted, J.L.; Giesy, J.P.; Ankley, G.T.; Tillitt, D.E.; Crawford, R.A.; Gooch, J.W.; Jones, P.D.; Denison, M.S. (1995) Development of toxic equivalency factors for PCB congeners and the assessment of TCDD and PCB mixtures in rainbow trout. Environ. Toxicol. Chem. 14(5):861-871.

Nikolaidis, E.; Brunstrom, B.; Dencker, L. (1988) Effects of TCDD and its congeners 3,3,4,4-tetrachlorazoxybenzene and 3,3,4,4-tetrachlorobiphenyl on lymphoid development in the thymus of avian embryos. Pharmacol. Toxicol. 63:333-336.

Norris, L.A.; Miller, R.A. (1974) The toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in guppies (*Poecilia reticulatus* Peters). Bull. Environ. Contam. Toxicol. 12(1):76-80.

Nosek, J.A.; Craven, S.R.; Sullivan, J.R.; Olson, J.R.; Peterson, R.E. (1992a) Metabolism and dispostion of 2,3,7,8-tetrachlorodibenzo-p-dioxin in ring-necked pheasant hens, chicks, and eggs. J. Toxicol. Environ. Health 35:153-164.

Nosek, J.A.; Sullivan, J.R; Hurley, S.S.;Craven, S.R.; and Peterson, R.E. (1992b) Toxicity and reproductive effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity in ring-necked pheasant hens. J. Toxicol. Environ. Health. 35:153-164.

Nosek, J.A.; Sullivan, J.R.; Amundson, T.E.; Carven, S.R.; Miller, L.M.; Fitzpatrick, A.G.; Cook, M.E.; Peterson, R.E. (1992c) Embryotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in ring-necked pheasants. Environ. Contam. Toxicol. (In press).

Pohl, R.J.; Fouts, J.R.; Bend, J.R. (1975) Response of hepatic microsomal mixed-function oxidases in the little skate, *Raja erinacea*, and the winter flounder, *Pseudopleuronectes americanus* to pretreatment with TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) or DBA (1,2,3,4-dibenzanthracene). Bull. Mt. Desert Biol. Labs 15:64-66.

Prince, R.; Cooper, K.R. (1989) Differential embryo sensitivity to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in *Fundulus heteroclitus*. (Abstract). Toxicologist 9:42.

Prince, R.; Cooper, K.R. (1995) Comparisons of the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on chemically impacted and nonimpacted subpopulations of fundulus heteroclitus: I..Environ. Toxicol. Chem. 14(4):579-587.

Sample, B.E., Opresko, D.M. and G.W. Suter II. 1996. Toxicological Benchmarks for Wildlife: 1996 Revision. U.S. Department of Energy, Office of Environmental Management, Oak Ridge. ES/ER/TM-86/R3.

Schwetz, B.A.; Norris, J.M.; Sparschu, G.L.; Rowe, V.K.; Gehring, P.J.; Emerson, J.L.; Gergib, C.G. (1973) Toxicology of chlorinated dibenzo-p-dioxins. Environ. Health Perspect. 5:87-99.

Spitsbergen, J.M.; Kleeman, J.M.; Peterson, R.E. (1988a) Morphologic lesions and acute toxicity in rainbow trout (*Salmo gairdneri*) treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Toxicol. Environ. Health 23:333-358.

Spitsbergen, J.M.; Kleeman, J.M.; Peterson, R.E. (1988) Morphologic lesions and acute toxicity in rainbow trout (*Salmo gairdneri)* treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Toxicol. Environ. Health 23(3):333-358.

Spitsbergen, J.M.; Kleeman, J.M.; Peterson, R.E. (1988b) 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) with immune responses of rainbow trout. Vet. Immunol. and Immunopathol. 12:263-280.

Spitsbergen, J.M.; Kleeman, J.M.; Peterson, R.E. (1988b) 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity in yellow perch (*Perca flavescens). J. Toxicol. Environ. Health 23:359-383.*

Spitsberg, J.M.; Schat, K.A.; Kleeman, J.M.; Peterson, R.E. (1988c) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) or Aroclor 1254 on the resistance of rainbow trout, *Salmo qairdneri* Richardson, to infectious hematopoietic necrosis virus. J. Fish Dis. 11:73-83.

Spitsbergen, J.M.; Walker, J.R.; Olson, J.R.; Peterson, R.E. (1991) Pathological alterations in early life stages of lake trout, *Salvelinus namaycush*, exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin as fertilized eggs. Aquat. Toxicol. 19:41-72.

Sullivan, J.R.; Kubiak, T.J.; Amundson, T.E., Martini, R.E.; Olson, L.J.; Hill, G.A. (1987) A wildlife exposure assessment for landspread sludges which contain dioxins and furans. In: Proceed. Tenth Ann. Madison Internat. Waste Conf: Municip. Indust. Waste. Sept. 29-30, 1987. Madison, WI: Univ. of Wisconsin.

Thiel, D.A.; Martin, S.G.; Duncan, J.W.; Lemke, M.J.; Lance, W.R.; Peterson, R. (1988) Evaluation of the effects of dioxin-contaminated sludges on wild birds. In: Proceedings of the 1988 TAPPI Environmental Conference.

Tillitt, D. E. 1999. The Toxic Equivalents Approach for Fish and Wildlife. Hum and Ecol Risk Assess 5(1):25-32.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants.

U.S. EPA. 1984a. U.S. Environmental Protection Agency. Ambient water quality criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Washington, DC: EPA, Office of Water Regulations and Standards. EPA-440/5-84-007.

U.S. EPA. 1984b. U.S. Environmental Protection Agency. Health effects profile for tetra-, penta-, and hexachlorodibenzo-p-dioxins. Final draft. Cincinnati, OH: EPA, Office of Research and Development, Environmental Critical Assessment Office. ECAD-CIN-P004.

U.S. EPA . 1989. Risk Assessment Guidance for Superfund. Volume II: Environmental Evaluation Manual. Interim Final. EPA/540/1-89/001. March, 1989.

U.S. EPA. 1990. U.S. Environmental Protection Agency. Background document to the integrated risk assessment for dioxins and furans from chlorine bleaching in pulp and paper mills. Washington, DC: Office of Toxic Substances. EPA-560/5-90-014.

U.S. EPA. 1993a. U.S. Environmental Protection Agency. Interim report on data and methods for assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxins risks to aquatic life and associated wildlife. Washington, DC: Office of Research and Development.

U.S. EPA. 1993b. U.S. Environmental Protection Agency. Wildlife Exposure Factors Handbook. Volume I. Office of Research and Development, Washington, D.C. EPA/630/R-93/187a

Van den Berg, M.; et al. (1998) Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ. Health Perspect. 106(2):775-792.

Van der Weiden, M.E.J.; De Vries, L.P.; Fase, K.; Celander, M.; Seinen, W.; Van den Berg, M. (1994b) Relative potencies of polychlorinated dibenzo-p-dioxins (PCDDS), dibenzofurans (PCDFS) and biphenyls (PCBS), for cytochrome P450 1A induction in the... Aquat. Toxicol. 29(3/4):163-182.

Van der Weiden, M.E.J.; van der Kolk, J.; Bleumink, R.; Seinen, W.; van den berg, M. (1992) Concurrence of P450 1A1 induction and toxic effects after administration of a low dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to the rainbow trout (*Oncorhynchus mykiss*). Aquat. Toxicol. 24:123-142.

Walker, M.K. (1991) Toxicity of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and polychlorinated diphenyls during salmonid early development. Ph.D. thesis. University of Wisconsin, Madison, WI, August 1991.

Walker, M.K.; Spitsbergen, J.M.; Olson, J.R.; Peterson, R.E. (1991) 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Toxicity during early life stage development of lake trout (*Salvelinus namaycush)*. Can. J. Fish. Aquat. Sci. 48(5):875-883. In: Prog. Abstr. 32nd Conf. Int. Assoc. Great Lakes Res., May 30-June 2, 1989, Univ. of Wisconsin, Madison, WI: 114(ABS).

Walker, M.K.; Peterson, R.E. (1991) Potencies of polychlorinated dibenzo-p-dioxin, dibenzofuran, and biphenyl congeners, relative to 2,3,7,8-tetrachlorodibenzo-p-dioxin, for producing early life stage mortality in rainbow trout (*Oncorhynchus mykiss*). Aquat. Toxicol. 21:219-238.

Walker, M.K.; Spitsbergen, J.M.; Olson, J.R.; Peterson, R.E. (1991) 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxicity during early life stage development of lake trout (*Salvenlinus namaycush)*. Can. J. Fish. Aquat. Sci. 48:875-883.

Walker, M.K.; Hufnagle, Jr., L.C.; Clayton, M.K.; Peterson, R.E. (1992a) An egg injection method for assessing early life stage mortality of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in rainbow trout... Aquat. Toxicol. 22:15-38.

Walker, M.K.; Hufnagle, Jr. L.C.; Clayton, M.K.; Peterson, R.E. (1992) An egg injection method for assessing early life stage mortality of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in rainbow trout, (*Oncorhynchus mykiss*). Aquat. Toxicol. 22:15-38.

Walker, M.K. (1992) Toxicity of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls during salmonid early development. Diss. Abstr. Int. B Sci. Eng. 52(10:5177 (ABS).

Walker, M.K.; Cook, P.M.; Batterman, A.R.; Lothenbach, D.B.; Berini, C.; Hufnagle, L.; Peterson, R.E. (1993) Early life stage mortality associated with maternal transfer of 2,3,7,8-tetrachlorodibenzo-p-dioxin to lake trout oocytes. U.S. EPA. Environmental Research Laboratory, Duluth, MN. (In preparation).

Wannemacher, R.; Rebstock, A.; Kulzer, E.; Schrenk, D.; Bock, K.W. (1992) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on reproduction and oogenesis in zebrafish (*Brachydanio rerio*). Chemosphere 24:1361-1368.

Wisk, J.; Cooper, K.R. (1986) Comparison of toxicity between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and several tetrachlorodibenzofuran isomers (TCDF) in the Japanesa medaka embryo-larval bioassay. Proceedings of the 7th Annual Meeting of SETAC.

Wisk, J.D.; Cooper, K.R. (1990a) Comparison of the toxicity of several polychlorinated dibenzo-p-dioxins and 2,3,7,8-tetrachlorodibenzofuran in embryos of the Japanese medaka (*Oryzias...)*. Chemosphere 20(3-4):361-377.

Wisk, J.D.; Cooper, K.R. (1990b) The stage specific toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in embryos of the Japanese medaka *(Oryzias latipes)*. Environ. Toxicol. Chem. 9:1159-1169.

Yalkowsky, S.H.; Valvani, S.C.; Mackay, D. (1983) Estimation of the aqueous solubility of some aromatic compounds. Residue Rev. 85:43-55.

Yockum, R.S.; Isensee, A.R.; Jones, G.E. (1978) Distribution and toxicity of TCDD and 2,4,5-T in an aquatic model ecosystem. Chemosphere 7:215-220.

Zabel, E.W.; Walker, M.K.; Hornung, M.W.; Clayton, M.K.; Peterson, R.E. (1995) Interactions of polychlorinated dibenzo-p-dioxin, dibenzofuran, and biphenyl congeners for producing rainbow trout early life stage mortality. Toxicol. Appl. Pharmacol. 134:204-213.

Zabel, E.W.; Cook, P.M.; Peterson, R.E. (1995b) Toxic equivalency factors of polychlorinated dibenzo-p-dioxin, dibenzofuran and biphenyl congeners based on early life stage mortality in rainbow trout. Aquat. Toxicol. 31(4):315-328.

Zabel, E.W.; Cook, P.M.; Peterson, R.E. (1995c) Potency of 3,3',4,4',5-pentachlorobiphenyl (PCB 126), alone and in combination with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), to produce lake trout. Environ. Toxicol. Chem. 14(12):2175-2179.

Zabel, E.W.; Peterson, R.E. (1996) TCDD-like activity of 2,3,6,7-tetrachloroxanthene in rainbow trout early life stages and in a rainbow trout gonadal cell line (RTG-2). Environ. Toxicol. Chem. 15(12):2305-2309.

3. Other Supporting Documents

Citation

U.S. EPA 1986. Pentachlorophenol in Log Home: A Study of Environmental and Clinical Aspects. Office of Toxic Substances. Washington, DC. EPA-560/5-87-001. December, 1986.

U.S. EPA 1989. Risk Assessment Guidance for Superfund. Vol I. Human Health Evaluation Manual (Part A). Office of Emergency and Remedial Response. Washington, D.C. EPA/540/1-89/002.

U.S. EPA. 1997. Pentachlorophenol-Report of the Hazard Identification Assessment Review Committee. December 8, 1997.

U.S. EPA. 1998. Integrated Risk Information System (IRIS) database.

U.S. EPA. 1998. Series 875 - Occupational and Residential Exposure Test Guidelines, Group B - Postapplication Exposure Monitoring Test Guidelines, Version 5.4. Office of Pesticide Programs, Health Effects Division. February 1998.

U.S. EPA 2002. Child-Specific Exposure Factors Handbook. National Center for Environmental Assessment-Washington. Office of Research and development. USEPA. Washington D.C. 20460. EPA-600-P-00-002B, September 2002.

Dioxins in San Francisco Bay, 2004: Conceptual Model/Impairment Assessment by: Mike Connors, Donald Yee, Jay Davis, and Christine Werne (San Francisco Estuary Institute), SFEI Contribution # 309.

Appendix E. Generic Data Call-In

The Agency intends to issue a Generic Data Call-In at a later date. See Chapter V of the Pentachlorophenol RED for a list of studies that the Agency plans to require.

Appendix F. Product Specific Data Call-In

The Agency intends to issue a Product Specific Data Call-In at a later date for:

Pentachlorophneol (Case 2505) PC Code: 063001

Appendix G. Batching of Pentachlorophenol Products for Meeting Acute Toxicity Data Requirements for Reregistration

Appendix H. List of All Registrants Sent the Data Call-In

A list of registrants sent the data call-in will be posted at a later date.

Dear Mr. Lipman.

This letter is regarding the Hollydale High Voltage Transmission Line ["HVTL"] route permit application, MN PUC docket number E002 / TL-11-152, OAH docket number 8-2500-22806-2.

1. **<u>The 1971 landscape versus today's:</u>**

    a. The current, 69kV transmission line ["Existing Line"] was put in place circa 1971, when most of the area was farmland. This is evident by the way the Existing Line cuts through the landscape in straight lines and at right angles, not following any of the current major thoroughfares.

    b. Since 1971, Plymouth's population has more than quadrupled, and the landscape has filled with densely populated residential communities. Consequently, the Existing Line now abuts hundreds of residential properties which were not there when the line was originally put in place.

    c. Routing the proposed HVTL along the existing easements would impact hundreds of households and bring about significant aggregate devaluation of property, all in the interest of saving Xcel and GRE ["The Applicants"] money.

    d. Routing the proposed HVTL along the existing easements would also open the door to future increases in voltage or double circuit design implementation, further devaluing the hundreds of residential properties along the proposed route. While The Applicants state that this is not in their plans at this time, routing a 115kV HVTL through densely populated residential areas was probably not in their plans in 1971 either, when the current easement was acquired.

2. **<u>Expectation of the public regarding use of Existing Line as an emergency backup line only:</u>**

    a. During the public meeting held June 7th, 2012, it was evident that the public understood and expected that the portion of the Existing Line that connects the Hollyale and Medina substations serves as a backup only, and is not in frequent use. During that meeting, The Applicants claimed that this portion is, in fact, used very frequently.

    b. To show just one example that the public's expectation is based in formal publications, I kindly refer you to MTEP 11, appendix D1 West (https://www.midwestiso.org/Library/Repository/Study/MTEP/MTEP11/MTEP11%20Appendix%20D1%20West.pdf), page 177, which states that "**The Hollydale load is currently supported by a 35 kV feeder from Gleason Lake. The 69 kV GRE line is only used as an emergency backup.**" MTEP stands for "MISO Transmission Expansion Plan", where MISO is the Midwest Independent System Operator, in charge of providing "an independent platform for transparent regional energy markets", as stated on its website.

    c. Any claim that residents living next to or near the Current Line knew that they were buying property next to a fully active transmission line with the possibility of an upgrade

is unsubstantiated. I have shown that the public has been led to believe that the Existing Line is used only as a backup.

3. **<u>Expectation that the Existing Line will not be upgraded:</u>**

   a. The easement for the Existing Line running along the east and south side of Bridlewood Farm is limited to "single pole, wooden structures". Below is part of the relevant easement.

3714289 39A

Easement

KNOW ALL MEN BY THESE PRESENTS, that (We) the undersigned William G. Mitchell and Nancy G. Mitchell (husband and wife), Merrill H. Pearson and Wilma Pearson (Husband and Wife) whose post office address is R#1-Box 572 Excelsior, Minn. 55331 in consideration of one dollar and other good and valuable considerations, the receipt whereof is hereby acknowledged, do hereby grant unto The RURAL COOPERATIVE POWER ASSOCIATION, whose post office address is Elk River, Minnesota, and to its successors or assigns the right to enter upon the following described lands of the undersigned, situated in Hennepin County, Minnesota, to wit:

The South one-half of the Southwest quarter (S½ of SW¼) of Section 18, Township 118, Range 22.

The South one-half of the Northeast quarter of the Southwest quarter (S½ of NE¼ of SW¼) of Section 18, Township 118, Range 22, lying South of County Road No. 48.

and to construct, operate and maintain thereon, and in or upon all streets, roads or highways abutting said lands, an electric transmission line or system consisting of single pole wood structures.

   b. During the June 7th, 2012 meeting, The Applicants explained that the preferred design for the 115kV HVTL was based on steel poles. While The Applicants stated that wooden poles can support the 115kV line, The Applicants made it clear that it is not the **preferred design** for a 115kV HVTL.

   c. Why would GRE, the current owner of the easement, limit the easement to wooden poles if there was ever an expectation that the line would be upgraded to 115kV, for which the preferred design is based on steel poles? I believe that the answer is that there was never such an expectation.

4. **<u>Creosote and pentachlorophenol ["PCP"]:</u>**

   a. As stated earlier, the easement for the Existing Line running along the east and south side of Bridlewood Farm is limited to "single pole, wooden structures".

   b. In order to make the wooden poles resistant to weather, insects and fungi, they are pressure treated with either the biocide creosote or the biocide PCP. These two materials are known carcinogens and mutagens, and are not approved for household use.

   c. The attached MSDS (material safety data sheet) document states that creosote pressure treated wood hazards include: "harmful if inhaled, harmful on contact with the skin,

respiratory tract irritation, skin irritation, eye irritation, allergic reactions, nasal/sinus cancer, lung cancer, skin cancer."

d. The U.S. Department of Health and Human Services, in its September 2001 Toxicological Profile For Pentachlorophenol document states that "The International Agency for Research on Cancer (IARC) has determined that pentachlorophenol is possibly carcinogenic to humans, and the EPA has classified pentachlorophenol as a probable human carcinogen."

e. The U.S. Department of Health and Human Services, in its September 2002 Toxicological Profile For Creosote (attached), page 34, states, "coal tar creosote has been identified by EPA as a hazardous waste." Also, "Studies of workers exposed to coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles in various industrial environments have found increased cancer risk involving a number of tissues including the respiratory tract, skin, lung, pancreas, kidney, scrotum, prostate, rectum, bladder, and central nervous system. Leukemia and lymphoma have also been diagnosed."

f. In the attached file, the MN Pollution Control Agency cites creosote and PCP as two of the "more toxic" wood treatment chemicals. It claims that, "They are generally more toxic; use them only when necessary."; "Do not use any type of treated wood for applications in which the wood will come into direct or indirect contact with drinking water supplies."; and "Do not use CCA-, PCP-, or creosote-treated wood for residential use, for playground equipment, or in any use in which it may come into contact with domestic animal or livestock drinking water."

g. The U.S. EPA, in its August 2007 preliminary risk assessment regarding creosote (http://www.epa.gov/pesticides/factsheets/chemicals/creosote_prelim_risk_assess.htm), claims that, "There are no approved uses of creosote to treat wood for residential use. The Agency is aware that creosote-treated railroad ties are being used in the residential setting for landscape purposes and, in some instances, as a border around gardens. Such uses in residential settings are not intended uses of creosote [...]"

h. The U.S. EPA, in its September 2008 Reregistration Eligibility Decision For Pentachlorophenol document (attached), page 36, states that "a reasonably strong argument can be made that exposure to pentachlorophenol is associated with increased risks of a number of diseases, namely chloracne, soft tissue sarcoma (STS), and non-Hodgkin's lymphoma (NHL)."

i. The attached Competent Authority (CA) report, submitted to the European Commission, states on page 14, "Creosote is a complex mixture which contains several substances that are regarded as carcinogenic and mutagenic."

j. Putting up new wooden poles is tantamount to coercing the entire affected population to household use of substances that are banned from such use.

k. One may claim that we have the option of either agreeing to steel poles, thereby allowing The Applicants to breach the terms of the easement and avoid this additional exposure to creosote and or PCP, or to abide by the terms of the easement and expose

our families to these chemical mutagens and carcinogens. However, I feel that this would be tantamount to coercion.

5. **<u>No geographically distinct alternate routes proposed by The Applicants west of Hollydale substation:</u>**

    a. Part B in Page 4 of ORDER--NOTICE AND ORDER FOR HEARING UNDER MINNESOTA RULES CHAPTER 1405, document number 20125-74462-01 in docket 11-152, states that "…the Applicants state that their application contains the information required for either the full or alternative process – including information about alternative routes, and the reasons supporting the Applicants' preferred route."

    b. During the June 7th public meeting, The Applicants submitted that they are required to submit at least one alternate route when submitting applications for the full route permitting process.

    c. In this case, no geographically distinct alternate routes were proposed by The Applicants west of the Hollydale substation. This is an area potentially impacting over 134 households. I hereby request that The Applicants submit at least one alternate route west of Hollydale substation that is geographically distinct from the proposed route.

    d. The record already contains several alternate routes submitted by the public for this area. However, submitting at least one geographically distinct alternate route in this area will constitute a significant departure from The Applicants' current stance that the proposed route is the only one that is acceptable to them, and the only one that they support. I believe that the law requires this precisely for this reason: so that applicants do not become entrenched with one route that, as in this case, maximizes impact.

6. **<u>Aggregate property devaluation:</u>**

    a. Xcel is a for-profit, publicly traded corporation. Publicly traded corporations serve their shareholders first and foremost.

    b. By proposing the Existing Line as the basis for the proposed route, Xcel is clearly serving its shareholders via a cost-cutting effort for this project. However, in the process, Xcel is maximizing overall impact, potentially impacting hundreds of households and bringing about millions of dollars of aggregate property devaluation.

    c. As a case in point:

        i. There are 134 properties within 300 feet of the proposed route west of the Hollydale substation and east of Holy Name Drive, compared to 33 properties along alternate route G. This is a difference of 101 properties, or 75% less overall impact.

        ii. If we take a very conservative view and assume an extremely low average property value of $250k, and a very low 10% average devaluation for each property ($25k devaluation per property, on average), we arrive at over $2.5 million in incremental aggregate property devaluation that could be avoided for

this portion of the line alone. This is not accounting for the devaluation of additional properties through the domino effect of lower comparables for the entire area.

iii. Table 7 on page 20 of the Load Serving Study, document number 20122-71170-01 in docket 11-152, shows $922k per mile for the line cost (https://www.edockets.state.mn.us/EFiling/edockets/searchDocuments.do?method=showPoup&documentId={9F8BB9A5-13C1-4969-B97B-8B1457A47ADA}&documentTitle=20122-71170-01).

iv. The length of the proposed line from Hollydale to Holy Name Drive is 1.41 miles, while the length of alternate route G for the same portion is 2.57 miles (route lengths estimated using www.mapmyrun.com). This leads to an incremental $1.1 million in cost for The Applicants, as compared to the very conservative incremental property devaluation estimate of $2.5 million.

v. The length of alternate route G1 for the same portion is 1.67 miles, leading to an incremental $240 thousand in cost for The Applicants, as compared to the very conservative incremental property devaluation estimate of $2.5 million, assuming that route G1 impacts as many properties as alternate route G, though it probably impacts fewer properties.

Route	Length (miles)	Cost ($ millions @ $0.922 million per mile)	Impact (# Properties)	Impact ($ millions @ $0.025 million per property)	Incremental Cost ($ millions)	Aggregate property devaluation avoided ($ millions)
Proposed	1.4	1.3	134	3.4		
Alternate G	2.6	2.4	33	0.8	1.1 (2.4 minus 1.3)	2.5 (3.4 minus 0.8)
Alternate G1	1.7	1.5	33	0.8	0.24 (1.5 minus 1.3)	2.5 (3.4 minus 0.8)

d. The $1.1 million and $240 thousand incremental cost to implement alternate routes G and G1, respectively, versus the $2.5 million aggregate property devaluation they would avoid, highlights how impactful the proposed route is. Since it cuts directly through densely populated communities, it brings about tremendous aggregate property devaluation, much higher than the cost to implement an alternate route.

e. To summarize: via the proposed route, the applicants are requesting that the communities west of the Hollydale substation and east of Holy Name Drive lose over $2.5 million in incremental aggregate property value ($3.4M overall devaluation) so that they could save between $240k and $1.1 million. This hardly seems a fair request.

f. Throughout this example, I used a very conservative value of $25k average devaluation per property. I believe the average property devaluation will be closer to 30%.

g. The Hennepin County website offers property value estimates. The County estimates property values next to the Existing Line to average $396k in Bridlewood Farm.

h. 30% devaluation on an average $396k property makes for a more realistic value of $119k average devaluation per property, and an incremental aggregate devaluation of approximately $12.0 million for the 101 property differential between the proposed route and alternate route G.

i. Even if The Applicants claim that the $0.922 million per mile value is wrong, and the actual value is higher, it does not change the fact that if granted permit, the proposed route will bring about tremendous aggregate residential property devaluation throughout Plymouth and Medina, all in the interest of cutting costs for a publicly traded, for profit company.

7. <u>Electromagnetic fields ["EMF"]:</u>

a. Health concerns:

i. Epidemiology studies show a statistical association between chronic exposure to EMF and childhood leukemia.

ii. To date, lab experiments cannot reliably prove that EMF is a probable carcinogen. Furthermore, there is no established physiological mechanism.

iii. Childhood leukemia is a rare disease, and reliably proving the carcinogenic properties of EMF requires following very large study and control groups over many years. In short, the correlation is extremely difficult to reliably prove in a lab setting. It is equally as difficult to establish a mechanism.

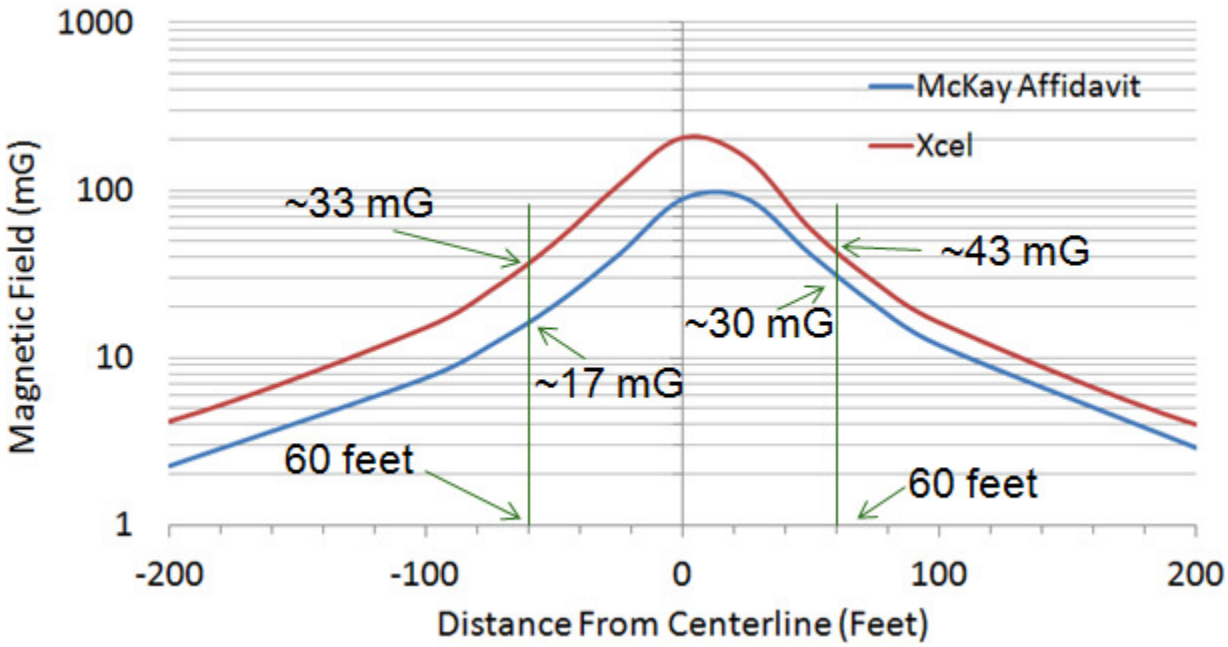
iv. The combination of positive epidemiological statistical association, negative lab experimental results, and lack of proven mechanism has led The International Agency for Research on Cancer ["IARC"] to find that "**extremely low-frequency magnetic fields are possibly carcinogenic to humans**" (http://monographs.iarc.fr/ENG/Monographs/vol80/volume80.pdf)

b. Magnetic field exposure:

i. On page 1 of LETTER--RESPONSE TO PAUL ABLACK AND KIM CARLSTROM TO REQUEST FOR INFORMATION, document number 20126-75380-01 in docket 11-152, answer number 3, The Applicants state that there is potential for the 115kV HVTL to feed three transformers with a rating of 50 MVA each. This makes for a potential power of 150 MVA flowing through the HVTL.

ii. When using a value of 115kV for voltage and the square root of 3 (1.732) as a power factor, this yields a current of 753 A.

iii. Below are the EMF profiles for a horizontal post, 115kV, single circuit design with 753A current.

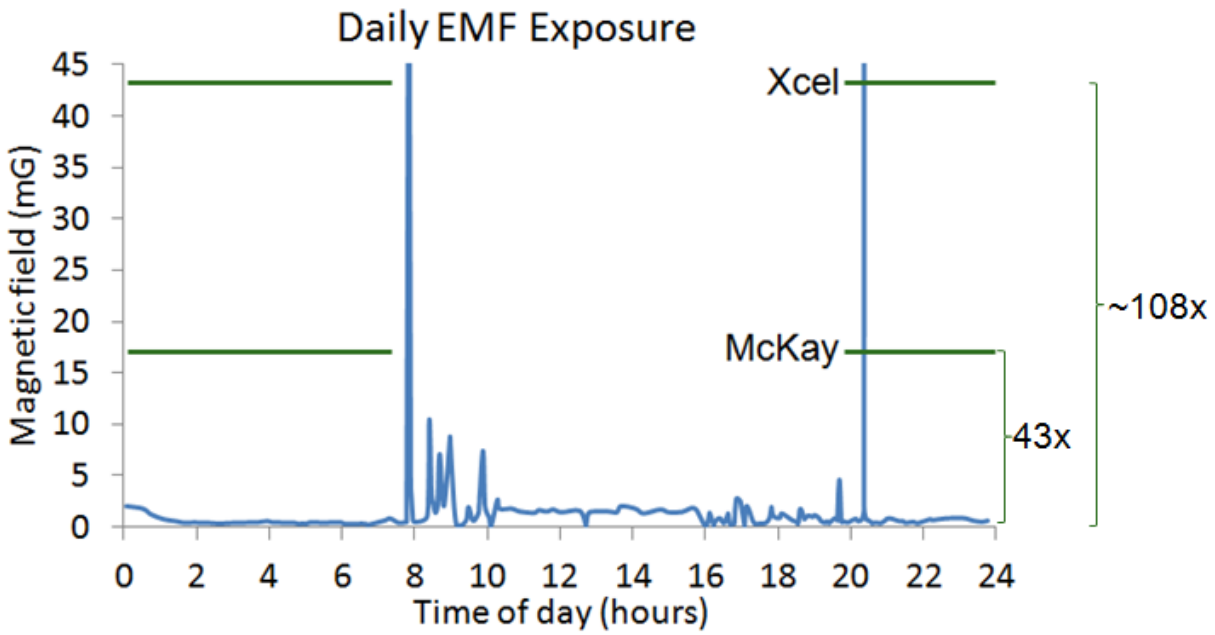


1. The blue curve, titled "McKay Affidavit", was calculated by dividing the values provided in the Affidavit of Bruce McKay, P.E., PUC docket no. E002/CN-10-694, by the current he used, and multiplying the resultant values by 753 (https://www.edockets.state.mn.us/EFiling/edockets/searchDocuments.do?method=showPoup&documentId={97EF41CC-3B69-4ACA-8A45-DA1C12BC45C9}&documentTitle=20114-61941-02).

2. The red curve, titled "Xcel", was provided by Xcel to certain members of the public via email. The original data are titled "Single Pole, Horizontal Post, 115 kV Single Circuit", and were calculated for a current of 250 A. I divided those values by 250 and multiplied by 753, the potential current flowing through the HVTL.

iv. The McKay profile shows that at 60 feet – the approximate distance from the Existing Line to my children's bedroom windows – the magnetic field will be approximately 17 to 30 mG, depending on which side of the pole our property will end up. The Xcel profile shows this value to be approximately 33 to 43 mG.

v. Below is a profile of EMF exposure by an adult over a period of one day (http://www.emfs.info/Sources+of+EMFs/exposure/). The profile shows that during the night hours, the person was exposed to approximately 0.4 to 0.5 mG on average. The plot also shows thick green horizontal lines, which indicate the chronic exposure my children will suffer. The bottom green line is at 17 mG, in accordance with Mr. McKay's "best case" profile. The top green line is at 43 mG, in accordance with Xcel's "worst case" profiles.



vi. My children spend at least 10 hours every day in their rooms, mostly sleeping. As they grow older, they will spend at least as much time in their rooms – if not longer – sleeping, doing their homework and generally hanging out in the only space in the house that affords them privacy.

vii. To summarize: if the proposed line is granted permit, my children will be chronically exposed to 17 to 43 mG, compared to a normal value of 0.4 mG. **That translates to chronic exposure of 43x to 108x the normal levels of a possible carcinogen for ten hours every day.**

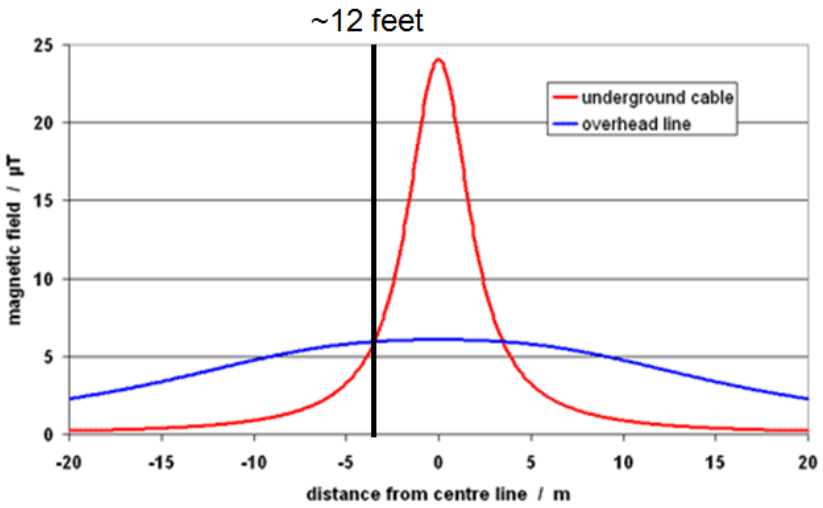
viii. My family is one of hundreds of families that would be so affected if the proposed route is granted permit, as the proposed route maximizes impact while minimizing cost to The Applicants.

ix. Minimizing overall impact should be the top most priority when considering routing for this project.

8. <u>Undergrounding:</u>

a. The plot below compares the magnetic field profiles of the same HVTL, once in an overhead configuration and another when undergrounding the conductors (http://www.emfs.info/Sources+of+EMFs/Underground/). The plot shows the much stronger decay of the magnetic field profile of the undergrounded conductors, crossing the overhead configuration at 12 feet from centerline and decaying to practically zero very fast. This is because the closer together the conductors are, the more they cancel each other's magnetic fields.

1 μT = 10 mG
1 m = ~3 feet



b. I request that, regardless of the route chosen for this project, the conductors be placed underground. This would eliminate the health, aesthetic, noise, safety, and most of the property devaluation concerns that are associated with the proposed HVTL.

c. I realize that the capital expense associated with undergrounding is significant. However, this is a great opportunity to set the vision for smarter routing of HVTL in Minnesota. I urge you, Mr. Lipman, to take that bold step!

9. <u>Guiding principles:</u>

a. The proposed route will bring about significant property devaluation for hundreds of families. Those are members of the community who invested or are committed to invest a substantial portion of their financial resources over decades to acquire their properties, and are now facing significant loss of years and years of their hard-earned money's worth. All because The Applicants are attempting to minimize their own costs.

b. To put this in perspective, I have a 30-year mortgage on my property. If I lose only 10% of my property's value – a very conservative estimate – it equates to three years of mortgage payments lost. If I lose a more reasonable 30% of my property value, it equates to nearly a **decade** of lost mortgage payments!

c. Xcel is a for-profit, publicly traded corporation. Publicly traded corporations serve their shareholders first and foremost.

d. From comments made during both the June 7th and 8th public hearings, it is clear that the public's expectation is that costs to The Applicants should be the last criterion to consider, far inferior in priority to considerations such as minimizing the number of properties affected and minimizing proximity to the line. It is certainly my expectation as well.

e. It is up to you, Mr. Lipman, to protect the public from this proposed route which is clearly meant to serve the shareholders of a publicly traded corporation via cost-cutting, while potentially impacting hundreds of households, bringing about millions of dollars of

property devaluation, and devastating entire communities throughout Plymouth and Medina.

f. Some parties will always be impacted by the route chosen. However, the environmental impact statement will show that some routes clearly act to minimize overall impact while others serve to minimize costs. I ask that when considering this matter, you follow these guiding principles:

   i. Minimizing overall impact: overall impact should be determined by the number of properties affected and their proximity to the line.

   ii. Routing the line along major thoroughfares.

10. **Alternate routes.** In contemplating alternate routes, I considered only routes that significantly reduce impact, that follow major thoroughfares, and, where the latter is not possible, that follow roads or property lines. I utilized the Hennepin County GIS interactive map in "Hybrid" view (http://gis.co.hennepin.mn.us/Property/Map/default.aspx) to identify property lines. I hereby propose the following alternate routes, highlighted in thick lines. For each region, I first attach the hybrid view without the lines that denote the alternate routes. Below that, I attach the exact same view, with the lines denoting alternate routes overlaid.

    a. The first set of alternate routes connects the Hollydale substation to the corner of Brockton Lane N and Medina Road, or a little to the west of that junction. From there, the alternate route can follow any of the previously proposed alternate routes.

    b. It is my intention that all possible combinations be explored. For example, in the first set of routes, connecting the Hollydale substation to Brockton Ln N, the light green line could be reached either via the black or the light blue lines. The dark blue line in the western part of the first set of routes can be reached via the red or the black lines, the purple line on the second set of routes, connecting the Hollydale substation to the Medina substation, could be reached via either the dark green or the red lines, etc.

    c. In keeping true to the guiding principles of minimizing impact and routing along major thoroughfares as much as possible, I have generated the second set of routes, which runs far west along highway 55. It then runs along roads to the highest degree possible. Where not possible, it runs along property lines. While more costly to The Applicants, I believe that these routes will prove to have practically zero impact, and should elicit practically no resistance from any community. I very much expect and request that these routes are included in the scoping decision despite their longer length and resultant higher cost to The Applicants.

Mr. Lipman, I will conclude by saying that there is a reason that energy facility permitting is regulated by the State. There's also a reason that "contested cases" require an ALJ to make a recommendation to the Commission. It is meant to provide an unbiased, external perspective that is divorced from corporate financial considerations. In economic theory this is termed an "externality". The term stems from the fact that the invisible hand of the market only self-regulates and optimizes price and financial

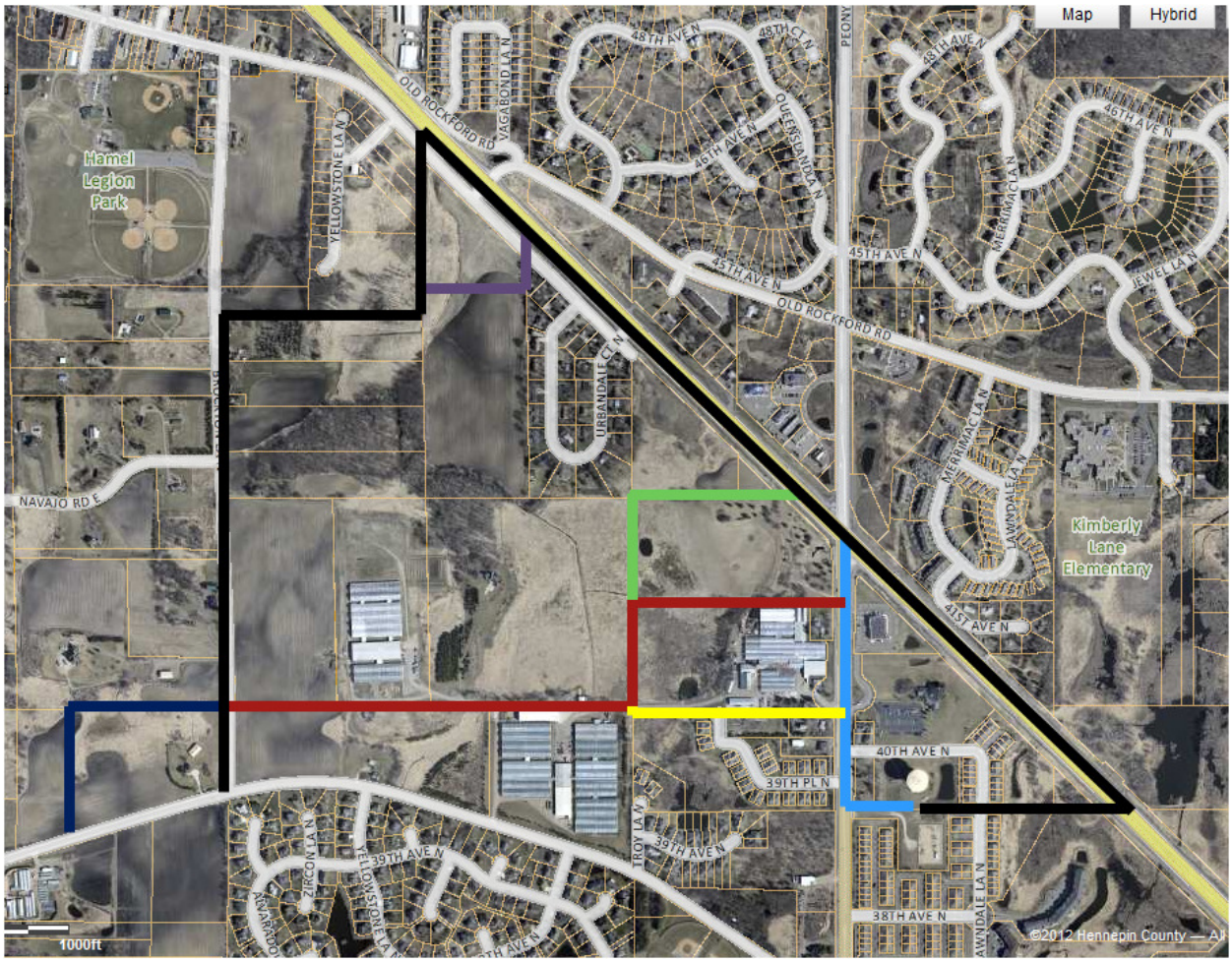
considerations, but does not account for things that our society cares about, such as pollution and other environmental concerns. This is a clear case of a publicly-traded, for-profit corporation trying to serve its shareholders by minimizing cost at the expense of the community. The affected communities look to you to become that “externality”, the voice of reason, compassion and common sense that tells The Applicants that the proposed route cannot and will not be permitted.

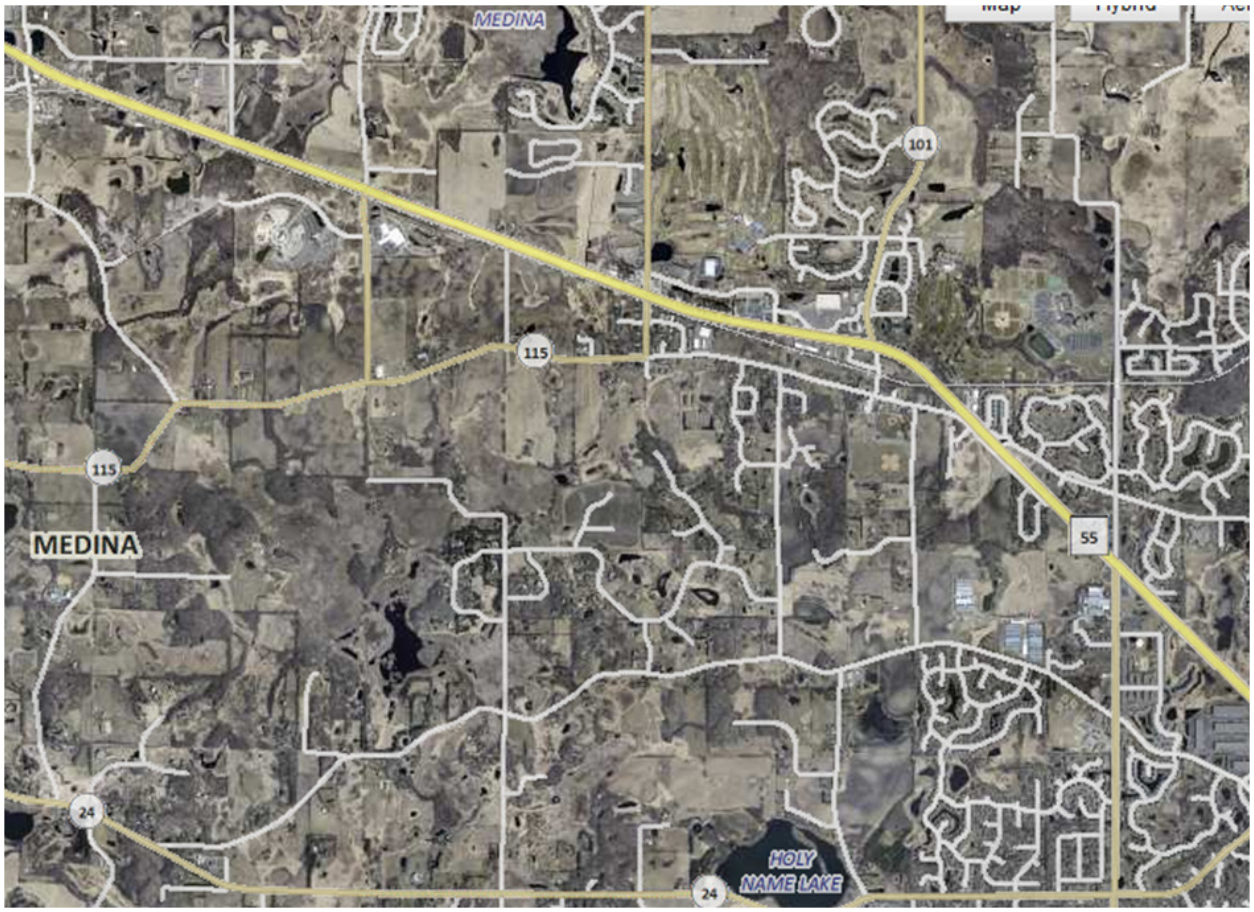
Thank you for the opportunity to submit comments.

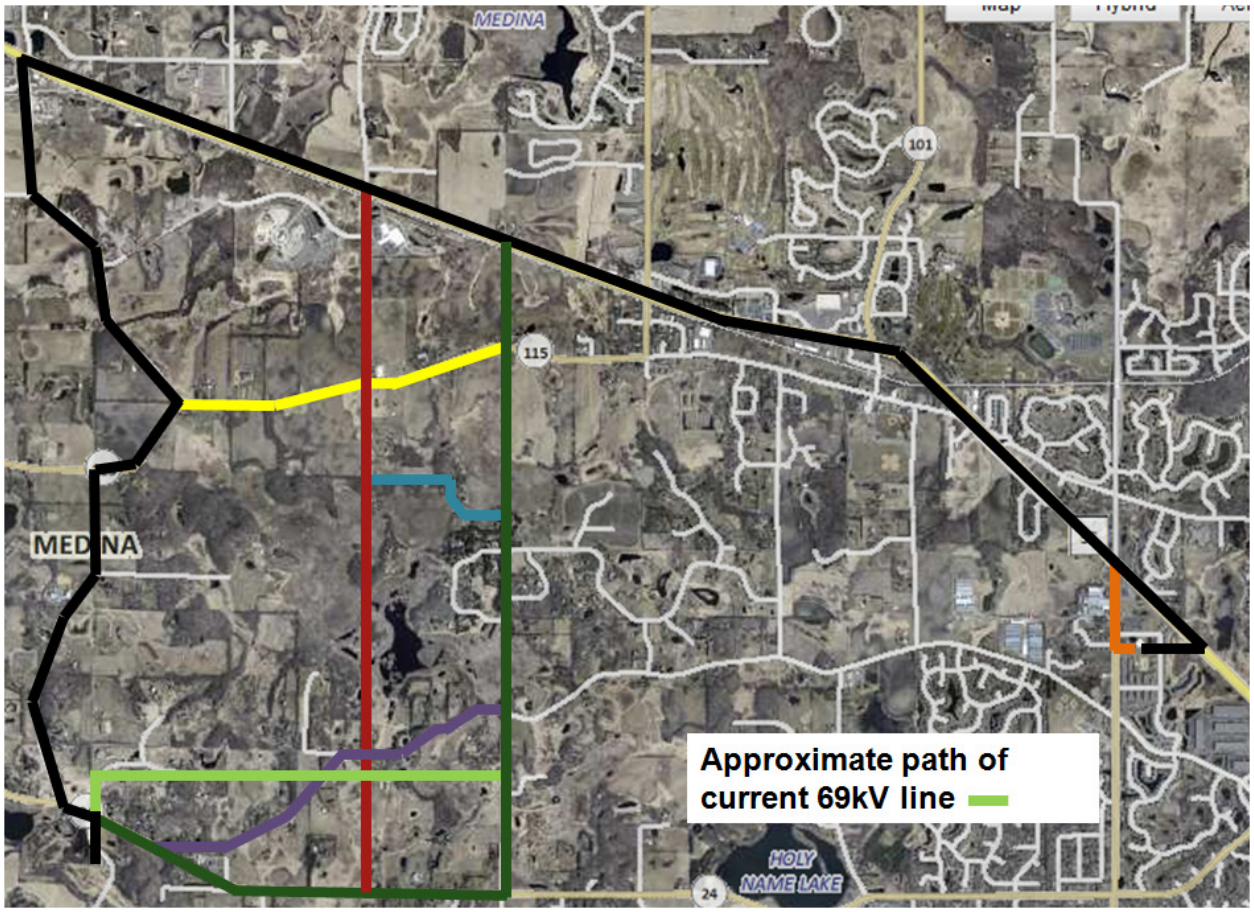
With warmest regards,

Ilan Zeroni

Map
Hybrid
Hamel Legion Park
Kimberly Lane Elementary
OLD ROCKFORD RD
VAGABOND LA N
YELLOWSTONE LA N
BROCKTON LA N
NAVAJO RD E
URBANDALE CT N
48TH AVE N
48TH CT N
46TH AVE N
QUEENSLANDA N
45TH AVE N
PEONY
MERRIMAC LA N
JEWEL LA N
LAWNDALE LA N
41ST AVE N
40TH AVE N
39TH PL N
39TH AVE N
TROY LA N
ZIRCON LA N
38TH AVE N
1000ft
©2012 Hennepin County — Al


Map
Hybrid
Hamel Legion Park
Kimberly Lane Elementary
OLD ROCKFORD RD
VAGABOND LA N
48TH AVE N
48TH CT N
QUEENSLAND LA N
46TH AVE N
45TH AVE N
PEONY
YELLOWSTONE LA N
MERRIMAC LA N
JEWEL LA N
URBANDALE CT N
LAWNDALE LA N
NAVAJO RD E
41ST AVE N
40TH AVE N
39TH PL N
39TH AVE N
TROY LA N
ZIRCON LA N
38TH AVE N
1000ft
©2012 Hennepin County — All


MEDINA
101
115
115
MEDINA
55
24
HOLY
NAME LAKE
24


MEDINA
101
115
MEDINA
Approximate path of current 69kV line
HOLY NAME LAKE
24

Minnesota Pollution Control Agency

Treated Wood

Use, disposal and alternatives for businesses

Waste/Hazardous waste #4.67 • September 2010

Contents

Background 1
Guidance for households1
Prevention 1
Before you buy 1
Types of wood treatments..... 1
Use guidelines..... 2
Handling precautions..... 2
Reuse and recycling..... 2
Disposal requirements... 2
More information 3

Background

Treating wood with chemical preservatives or pesticides lengthens its useful life; however, many of the chemicals used in treating wood are toxic to people and the environment. To minimize the potential for treated wood to cause adverse health and environmental impacts, select, use and dispose of treated wood products safely and appropriately.

Guidance for households

In this document, the Minnesota Pollution Control Agency (MPCA) provides guidance to businesses purchasing, using, and disposing of treated wood.

For guidance for households, see MPCA household hazardous waste fact sheet #4.75, Treated Wood - Use, Disposal, and Alternatives for Consumers available on the MPCA's household publications Web page at www.pca.state.mn.us/index.php/household-hazardous-waste.html.

Prevention

Consider how you intend to use treated wood. Although other building materials may not be completely environmentally friendly, they may not have the same potential for adverse impacts to drinking water, groundwater or surface water. For example, consider alternatives:

- Docks made from recycled or new metal or plastic materials
- Untreated cedar for decks and playgrounds
- Landscape blocks
- Steel or reinforced plastic pilings

Before you buy

Before you buy treated wood, ask yourself:

- Will it be used indoors or outdoors?
- Will it come into direct contact with people or animals?
- Will it come into contact with any drinking water source, any surface water (such as a lake or stream), or with groundwater?
- Is there a less toxic or non-toxic alternative?

Then, choose a product that conforms to your intended use.

The U.S. Environmental Protection Agency (EPA) and the wood-treating industry have established guidelines for using treated wood. These guidelines, published as Consumer Information Sheets, are available from lumber suppliers. Ask for them where you purchase your lumber.

Types of wood treatments

More toxic

The following types of treated wood are still in use or commonly found in structures undergoing renovation or demolition. They are generally more toxic; use them only when necessary.

- **Chromated copper arsenate (CCA)** While residential use of CCA was voluntarily discontinued in 2003, you may still find CCA-treated wood in industrial uses. You may also find treated wood, including CCA, in buildings undergoing renovation or demolition.

Minnesota Pollution Control Agency • 520 Lafayette Rd. N., St. Paul, MN 55155-4194 • www.pca.state.mn.us
651-296-6300 • 800-657-3864 • TTY 651-282-5332 or 800-657-3864 • Available in alternative formats

- **Pentachlorophenol** (PCP or 'penta')
  Commonly used for utility poles.
- **Creosote**
  Commonly used for railroad ties and construction pilings.

Less toxic

Although the following types of wood treatments are generally less toxic, they still may present a risk to the environment and human health. Some of these types are available for limited use only:

- Alkaline copper quaternary (ACQ)
- Ammoniacal copper zinc arsenate (ACZA)
- Azole compounds, including copper azole (CBA-A and CA-B), cyproconazole, and propiconazole
- Borate compounds, including disodium octaborate tetrahydrate (DOT)
- Copper dimethyldithiocarbamate (CDDC)
- Copper naphthenate
- Micronized copper-based compounds (MCQ, MCA, and µCA-C)
- Copper-8-quinolate (Oxine copper or Oxine-Cu)
- Copper dimethyldithiocarbamate (CDDC)
- Bis-N-cyclohexyldiazeniumdioxy copper (Copper HDO, Cu-HDO, or CX-A)

Use guidelines

Guidelines for the use of any treated wood include:

- Use the smallest amount of treated wood necessary.
- Do not use any type of treated wood for applications in which the wood will come into direct or indirect contact with drinking water supplies. Incidental contact is acceptable. An example of incidental contact is in docks or bridges, where treated wood is used for decking and not pilings. Less toxic alternatives exist for many of these uses; choose them whenever possible.
- Do not use any type of treated wood where the wood will come into contact with human or animal food or with beehives. Examples of uses to avoid include cutting boards, countertops, animal bedding, feed bunks, and mulch.
- Do not use CCA-, PCP-, or creosote-treated wood for residential use, for playground equipment, or in any use in which it may come into contact with domestic animal or livestock drinking water.
- If you raise organic crops or livestock, carefully review your certification standards. Treated wood use is heavily restricted by most organic certification standards and agencies.

Handling precautions

To protect your health, be careful when handling treated wood. Ensure all employees and others near the treated wood-handling area are properly protected.

- Wear gloves when handling treated wood.
- Wash hands and exposed areas thoroughly before eating, drinking, using the bathroom, or using tobacco products after handling treated wood.
- Wear a properly fitted dust mask and eye protection when cutting, drilling, and sanding treated wood.
- When possible, perform work that may generate treated wood dust or particles outside.
- Launder clothing worn when handling treated wood separately from other laundry.
- Contain and collect all dust, particles, and debris from treated wood. When disposing of this waste, follow the guidance in the 'Disposal requirements' section below.

Reuse and recycling

You may reuse treated wood as structural lumber as long as it is in good condition and you follow the use guidelines and handling precautions discussed in this document.

Do not recycle treated wood into mulch, compost, any type of fuel, or other wood- or fiber-based products nor use it as fill material without a specific beneficial use approval from the MPCA.

Do not burn treated wood at any residence or business either for fuel or for disposal, except for permitted solid waste incinerators.

Disposal requirements

Do not dispose of treated wood at a demolition landfill in Minnesota, even if evaluation shows it to be nonhazardous. Rather, segregate treated wood from other demolition debris and dispose of it at a permitted, lined, industrial or mixed solid waste landfill.

Do not chip, grind, burn, or bury treated wood for disposal.

Do not donate or sell treated wood for any prohibited use.

In Minnesota, the following items may be disposed of in a permitted, lined, industrial or mixed solid waste landfill provided the landfill operator is notified and approves the disposal. In this case, you do not need to evaluate to determine whether the waste is hazardous.

- Treated wood used for structural lumber (includes wood treated with all of the compounds discussed above)
- Dust, particles, and debris generated as a result of its structural use

Before disposing of treated wood used for other purposes, such as mulch or fiber-based products, evaluate and document that it is not a hazardous waste. If you do not evaluate, manage it as a fully-regulated hazardous waste. For more information on evaluating wastes, see MPCA hazardous waste fact sheet #1.01, Evaluate Waste; Determine Generator Size, available on the MPCA's Hazardous Waste Publications Web page at www.pca.state.mn.us/waste/pubs/business.html.

More information

Metropolitan counties and the Minnesota Pollution Control Agency have staff available to answer waste management questions. For more information, contact your metropolitan county hazardous waste office or the MPCA office closest to your county.

The Minnesota Technical Assistance Program (MnTAP) has staff who are able to help you find ways to improve efficiency and reduce waste.

Metro County Hazardous Waste Offices

Anoka 763-422-7093
Carver 952-361-1800
Dakota 952-891-7557
Hennepin 612-348-3777
Ramsey 651-266-1199
Scott County 952-496-8475
Washington County 651-430-6655
Web sites ..... www.co.[county].mn.us

Minnesota Pollution Control Agency

Toll free (all offices)..... 1-800-657-3864
Brainerd 218-828-2492
Detroit Lakes 218-847-1519
Duluth 218-723-4660
Mankato 507-389-5977
Marshall 507-537-7146
Rochester 507-285-7343
St. Paul 651-296-6300
Willmar 320-214-3786
Web site .....www.pca.state.mn.us

Minnesota Technical Assistance Program

Toll-free..... 1-800-247-0015
Metro area 612-624-1300
Web site.....www.mntap.umn.edu

TOXICOLOGICAL PROFILE FOR WOOD CREOSOTE, COAL TAR CREOSOTE, COAL TAR, COAL TAR PITCH, AND COAL TAR PITCH VOLATILES

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2002

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can Creosote Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to Creosote?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (404) 498-0057
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Gangadhar Choudhary, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Mario J. Citra, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

A. Rosa McDonald, Ph.D
Syracuse Research Corporation, North Syracuse, NY

Antonio Quiñones-Rivera, M.S.
Syracuse Research Corporation, North Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for creosote. The panel consisted of the following members:

1. Dr. Gary Pascoe, EA Engineering, Science and Technology Inc., 210 Taylor Street, Room 15, Port Townsend, Washington 98368;

2. Dr. Norman Trieff, University of North Texas, Health Science Center at Fort Worth, 35 Camp Bowie Boulevard, Fort Worth, Texas 76107-2699; and

3. Dr. David Warshawsky, University of Cincinnati, Environmental Health, Kettering 137, Cincinnati, Ohio 45267-0056.

These experts collectively have knowledge of creosote's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

CONTENTS

FOREWORD v

QUICK REFERENCE FOR HEALTH CARE PROVIDERS vii

CONTRIBUTORS ix

PEER REVIEW xi

LIST OF FIGURES xvii

LIST OF TABLES xix

1. PUBLIC HEALTH STATEMENT 1
   1.1 WHAT IS CREOSOTE? 1
   1.2 WHAT HAPPENS TO CREOSOTE WHEN IT ENTERS THE ENVIRONMENT? 3
   1.3 HOW MIGHT I BE EXPOSED TO CREOSOTE? 5
   1.4 HOW CAN CREOSOTE ENTER AND LEAVE MY BODY? 6
   1.5 HOW CAN CREOSOTE AFFECT MY HEALTH? 7
   1.6 HOW CAN CREOSOTE AFFECT CHILDREN? 8
   1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CREOSOTE? 10
   1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CREOSOTE? 13
   1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 14
   1.10 WHERE CAN I GET MORE INFORMATION? 15

2. RELEVANCE TO PUBLIC HEALTH 17
   2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CREOSOTE IN THE UNITED STATES 17
      2.1.1 Wood Creosotes 17
      2.1.2 Coal Tar and Coal Tar Products 17
   2.2 SUMMARY OF HEALTH EFFECTS 20
      2.2.1 Wood Creosotes 20
      2.2.2 Coal Tar and Coal Tar Products 21
   2.3 MINIMAL RISK LEVELS 23

3. HEALTH EFFECTS 27
   3.1 INTRODUCTION 27
   3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 27
      3.2.1 Inhalation Exposure 30
         3.2.1.1 Death 42
         3.2.1.2 Systemic Effects 45
         3.2.1.3 Immunological and Lymphoreticular Effects 54
         3.2.1.4 Neurological Effects 55
         3.2.1.5 Reproductive Effects 55
         3.2.1.6 Developmental Effects 56
         3.2.1.7 Cancer 57
      3.2.2 Oral Exposure. 63

3.2.2.1 Death . . . 64
3.2.2.2 Systemic Effects . . . 86
3.2.2.3 Immunological and Lymphoreticular Effects . . . 101
3.2.2.4 Neurological Effects . . . 102
3.2.2.5 Reproductive Effects . . . 103
3.2.2.6 Developmental Effects . . . 105
3.2.2.7 Cancer . . . 107
3.2.3 Dermal Exposure . . . 111
3.2.3.1 Death . . . 112
3.2.3.2 Systemic Effects . . . 113
3.2.3.3 Immunological and Lymphoreticular Effects . . . 131
3.2.3.4 Neurological Effects . . . 132
3.2.3.5 Reproductive Effects . . . 132
3.2.3.6 Developmental Effects . . . 134
3.2.3.7 Cancer . . . 135
3.4 TOXICOKINETICS . . . 154
3.4.1 Absorption . . . 154
3.4.1.1 Inhalation Exposure . . . 154
3.4.1.2 Oral Exposure . . . 157
3.4.1.3 Dermal Exposure . . . 158
3.4.2 Distribution . . . 161
3.4.2.1 Inhalation Exposure . . . 162
3.4.2.2 Oral Exposure . . . 163
3.4.2.3 Dermal Exposure . . . 164
3.4.3 Metabolism . . . 164
3.4.3.1 Inhalation Exposure . . . 167
3.4.3.2 Oral Exposure . . . 168
3.4.3.3 Dermal Exposure . . . 169
3.4.4 Elimination and Excretion . . . 172
3.4.4.1 Inhalation Exposure . . . 173
3.4.4.2 Oral Exposure . . . 175
3.4.4.3 Dermal Exposure . . . 177
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models . . . 179
3.5 MECHANISMS OF ACTION . . . 181
3.5.1 Pharmacokinetic Mechanisms . . . 181
3.5.2 Mechanisms of Toxicity . . . 184
3.5.3 Animal-to-Human Extrapolations . . . 185
3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS . . . 185
3.7 CHILDREN'S SUSCEPTIBILITY . . . 189
3.8 BIOMARKERS OF EXPOSURE AND EFFECT . . . 193
3.8.1 Biomarkers Used to Identify or Quantify Exposure to Creosote . . . 195
3.8.2 Biomarkers Used to Characterize Effects Caused by Creosote . . . 196
3.9 INTERACTIONS WITH OTHER CHEMICALS . . . 196
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE . . . 197
3.11 METHODS FOR REDUCING TOXIC EFFECTS . . . 199
3.11.1 Reducing Peak Absorption Following Exposure . . . 199
3.11.2 Reducing Body Burden . . . 200
3.11.3 Interfering with the Mechanism of Action for Toxic Effects . . . 201
3.12 ADEQUACY OF THE DATABASE . . . 201
3.12.1 Existing Information on Health Effects of Creosote . . . 202

3.12.2 Identification of Data Needs . . . 204
3.12.3 Ongoing Studies . . . 213

4. CHEMICAL AND PHYSICAL INFORMATION . . . 216
4.1 CHEMICAL IDENTITY . . . 216
4.2 PHYSICAL AND CHEMICAL PROPERTIES . . . 216
4.2.1 Wood Creosote . . . 216
4.2.2 Coal Tar Creosote, Coal Tar, and Coal Tar Pitch . . . 220

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL . . . 232
5.1 PRODUCTION . . . 232
5.2 IMPORT/EXPORT . . . 233
5.3 USE . . . 233
5.4 DISPOSAL . . . 237

6. POTENTIAL FOR HUMAN EXPOSURE . . . 240
6.1 OVERVIEW . . . 240
6.2 RELEASES TO THE ENVIRONMENT . . . 242
6.2.1 Air . . . 246
6.2.2 Water . . . 247
6.2.3 Soil . . . 248
6.3 ENVIRONMENTAL FATE . . . 249
6.3.1 Transport and Partitioning . . . 250
6.3.2 Transformation and Degradation . . . 252
6.3.2.1 Air . . . 252
6.3.2.2 Water . . . 253
6.3.2.3 Sediment and Soil . . . 255
6.3.2.4 Other Media . . . 257
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT . . . 257
6.4.1 Air . . . 257
6.4.2 Water . . . 257
6.4.3 Sediment and Soil . . . 258
6.4.4 Other Environmental Media . . . 260
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE . . . 261
6.6 EXPOSURES OF CHILDREN . . . 269
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES . . . 272
6.8 ADEQUACY OF THE DATABASE . . . 274
6.8.1 Identification of Data Needs . . . 274
6.8.2 Ongoing Studies . . . 279

7. ANALYTICAL METHODS . . . 282
7.1 BIOLOGICAL MATERIALS . . . 282
7.2 ENVIRONMENTAL SAMPLES . . . 286
7.3 ADEQUACY OF THE DATABASE . . . 294
7.3.1 Identification of Data Needs . . . 294
7.3.2 Ongoing Studies . . . 296

8. REGULATIONS AND ADVISORIES . . . 298

9. REFERENCES . . . 302

10. GLOSSARY 348

APPENDICES

D. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS A-1

E. USER'S GUIDE B-1

F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS C-1

G. INDEX D-1

LIST OF FIGURES

2-1 Origin of Wood Creosotes and Coal Tar Products 18

3-1 Levels of Significant Exposure to Creosote—Inhalation 38

3-2 Levels of Significant Exposure to Creosote—Oral 71

3-3 Levels of Significant Exposure to Wood Creosote—Oral 82

3-4 Proposed Metabolic Scheme for Benzo[a]pyrene 165

3-5 Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance 182

3-6 Existing Information on Health Effects of Creosote 203

6-1 Frequency of NPL Sites with Creosote Contamination 241

LIST OF TABLES

3-1 Levels of Significant Exposure to Creosote—Inhalation 31

3-2 Levels of Significant Exposure to Creosote—Oral 65

3-3 Levels of Significant Exposure to Wood Creosote—Oral 75

3-4 Levels of Significant Exposure to Creosote—Dermal 114

3-5 Levels of Significant Exposure to Wood Creosote—Dermal 119

3-6 Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vivo* 150

3-7 Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vitro* 152

4-1 Chemical Identity of Wood Creosote 217

4-2 Chemical Identity of Coal Tar Creosote 218

4-3 Chemical Identity of Coal Tar 219

4-4 Identity of Major Components of Wood Creosote 221

4-5 Physical and Chemical Properties of Wood Creosote 222

4-6 Identity of PAH Components of Coal Tar Pitch 224

4-7 Physical and Chemical Properties of Coal Tar Creosote 225

4-8 Physical and Chemical Properties of Coal Tar 230

5-1 Facilities that Produce, Process, or Use Coal Tar Creosote 234

5-2 Import/Export Volumes for Creosote 236

6-1 Releases to the Environment from Facilities that Produce, Process, or Use Coal Tar Creosote 244

7-1 Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Biological Samples 284

7-2 Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Environmental Samples 287

8-1 Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles 299

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Coal tar creosote, coal tar, and coal tar pitch have been found in at least 46 of the 1,613 current or former NPL sites. However, the total number of NPL sites evaluated for these substances is not known. As more sites are evaluated, the sites at which coal tar creosote, coal tar, and coal tar pitch are found may increase. This information is important because exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS CREOSOTE?

Creosote is the name used for a variety of products that are mixtures of many chemicals. Wood creosotes are derived from the resin from leaves of the creosote bush (*Larrea*, referred to herein as creosote bush resin) and beechwood (*Fagus*, referred to herein as beechwood creosote). Coal tars are by-products of the carbonization of coal to produce coke or natural gas. Coal tar

creosotes are distillation products of coal tar, and coal tar pitch is a residue produced during the distillation of coal tar. Coal tar pitch volatiles are compounds given off from coal tar pitch when it is heated. Coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles are rarely formed in nature. Coal tar creosote, coal tar, and coal tar pitch are mixtures of similar compounds. For this reason, many times throughout the profile, we will refer to coal tar creosote, coal tar, and coal tar pitch simply as creosote. Creosotes are created by high-temperature treatment of beech and other woods (beechwood creosote) or coal (coal tar creosote), or from the resin of the creosote bush (creosote bush resin). Wood creosote is a colorless to yellowish greasy liquid with a characteristic smoky odor and sharp burned taste. It is relatively soluble in water. Creosote prepared from coal tar is the most common form of creosote in the workplace and at hazardous waste sites in the United States. Coal tar creosote is a thick, oily liquid that is typically amber to black in color. It is easily set on fire and does not dissolve easily in water. Coal tar and coal tar pitch are the by-products of the high-temperature treatment of coal to make coke or natural gas. They are usually thick, black or dark brown liquids or semisolids with a smoky or aromatic odor. Coal tar residues can also be found in the chimneys of homes heated with coal, especially if insufficient oxygen is present. Chemicals in the coal tar pitch can be given off into the air as coal tar pitch volatiles when coal tar pitch is heated.

Beechwood creosote has been used as a disinfectant, a laxative, and a cough treatment. In the past, treatments for leprosy, pneumonia, and tuberculosis also involved eating or drinking beechwood creosote. It is rarely used today in the United States by doctors since it has been replaced by better medicines, and it is no longer produced by businesses in the United States. It is still available as an herbal remedy, and is used as an expectorant and a laxative in Japan. The major chemicals in beechwood creosote are phenol, cresols, and guaiacol.

Coal tar creosote is the most widely used wood preservative in the United States. It is also a restricted-use pesticide, so it can be used only by people who have been trained to use it safely. Coal tar products are ingredients in medicines used to treat skin diseases such as psoriasis. These products are also used as animal and bird repellents, insecticides, animal dips, and fungicides. Coal tar, coal tar pitch, and coal tar pitch volatiles are used or produced in several

industries, including road paving, roofing, aluminum smelting, rubber producing, and coking. The major chemicals in coal tar creosote, coal tar, and coal tar pitch that can cause harmful health effects are polycyclic aromatic hydrocarbons (PAHs), phenol, and cresols. Coal tar pitch volatiles vary depending on the makeup of the coal tar product that is being heated. About 300 chemicals have been identified in coal tar creosote, but as many as 10,000 other chemicals may be in this mixture. Because coal tar creosote is the major type found in the environment and at hazardous waste sites in the United States, we will emphasize its effects on human health in this profile. The health effects of coal tar and coal tar pitch will also be described.

This profile is specifically about the toxicity of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, so we will not discuss in detail the health effects of individual chemicals in them, such as PAHs or phenol. In the chapters describing what happens to creosote in the environment and exposure to creosote, we will discuss some of the individual chemicals or groups of chemicals (such as PAHs) because many of the tests done in the scientific laboratories can tell us which of these chemicals are present in the soil, water, and air.

The Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (1995), the ATSDR *Toxicological Profile for Cresols* (1992), and the ATSDR *Toxicological Profile for Phenol* (1998) provide more information on these chemicals. For more information on the chemical and physical properties of creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles, see Chapter 4. For more information on these substances in the environment, see Chapters 5 and 6.

1.2 WHAT HAPPENS TO CREOSOTE WHEN IT ENTERS THE ENVIRONMENT?

No information is available on what happens to wood creosote when it enters the environment. Coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles do not occur in the environment naturally, but are by-products produced in coke or gas manufacturing plants using high-temperature processes. Coal tar creosote is released to water and soil mainly as a result of its use in the wood preservation industry. In the past, waste water from wood-treatment facilities was often discharged to unlined lagoons where it formed a sludge. Also, companies that

preserve wood with coal tar creosote may treat their water wastes in treatment plants or release the waste water to the municipal water treatment system. This is still the largest source of coal tar creosote in the environment. However, new restrictions from EPA have caused changes in the treatment methods that have decreased the amount of creosote available to move into soil from waste water effluents. Coal tar creosote contains some components that dissolve in water and some that do not. Coal tar creosote components that dissolve in water may move through the soil to eventually reach and enter the groundwater, where they may persist. Once in the groundwater, breakdown may take years. Most of the components that are not water soluble will remain in place in a tar-like mass. Migration from the site of contamination is not extensive. Breakdown in soil can take months for some components of coal tar creosote, and much longer for others. Sometimes, the small amounts of chemical remaining in the soil or water that take a long time to break down are still toxic to some animals and possibly to humans. Coal tar creosote components may also be found in the soil as a result of leaking or seeping from treated timber. More complete information on how creosote enters the environment and what happens to creosote in the environment can be found in Chapters 5 and 6 of this profile.

Volatile chemicals in coal tar creosote may evaporate and enter the air. About 1–2% of the coal tar creosote applied to treated wood is released to the air. This is a small amount compared with the amount of coal tar creosote found in waste water or soil. Volatile chemicals in coal tar and coal tar pitch are released into the environment in a similar way. They are most often found in and around coke- or natural gas-producing factories, in industrial plants where coal tar and coal tar sludges are used, or at abandoned coke or gas factory sites. Water or soil surrounding these areas may contain detectable levels of coal tar or coal tar pitch.

Once coal tar creosote is in the environment, both plants and animals can absorb parts of the creosote mixture. Some components of coal tar creosote have been found in plants exposed to creosote-treated wood in nearby soil. The plants absorb very little (less than 0.5% of the amount available to the plant). Animals such as voles, crickets, snails, pill bugs, and worms take up coal tar creosote components from the environment that are passed into the body through skin, lungs, or stomachs. Animals that live in the water, such as crustacea, shellfish, and worms, also take up coal tar creosote compounds. For instance, mussels attached to creosote-treated pilings and

snails and oysters living in water near a wood-treatment plant had creosote in their tissues. Coal tar creosote components are also broken down by microorganisms living in the soil and natural water. The components of coal tar and coal tar pitch move in the environment in a similar way.

1.3 HOW MIGHT I BE EXPOSED TO CREOSOTE?

Most people are exposed to very low levels of creosote. People who are exposed to higher concentrations than the general population are those exposed to creosote in their jobs and those who use products that contain creosote to improve a health problem such as eczema or psoriasis.

Some people are exposed to creosote by using shampoos for psoriasis that contain creosote. Herbal remedies containing the leaves from the creosote bush (chaparral) are available as a dietary supplement and are a source of exposure to wood creosote. People who drink chaparral tea could be exposed to wood creosote. Hazardous waste sites are a major source of contamination with creosote, coal tar, and coal tar pitch. Individuals working in the wood-preserving industry make up the largest part of the population that might be exposed to coal tar creosote. Individuals who live in areas that used to be sites of wood-preserving facilities may be exposed if the soil was never cleaned up. The most common way that creosote will enter the body when it is present in soils is through the skin. In addition, children may also ingest creosote if they put their unwashed hands in their mouths after touching soil or wood contaminated with creosote. The most common way that it will enter the body for individuals in the wood-preserving industry is through the lungs.

Asphalt workers; rubber, aluminum, iron, steel, and tire factory workers; and people working in the coke-producing industries are also at risk for potential exposure to coal tar pitch and coal tar pitch volatiles. They may breathe in vapors from or have direct skin contact with wood-preservation solutions, freshly treated wood, asphalt mixtures, or other products of coke-producing industries. Workers who use creosote-treated wood in building fences, bridges, or railroad tracks or installing telephone poles may be exposed; those who inspect or maintain these materials, or apply asphalt or other coal tar pitch-containing materials, may also be exposed. Homeowners, farmers, or landscapers who apply coal tar creosote to wood in noncommercial

settings using a brush or dip procedure (which is no longer allowed by law unless you have been trained to safely use creosote as a wood preservative), or who use railroad ties or telephone poles in landscaping, or who reclaim scrap lumber from a treated structure may also be exposed. In addition, people who work or live in treated-wood houses (log cabins) may be exposed through the air or by direct contact with the wood. Exposure to coal tar products may also occur in the natural gas and aluminum smelting industries. You can be exposed by any contact with water, soil, air, or plant and animal tissues that contain creosotes, coal tar, coal tar pitch, or its volatile components. Intentional or accidental eating of coal tar creosote has resulted in poisoning. If your activities bring you into contact with these mixtures, such as at hazardous waste sites, in contaminated groundwater, in wood products treated with creosote, or in contaminated shellfish, you will be exposed to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles.
You can also be exposed by drinking water contaminated by a hazardous waste site. For more information on human exposure to these substances, see Chapter 6.

1.4 HOW CAN CREOSOTE ENTER AND LEAVE MY BODY?

Creosotes and coal tar products can enter your body through the lungs, stomach, intestines, and skin. No information that describes how fast or how much creosote or its components might enter the body after one or many exposures is available. The amount that enters the body depends on how you come in contact with it (via air, food, water, skin), how much of the mixture is present, and how long you are exposed to it. Many of the parts of the coal tar creosote mixture (for example, PAHs) are rapidly absorbed through the lungs, stomach, and intestines. Prolonged exposure through the skin, without washing, may increase the amount of the creosotes or coal tar products that pass into the bloodstream. Individual components of coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles may be stored in body fat. In the body, some coal tar components may be metabolized. For example, pyrene can be metabolized to 1-hydroxypyrene. Some studies indicate that creosotes may cross the placenta into the tissue of the developing fetus. Because coal tar products may be stored in body fat, they may be found in breast milk. Creosotes leave the body primarily in the stool; a smaller amount leaves the body in the urine. See Chapter 3 for more information on how creosotes and coal tar products enter and leave the body.

1.5 HOW CAN CREOSOTE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

Exposure to creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles may be harmful to your health. Eating food or drinking water contaminated with a high level of these compounds may cause a burning in the mouth and throat as well as stomach pain. Taking herbal remedies containing creosote bush leaves may result in damage to the liver or kidney. Reports describing poisoning in workers exposed to coal tar creosote, or in people who accidentally or intentionally ate coal tar creosote prove that these chemicals can be harmful. These reports indicate that brief exposure to large amounts of coal tar creosote may result in a rash or severe irritation of the skin, chemical burns of the surfaces of the eye, convulsions and mental confusion, kidney or liver problems, unconsciousness, or even death. Longer exposure to lower levels of coal tar creosote, coal tar, coal tar pitch or coal tar pitch volatiles by direct contact with the skin or by exposure to the vapors from these mixtures can also result in increased sensitivity to sunlight, damage to the cornea, and skin damage such as reddening, blistering, or peeling. Longer exposures to the vapors of the creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles can also cause irritation of the respiratory tract. Skin cancer and cancer of the scrotum have also resulted from long exposure to low levels of these chemical mixtures, especially through direct contact with the skin during wood treatment or manufacture of coal tar creosote-treated products, or in coke or natural gas factories. Prolonged skin exposure to soot and coal tar creosote has been associated with cancer of the scrotum in chimney sweeps. These levels are much higher than the levels that you are likely to be exposed to in groundwater, food, air, or soil.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and

compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Rats and mice fed a large amount of wood creosote at one time had convulsions and died. Rats fed a smaller amount of wood creosote for a long period developed kidney and liver problems, and died. Exposure to coal tar products through the skin has resulted in skin cancer in animals. Laboratory animals that ate food containing coal tar developed cancer of the lungs, liver, and stomach, and animals exposed to coal tar in the air developed lung and skin cancer.

The International Agency for Research on Cancer (IARC) has determined that coal tar is carcinogenic to humans and that creosote is probably carcinogenic to humans. EPA has also determined that coal tar creosote is a probable human carcinogen.

1.6 HOW CAN CREOSOTE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Children are generally exposed to very low levels of creosote, but intentional or accidental eating of coal tar creosote has resulted in poisoning. Children who live in hazardous waste areas contaminated with creosote may be exposed by drinking contaminated water or from contact with soil. The most common way that creosote will enter the body when it is present in soils is through the skin. However, children may also swallow creosote if they eat dirt or put their unwashed hands in their mouths after touching soil or wood contaminated with creosote. In addition, children may be exposed to creosote compounds if they eat fish and shellfish from contaminated areas. Children may also be exposed to creosote if they use products that contain creosote to improve a health problem such as dandruff, eczema, or psoriasis, or if they are given an herbal remedy containing the leaves from the creosote bush (chaparral).

Children may also be exposed to creosote if they breathe in vapors from or have direct skin contact with freshly treated wood found in fences, bridges, railroad ties, or telephone poles. In

addition, children who live in treated-wood houses (log cabins) may be exposed through the air or by direct contact with the wood. The use of creosote to protect wooden playground equipment or wooden decks for the yard is not recommended, but children may be exposed to creosote if it has been applied to wood in or around the home in the past. Children could also be exposed to creosote on their parent's clothing or shoes if these have been contaminated with creosote at the workplace. Children are not more likely to be exposed to creosote than adults, and there is no unique exposure of children to creosote.

Children who played on soil contaminated with creosote had more skin rashes than children who played in uncontaminated areas. Apart from this, the health effects of creosote have not been studied in children, but they would likely experience the same health effects seen in adults exposed to creosote. We do not know whether children differ from adults in their susceptibility to health effects from creosote. Children could be more susceptible to cancer because they might have a longer time in which to develop it, but this association has not been studied.

No effects have been reported for children exposed to creosote before birth. Experiments in laboratory animals have shown birth defects, such as cleft palates, in the young of mothers exposed to high levels of creosote during pregnancy, but whether creosote could induce such defects in humans is not known. Some animal studies indicate that creosotes may cross the placenta into the tissue of the developing fetus. Because chemical components of coal tar may be stored in body fat, they may be found in breast milk and therefore could be transferred to newborns and infants. For more information on the effects of creosote on children, see Section 3.7.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CREOSOTE?

If your doctor finds that you have been exposed to significant amounts of creosote, coal tar, coal tar pitch, or coal tar pitch volatiles, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Families may reduce the risk of exposure to coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles in several ways if they find that they are at risk of such exposures. If you live in a residential area that used to have a wood preservation facility or gas manufacturing plant located nearby, you should use precautions to decrease or limit your exposure to creosote that may be present in the soil or water. This may include wearing long-sleeved shirts and long pants when working or playing outside and avoiding using water contaminated with creosote. If the soil in your yard was contaminated by creosote in the past, you should probably not grow food in it. You will need to wash your hands and any other exposed skin carefully after you are in contact with the contaminated soil or water outside. This is especially true for children since they have a tendency to put their hands in their mouths. Some children eat a lot of dirt. It is not fully understood how much of the creosote bound to dirt may come off the dirt when it is inside your body. You should discourage children from eating dirt. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or from engaging in other hand-to-mouth activity.

Children may be exposed to creosote during their outdoor play activities. You should encourage your children not to play in contaminated areas, particularly in those that may be abandoned waste sites or waste sites undergoing cleanup. Some children will ignore signs posted at the sites that alert the public to possible dangers and declare the areas off limits. Encourage your children to follow the instructions on the signs and to play elsewhere. Children may come into contact with creosote-treated wood when playing on or near railroad tracks, in ditches close to utility poles, in old barns or other farm structures, or on bridges or piers. Children may also be exposed to creosote through ingestion if they chew or place their mouths on creosote-treated objects such as fence posts or pier railings. You should discourage your children from such behavior and from putting foreign objects in their mouths.

Drinking chaparral tea may result in exposure to wood creosote by swallowing. If you drink chaparral tea you may expose your children. Creosote is also found in coal tar shampoos used for anti-dandruff therapy, in coal tar ointments used for treatment of eczematous dermatitis and in mineral coal tar for the treatment of psoriasis. You may expose your children to creosote if you use any of these products. Ask your doctor to suggest alternative treatments that do not involve the use of these products.

It is sometimes possible to carry creosote into the home on work clothing or shoes that may have been exposed to coal tar creosote, coal tar, or coal tar pitch at the workplace. This may be of more importance for people who work in the wood-preserving industry or in jobs such as roofing, paving, and chimney cleaning than for people who work in the coking industry, or in other plants that use coal tar-derived products and for which the main route of exposure is through breathing in contaminated dust. You can contaminate your car, home, or other locations outside work where children might be exposed to creosote. You should know about this possibility if you work with creosote. Long-term exposure to low levels of creosote through direct contact with skin has resulted in skin cancer. For workers in wood preservation facilities, the American Wood Preservers Institute (AWPI) recommends washing work clothes separately from other household clothing if oily creosote residues or sawdust from creosote-treated wood are present on the clothes. Adults with contaminated work clothes should wash them before reusing them. If you work in an industry in which creosote is used, your occupational health and safety officer at work should tell you whether this or other chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Your employer should have Material Safety Data Sheets (MSDSs) for many of the chemicals used at your place of work, as required by the Occupational Safety and Health Administration (OSHA). Information on these sheets should include chemical names and hazardous ingredients, important properties (such as fire and explosion data), potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in an emergency. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your OSHA-

approved state occupational safety and health program or OSHA can answer any further questions and help your employer identify and correct problems with hazardous substances. Your OSHA-approved state occupational safety and health program or OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to optimal safety and health on the job without fear of punishment.

Your children may be exposed to creosote compounds by eating certain types of fish and shellfish caught from certain locations. Certain states, American Indian tribes, and U.S. territories have issued freshwater fish advisories to warn people about creosote-contaminated fish. Each state, American Indian tribe, or U.S. territory sets its own criteria for issuing fish advisories. A fish advisory will specify which bodies of water have restrictions. The advisory will tell you what types and sizes of fish are of concern. The advisory may completely ban eating fish or tell you to limit your meals of a certain fish type. For example, an advisory may tell you to eat a certain type of fish no more than once a month. The advisory may tell you to eat only certain parts of the fish and how to prepare or cook the fish to decrease your exposure to creosote. The fish advisory may be stricter to protect pregnant women, nursing mothers, and young children. Chemicals in creosote have been found in breast milk and may cross the placenta. To reduce your child's exposure to creosote, obey fish advisories. Information on fish and wildlife advisories in your home state is available from your state health or natural resources department. Signs might also be posted in certain fishing areas.

Creosote is a restricted-use pesticide, meaning that it is only supposed to be applied by people who are trained to use it safely and who have been tested and approved to use it. It is not available over-the-counter for use in the home or garden. The AWPI does not recommend the use of creosote to protect wooden playground equipment or wooden decks for the yard. Other pesticides are generally used for preserving playground equipment and decks. Your children may be exposed to creosote if an unqualified person applies it to wood in or around your home, such as to sundecks or to wooden equipment your children play on. In some cases, the improper use of pesticides banned for use in homes has turned homes into hazardous waste sites. Make sure that any person you hire is licensed and, if appropriate (as is the case for creosote), certified to apply pesticides. Your state licenses each person who is qualified to apply pesticides

according to EPA standards and further certifies each person who is qualified to apply restricted-use pesticides. Ask to see the license and certification. Also ask for the brand name of the pesticide, an MSDS, the name of the product's active ingredient (the chemical that makes the pesticide work), and the EPA registration number. Ask whether EPA has designated the pesticide "for restricted use" and what the approved uses are. This information is important if you or your family react to the product.

If you feel sick after a pesticide has been used in your home, consult your doctor or local poison control center.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CREOSOTE?

No medical test will determine if you have been exposed to wood creosote, coal tar creosote, coal tar, coal tar pitch mixtures, or coal tar pitch volatiles. However, chemicals contained in creosote (such as PAHs or phenol) may be detected and measured in body tissues (organs, muscle, or fat), urine, or blood after exposure to creosote. Typically, this may be done for employees in industry who work with coal tar creosote, coal tar, and coal tar pitch to monitor their exposure. For example, the metabolite 1-hydroxypyrene, which can be detected in urine after exposure to pyrene, has been used to test for exposure to creosote because pyrene is a component of creosote. This test would determine only whether you have recently been exposed to pyrene, but cannot positively identify the source of the pyrene as creosote or accurately predict whether you will experience any adverse health effects. Moreover, analyses of urine samples for 1-hydroxypyrene are not normally done in a doctor's office because they require special equipment.

For more information on tests to measure coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles in the body, see Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the EPA, the OSHA, and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the ATSDR and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-be-exceeded levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-be-exceeded levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for creosote include the following:

On December 10, 1992, FDA issued a nationwide warning to consumers (FDA Press Release, P92-38) about chaparral, an herbal product derived from the leaves of the creosote bush, because of reports of acute toxic hepatitis after its use. The press release can be found at the FDA Web site, http://www.fda.gov.

Regulatory standards and guidelines for air and water exist for the most important individual PAHs and phenols contained in wood creosote, coal tar creosote, coal tar, and coal tar pitch. EPA has designated coal tar creosote a restricted-use pesticide. This means it can only be bought and used by certified applicators and only for those uses covered by the applicator's certification. In addition, coal tar creosote has been identified by EPA as a hazardous waste.

The federal government has developed regulatory standards and guidelines to protect workers from the potential health effects of other coal tar products in air. OSHA has set a Permissible Exposure Limit (PEL) of 0.2 milligrams of coal tar pitch volatiles per cubic meter of air (0.2 mg/m^3) in workroom air to protect workers during an 8-hour shift.

For more information on regulations and advisories for coal tar creosote, coal tar, and coal tar pitch exposure, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333
Web site: http://www.atsdr.cdc.gov

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: 1-404-498-0057

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CREOSOTE IN THE UNITED STATES

This profile addresses several substances: wood creosotes, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles. Figure 2-1 shows how these substances are produced.

Creosote has been identified in at least 46 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for creosote is not known. Of these sites, all 46 are located within the United States.

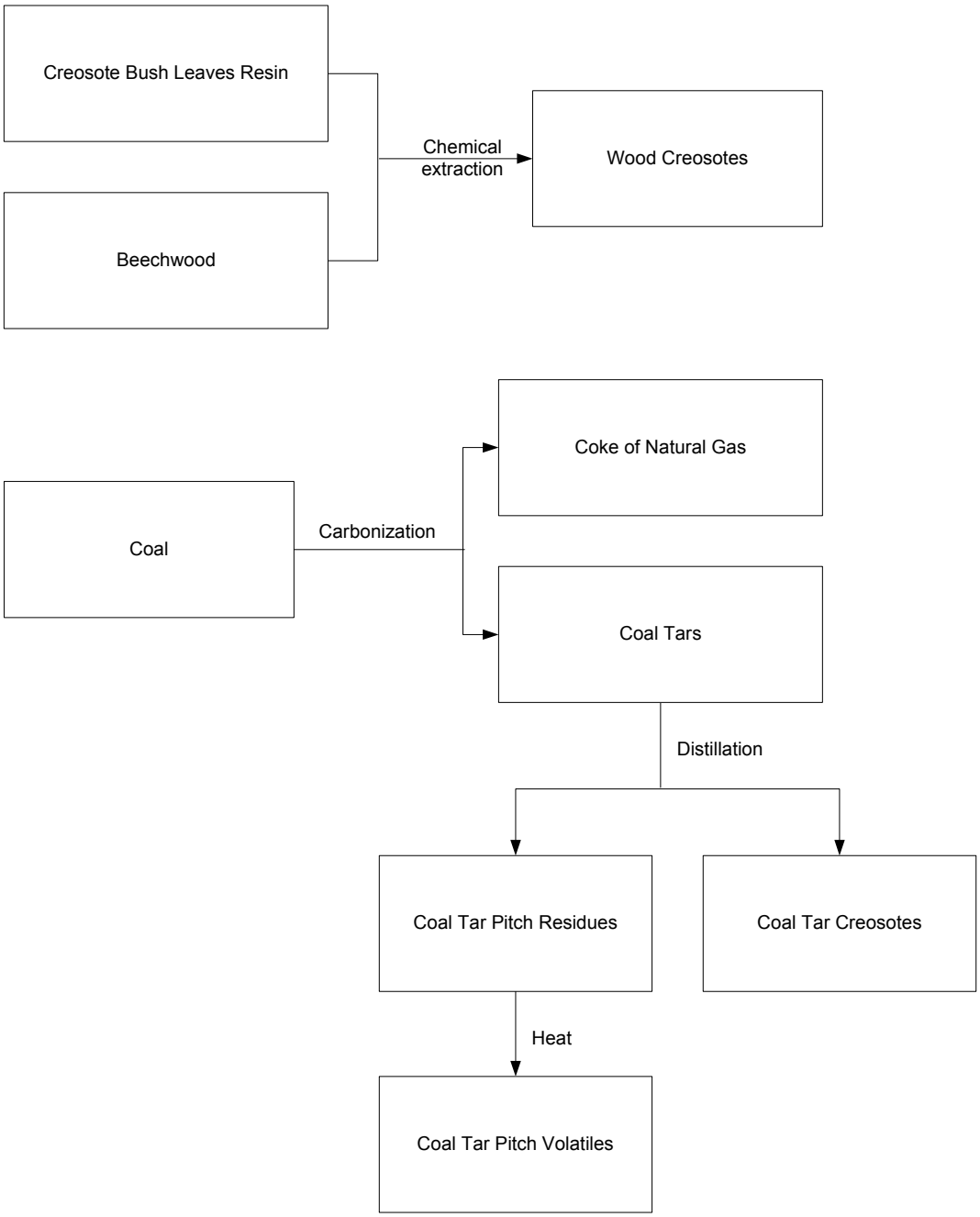
2.1.1 Wood Creosotes

Wood creosotes are derived from the resin from leaves of the creosote bush (*Larrea*, referred to herein as creosote bush resin) and beechwood (*Fagus*, referred to herein as beechwood creosote). Creosote bush resin consists of phenolic (e.g., flavonoids and nordihydroguaiaretic acid), neutral (e.g., waxes), basic (e.g., alkaloids), and acidic (e.g., phenolic acids) compounds. The phenolic portion comprises 83–91% of the total resin, while nordihydroguaiaretic acid accounts for 5–10% of the dry weight of the leaves. Extracts of the creosote bush are used in homeopathic medicine, and the leaves are used to make an infusion called chaparral. Beechwood creosote consists mainly of phenol, cresols, guaiacol, xylenol, and cresol. It is a colorless or pale yellowish liquid, and has a characteristic smoky odor and burnt taste. It had therapeutic applications in the past as a disinfectant, laxative, and stimulating expectorant, but it is not a major pharmaceutical ingredient today in the United States. Exposure to wood creosotes appears to be confined to dermal contact with the plants and ingestion of plant extracts such as chaparral.

2.1.2 Coal Tar and Coal Tar Products

Coal tars are by-products of the carbonization of coal to produce coke and/or natural gas. Coal tar creosotes are distillation products of coal tar, while coal tar pitch is a residue produced during the distillation of coal tar. Coal tar pitch volatiles are compounds given off from coal tar pitch when it is heated. Coal tar creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles are composed of many

Figure 2-1. Origin of Wood Creosotes and Coal Tar Products



individual compounds of varying physical and chemical characteristics. In addition, the composition of each, although referred to by specific name (e.g., coal tar creosote) is not consistent. For instance, the components and properties of the mixture depend on the temperature of the destructive distillation (carbonization) and on the nature of the carbon-containing material used as a feedstock for combustion.

Usually, coal tars are viscous liquids or semisolids that are black or dark brown with a naphthalene-like odor. Coal tars are complex combinations of polycyclic aromatic hydrocarbons (PAHs), phenols, heterocyclic oxygen, sulfur, and nitrogen compounds. PAH composition of coal tars is variable. Analyses of PAHs in four coal tar samples revealed 2- to 20-fold differences in concentration of selected PAHs among the samples. For example, benzo[a]pyrene ranged from nondetectable levels to 1.7, 3.9, and 6.4 g/kg of coal tar. By comparison, coal tar creosotes have an oily liquid consistency and range in color from yellowish-dark green to brown. The coal tar creosotes consist of PAHs and PAH derivatives. At least 75% of the coal tar creosote mixture is PAHs. Coal tar pitch is a shiny, dark brown-to-black residue that contains PAHs and their methyl and polymethyl derivatives, as well as heteronuclear compounds. Coal tar creosote, coal tar, and coal tar products are used as wood preservatives, herbicides, fungicides, insecticides, and disinfectants. Volatile components of the coal tar pitch can be given off during operations involving coal tar pitch, including transporting, and in the coke, aluminum, and steel industries.

There are no known natural sources of coal tar creosote. Coal tar creosote has been widely used as a wood-treatment pesticide since the turn of the 20th century, and workers in the wood-preserving industry have been exposed to coal tar creosote by the dermal and inhalation routes. Potential sources of non-occupational human exposure to coal tar creosote include contact with coal tar creosote-treated wood products (e.g., railroad ties used for landscaping), incineration of coal tar creosote-treated scrap lumber, contact with contaminated environmental media at hazardous waste sites (e.g., ingestion of contaminated groundwater), and the use of pharmaceutical products (e.g., shampoos) containing coal tar creosote. The EPA canceled all nonwood uses of coal tar creosote and restricted use of coal tar creosote products to certified applicators in January 1986. No information was found in the available literature regarding ambient atmospheric or water concentrations of coal tar creosote-derived components (i.e., PAHs) in the United States. PAHs have been measured in surface and subsurface soils around abandoned coal tar creosote wood treatment facilities at levels ranging from nondetectable to 1,000 ppm. Since coal tar creosotes are complex mixtures, techniques for relating apparent bioaccumulation or biomagnification in food chains to human health concerns are not well defined. Fish or shellfish directly exposed to coal tar creosote wastes will be tainted by offensive odors and tastes. In addition, fish and shellfish may

accumulate coal tar creosote constituents at concentrations high enough to prompt public health officials to issue consumption advisories. The potential for human exposure to coal tar creosote is discussed in detail in Chapter 6 of this profile.

2.2 SUMMARY OF HEALTH EFFECTS

2.2.1 Wood Creosotes

Exposure to wood creosotes appears to be confined to ingestion of plant extracts and dermal contact with the plants. Most of the toxicity data for oral exposure to wood creosotes comes from reports of individuals who ingested plant extracts such as chaparral, an herbal extract prepared by grinding leaves of the creosote bush, or "seirogan", a Japanese folk remedy made with wood creosote that is typically taken for stomachaches.

Several reports suggest that repeated exposure to chaparral is associated with adverse liver effects. There are isolated reports of renal failure, and of cystic renal disease and cystic adenocarcinoma of the kidney in individuals taking chaparral tea for periods ranging from 3 to 10 months. However, because of the limited amount of data, it is not possible to attribute the findings of renal effects to ingestion of chaparral tea. Cases of acute allergic dermatitis from dermal exposure to the creosote bush have been reported.

Information on health effects associated with the use of beechwood creosote is also very limited. It has been observed that the distribution of cancer cases in Japan coincided with "seirogan" production areas, but an association between cancer incidence in Japan and the use of "seirogan" cannot be made with the available data. It should be noted that beechwood creosote doses of up to 394 mg/kg/day in the diet for 96 weeks induced signs of toxicity in rats, but failed to produce treatment-related increases in the incidence of tumors. Organs examined for tumors include testis, ovary, pancreas, breast, thyroid and adrenal glands, lungs, and lymph nodes. Similar results were seen in a 52-week study with mice. In humans, dermal administration of beechwood tar for up to 8 weeks did not impair renal function or produce other adverse effects; however, animal studies suggest that long-term oral exposure to beechwood creosote has the potential to induce adverse effects in the kidney. The available data suggest that hepatic and dermal effects are the main adverse outcomes that result from oral or dermal exposure, respectively, to wood creosotes.

Hepatic Effects. Icterus, jaundice, abdominal pain, liver failure, acute toxic hepatitis, and elevated serum liver enzymes were among the effects reported in four individuals who repeatedly ingested chaparral capsules (160–1,500 mg chaparral/day) over a period ranging from 6 weeks to 10 months. Liver transplant was required for one of the patients. Elevated liver enzymes returned to normal levels 3–6 weeks after exposure to chaparral was discontinued. Increased liver-to-body weight ratio has been observed in rats and mice orally exposed to beechwood creosote for as little as 3 months. The effect was generally seen at doses >143 mg/kg/day. However, no treatment-related liver histopathological alterations were observed in these animals. These findings are relevant for individuals in the general population who ingest chaparral capsules or chaparral tea.

Dermal Effects. There are reports of seven cases of acute allergic dermatitis following contact with the creosote bush. The patients presented erythematous and vesicular dermatitis of the face, the upper part of the neck, and the backs of the hands. An allergic component to these reactions was confirmed by patch tests. Beechwood creosote has been found to irritate the periapical tissue (the connective tissue surrounding the apex of the tooth) in dogs 7 days after its application. Localized inflammatory changes and occasional abscess formation were observed in these animals. Application of birch tar to the ear of rabbits for 3 weeks was associated with the formation of comedones on the ear. These findings show that members of the general population who come into contact with the creosote bush may develop acute allergic reactions of the skin.

2.2.2 Coal Tar and Coal Tar Products

Exposures to coal tar and coal tar products may take place in industrial and non-industrial settings and can occur through a number of different routes of exposure. Information regarding the adverse human health effects of coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles is available from occupational surveys and retrospective health studies. Unfortunately, the usefulness of many of the occupational studies is hampered by incomplete characterization of worker exposure and the difficulty in ascribing adverse effects to a particular exposure route. Additional health effects information is available from the use of coal tar products in the medical treatment of psoriasis patients. There are no reports of adverse reproductive or developmental outcomes in humans exposed to coal tar and coal tar products. Sperm counts and sperm characteristics were found to be unaffected in workers exposed to coal tar pitch volatiles. Women treated with coal tar for psoriasis or dermatitis (ages at treatment were 18–35 years) did not exhibit an increase in spontaneous abortions or congenital disorders in their offspring. There were no changes in reproductive outcomes, such as number of pregnancies, live, premature, and still births, or

spontaneous abortions, among women who reside in a housing development built on contaminated land formerly occupied by a coal tar creosote wood treatment plant. Some studies have found adverse developmental effects in animals that were administered coal tar orally during gestation. There is, however, evidence of maternal toxicity in these studies. Estrogenic effects were not seen in mice orally administered coal tar creosote. The available information suggests that increased carcinogenicity risk and adverse dermal and respiratory effects are the most important health concerns related to exposure to coal tar and coal tar products.

Cancer. Studies of workers exposed to coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles in various industrial environments have found increased cancer risk involving a number of tissues including the respiratory tract, skin, lung, pancreas, kidney, scrotum, prostate, rectum, bladder, and central nervous system. Leukemia and lymphoma have also been diagnosed. These adverse effects are not apparent in patients undergoing coal tar therapy. Animal studies have demonstrated the carcinogenic potential of dermally-applied coal tar products. Less typical lesions include the development of cancer of the lip in a group of men involved in fishing net repair. These men typically held a creosote-laden wooden needle in their mouths during their work. Laboratory studies have found increases in mortality due to lung tumors in female Wistar rats exposed to coal tar pitch aerosol for 10 or 20 months. These findings are relevant to workers exposed to coal tar and coal tar products and individuals using coal tar therapeutically.

IARC has classified creosotes as a Group 2A mixture, probable human carcinogen, based on limited human evidence and sufficient animal evidence of carcinogenicity. IARC classified coal tar and coal tar pitches as Group 1 mixtures, carcinogenic to humans, based on sufficient evidence of human and animal carcinogenicity. EPA has classified creosote as a Group B1 probable human carcinogen, based on sufficient evidence from animal studies and limited evidence from human studies.

Dermal Effects. Dermal effects have been documented in populations occupationally and non-occupationally exposed to coal tar and coal tar products. In patients medically treated with 5% coal tar, dermal applications induced a photosensitizing effect in all patients within 30 minutes of treatment. The Texas Department of Health documented an increased incidence of skin rashes among residents of a housing development built on contaminated land formerly occupied by a coal tar creosote wood treatment plant. The rashes were associated with contact with the soil in the housing area. In workers exposed to coal tar and coal tar products, the observed dermal effects appear to be generally limited to unprotected areas such as the hands, face, and neck, including the posterior part of the neck. There is also a report of

erythematous, papular, and vesicular eruptions seen in the ankle region of men that came in contact with coal tar creosote from freshly coated wood. Most of the chemical burns reported in workers who handled wood treated with coal tar creosote are mild; however, the remainder can lead to subsequent pigmentation and desquamation. Dermal irritation, burning, erythema, dry peeling skin on the face and neck with irritation, and folliculitis on the forearms have been reported in workers handling creosote-treated wood. The symptoms appeared to worsen on hot sunny days, which suggests a phototoxic effect. Similar effects were seen in workers exposed to coal tar pitch and coal tar. A skin lesion classified as a benign squamous cell papilloma was diagnosed in a man who was "heavily exposed" while dipping wood in coal tar creosote tanks. In laboratory animals, skin irritation and the formation of comedones have been observed following short-term dermal exposure to coal tar creosote.

Respiratory Effects. Workers using coal tar and coal tar creosote in wood preservative plants exhibited mild to moderate pulmonary restrictive and obstructive deficits. There did not appear to be large differences between smokers and nonsmokers in the prevalence of these conditions. Adverse respiratory symptoms, including increased morbidity from obstructive lung disease, have also been associated with long-term exposure of workers in an electrode manufacturing plant and in the aluminum industry. A residential survey conducted by the Texas Department of Health as part of a site surveillance program did not detect any adverse respiratory effects among residents of a housing development built on contaminated land formerly occupied by a coal tar creosote wood treatment plant. Studies with animals exposed to vapors of coal tar creosote or coal tar have shown lesions of the olfactory epithelium, histiocytosis of the lung tissue, and chronic fibrosing pneumonitis with peribronchial adenomatosis.

2.3 MINIMAL RISK LEVELS

Minimal Risk Levels (MRLs) for wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles cannot be determined because available data are insufficient for acute, intermediate, and chronic exposures via the oral and inhalation routes. In addition, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles are extremely complex in their chemical compositions, thereby further complicating the MRL derivation process. The MRL is an estimate of the daily human exposure to a substance (noncarcinogenic) that is likely to be without an appreciable adverse risk over a specified duration of exposure. The primary limitation to deriving the MRL for these agents is that the MRL is, generally, based on measured biological effects of a single substance and not on the effects produced by mixtures of chemicals, which is the chemical nature of the wood creosotes, coal tar creosote, coal tar, and coal tar pitch. As stated in Section 1.1, creosote is a complex mixture originating from high temperature

treatments of coal tar and beechwood or occurring in the resin of the creosote bush. About 300 chemicals have been identified in coal tar creosote, and there may be 10,000 other chemicals present in the mixture. Creosote derived from plants is composed of various organic compounds including phenols, cresols, and guaiacol.

The derivation of the MRL is further complicated by the variability of the mixture's composition among wood creosote and coal tar creosote samples and the differences in mode of action of the individual components. The mixtures' composition is dependent on the sources and preparation parameters of wood creosote and coal tar creosote and, as a result, the creosote components are rarely consistent in their type and concentration. Hence, toxicological evaluations of one creosote sample, for instance, are most likely inadequate for extrapolation to other creosote samples, unless their compositions are similar. An example of the composition variability among creosote samples was presented by Weyand et al. (1991). In that study, the concentrations of several PAHs were analyzed in four samples of manufactured gas plant (MGP) residue, a form of coal tar. All of the PAHs identified exhibited 2- to nearly 20-fold differences in concentration among the four samples. Benzo[a]pyrene, a component whose individual toxicity has been examined extensively, ranged from nondetectable levels (detection limit 0.3 g/kg) to 1.7, 6.4, and 3.9 g/kg of coal tar. Other studies that illustrate the variability of samples include Wrench and Britten (1975), Niemeier et al. (1988), and Emmett et al. (1981).

The risk assessment of mixtures on human and environmental health is complicated by the paucity of approaches to assess environmental exposures and biological effects of chemical mixtures. Furthermore, the use of single-compound toxicity data to predict the toxicity and health effects of complex mixtures is highly speculative. The difficulty of using single-compound toxicity data to estimate the toxicity of complex mixtures is illustrated by the considerable variation in carcinogenicity of PAHs depending on the components of the mixture (Warshawsky et al. 1993). For instance, when benzo[a]pyrene, a potent animal carcinogen, is added at noncarcinogenic levels to mixtures of carcinogenic or noncarcinogenic PAHs, the skin tumorigenicity of the mixture, as well as the latency of tumor incidence, is changed. Hence, unless the actual complex mixture is evaluated directly for toxicity, it is unlikely that its toxic potency can be interpreted from that of its isolated components.

While there are no MRLs for the mixtures discussed in this profile, the interested reader should refer to Table 8-1 for some regulations and guidelines applicable to coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of creosote. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of creosote are indicated in Tables 3-1, 3-2, and 3-4 and Figures 3-1 and 3-2.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

This profile addresses the toxicological and toxicokinetics database for several substances, wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, whose production stems from the incomplete combustion or pyrolysis of carbon-containing materials. Creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles are composed of many individual compounds of varying physical and chemical characteristics. In addition, the composition of each, although referred to by specific name (e.g., wood creosote or coal tar creosote) is not consistent. For instance, the components and properties of the mixture depend on the temperature of the destructive distillation (carbonization) and on the nature of the carbon-containing material used as a feedstock for combustion.

Wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles differ from each other with respect to their composition. Wood creosotes are derived from beechwood (*Fagus,* referred to herein as beechwood creosote) and the resin from leaves of the creosote bush (*Larrea*, referred to herein as creosote bush resin). Beechwood creosote consists mainly of phenol, cresols, guaiacol, xylenol, and creosol. It is a colorless or pale yellowish liquid, and has a characteristic smoky odor and burnt taste (Miyazato et al. 1981). It had therapeutic applications in the past as a disinfectant, a laxative, and a stimulating expectorant, but it is not a major pharmaceutical ingredient today in the United States.

Creosote bush resin consists of phenolic (e.g., flavonoids and nordihydroguaiaretic acid), neutral (e.g., waxes), basic (e.g., alkaloids), and acidic (e.g., phenolic acids) compounds. The phenolic portion comprises 83–91% of the total resin. Nordihydroguaiaretic acid accounts for 5–10% of the dry weight of the leaves (Leonforte 1986). It is not known whether the health effects associated with creosote bush resin are attributable to the phenolic components.

Coal tars are by-products of the carbonization of coal to produce coke or natural gas. Physically, they are usually viscous liquids or semisolids that are black or dark brown with a naphthalene-like odor. The coal tars are complex combinations of polycyclic aromatic hydrocarbons (PAHs), phenols, heterocyclic oxygen, sulfur, and nitrogen compounds. By comparison, coal tar creosotes are distillation products of coal tar. They have an oily liquid consistency and range in color from yellowish-dark green to brown. At least 75% of the coal tar creosote mixture is PAHs. Unlike the coal tars and coal tar creosotes, coal tar pitch is a residue produced during the distillation of coal tar. The pitch is a shiny, dark brown to black residue which contains PAHs and their methyl and polymethyl derivatives, as well as heteronuclear compounds (American Wood Preserver's Association 1988). Coal tar creosote, coal tar, and coal tar products are used as wood preservatives, herbicides, fungicides, insecticides, and disinfectants (EPA 1981a, 1984a). Volatile components of the coal tar pitch can be given off during operations involving coal tar pitch, including transporting, and in the coke, aluminum, and steel industries (Bender et al. 1988; Mazumdar et al. 1975; NIOSH 1983; Rönneberg 1995b; Rönneberg and Anderson 1995).

Although beechwood creosote, creosote bush resin, and coal tar creosote have some components in common, such as phenols, the differences in composition are pronounced enough to assume with reasonable certainty that they will have different toxicological properties. Furthermore, coal tar creosote contains PAHs, some of which are carcinogenic to animals, and beechwood creosote does not. Thus, the relevance of health effects data on beechwood creosote to risk associated with exposure to coal tar creosote is not known.

Throughout this profile, every attempt is made to specify the characteristics of the creosote, coal tar, coal tar pitch, or coal tar pitch volatiles under discussion, and to indicate which health effects may be expected to be common to two or more forms. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. Therefore, the health effects of the individual components (e.g., PAHs, phenol, or others) will not be discussed in great detail even though it is likely that the toxicity of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles is due largely to these major individual components. However, it is understood that the toxicity of the individual components may not

be representative of the actual toxicity of the mixtures because of the possibility of synergistic and/or antagonistic interactions in the mixture. For more information on the health effects of these components, the reader can refer to the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons (Agency for Toxic Substances and Disease Registry 1992, 1995, 1998).

3.2.1 Inhalation Exposure

This section describes the health effects observed in humans and laboratory animals associated with inhalation exposure to coal tar pitch or coal tar pitch volatiles, for which reliable exposure levels could be determined. LSEs by the inhalation route presented in Table 3-1 and Figure 3-1 include studies using coal tar pitch volatiles or aerosols. All reliable exposure levels have been stated, where possible. No studies were located regarding the health effects in humans exposed solely by inhalation to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles. Studies of occupational exposure of humans (Armstrong et al. 1994; Bender et al. 1988; Bertrand et al. 1987; Bolt and Golka 1993; CEOH 1997; Costantino et al. 1995; Gibbs 1985; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Kromhout et al. 1992; Kunze et al. 1992; Lloyd 1971; Lloyd et al. 1970; Mazumdar et al. 1975; NIOSH 1982; Park and Mirer 1996; Persson et al. 1989; Petsonk et al. 1988; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Romundstad et al. 2000; Rönneberg 1995b; Rönneberg and Andersen 1995; Sakabe et al. 1975; Schildt et al. 1999; Siemiatycki et al. 1994; Spinelli et al. 1991; Stern et al. 2000; Swaen and Slangen 1997; TOMA 1979, 1981, 1982; Tremblay et al. 1995; Ward 1988; Wu et al. 1998; Yadav and Seth 1998) did not distinguish between inhalation, oral, or dermal exposure. Several studies were found describing health effects in animals of inhalation exposure to aerosols of coal tar or coal tar pitch (Heinrich et al. 1994a, 1994b; Hueper and Payne 1960; MacEwen et al. 1977; Pfitzer et al. 1965; Springer et al. 1982, 1986b, 1987). Beechwood creosote, creosote bush resin, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles have some components in common, however, it is not known which of these components produce the toxic effects.

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)	LOAEL Serious (mg/m**3)	Reference Chemical Form
	ACUTE EXPOSURE						
	Systemic						
1	Human	8 hr (occup)	Ocular		0.18 M (conjunctivitis)		Emmett 1986 CTPV
2	Rat (CD)	5 d Gd 12-16 6 hr/d	Resp	84 F	660 F (significant increase in lung weight)		Springer et al. 1982 coal tar aerosol
			Hepatic	660 F			
			Renal	660 F			
			Endocr	660 F			
			Bd Wt	84 F	660 F (significant decrease in body weight)		
	Immuno/lymphoret						
3	Rat (CD)	5 d Gd 12-16 6 hr/d		84 F	660 F (significant decrease in thymus weight and increase in spleen weight)		Springer et al. 1982 coal tar aerosol
	Reproductive						
4	Rat (CD)	5 d Gd 12-16 6 hr/d		84 F	660 F (significant increase in the incidence of mid- and late-gestational resorptions)		Springer et al. 1982 coal tar aerosol
	Developmental						
5	Rat (CD)	5 d Gd 12-16 6 hr/d		84	660 (reduced fetal size, weight and lung size, reduced ossification)		Springer et al. 1982 coal tar aerosol
	INTERMEDIATE EXPOSURE						
	Death						
6	Rat (Wistar)	10 mo 5 d/wk 17 hr/d				2.6 F (increased mortality)	Heinrich et al. 1994a, b coal tar pitch

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)	LOAEL Serious (mg/m**3)	Reference Chemical Form
	Systemic						
7	Rat (Fischer-344)	6 wk 5 d/wk 6 h/d	Cardio		700 M (20% elevation in arterial blood pressure)		Sasser et al. 1989 coal mixture
			Bd Wt		700 M (17.5 % decrease in body weight)		
8	Rat (Fischer- 344)	5 wk 5 d/wk 6 hr/d	Resp		30 (histiocytosis of lung)		Springer et al. 1986b coal tar aerosol
			Cardio	690			
			Gastro	140 M 690 F	690 M (epithelial hyperplasia and chronic inflammation in cecum)		
			Hemato	30	140 (significant decrease in red blood cells, hemoglobin, and volume of packed red cells, significant increase in reticulocytes)		
			Hepatic	140 M	690 M (significant increase in relative weight of liver and serum cholesterol)		
			Renal	30 F	30 M (significant increase in relative weight of kidney) 140 F	690 M (pelvic epithelial hyperplasia)	
			Endocr	690			
			Bd Wt	30	140 (7% decrease in body weight)		

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)		LOAEL Serious (mg/m**3)		Reference Chemical Form
	Systemic								
9	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp		30	(histiocytosis of lung)	690	(lesions of olfactory epithelium)	Springer et al. 1986b coal tar aerosol
			Cardio	690					
			Gastro	140	690	(epithelial hyperplasia, ulcers and chronic inflammation of cecum)			
			Hemato	30 M	140 M				
				140 F	690 F	(significant decrease in red blood cells, hemoglobin, and volume of packed red cells)			
			Hepatic	30 F	30 M	(significant increase in relative liver weight)	690	(presence of liver lesions, elevated cholesterol, blood urea nitrogen and alteration in activities of SGPT and LDH)	
					140 F				
			Renal	30	140	(significant increase in relative kidney weight)	140 M	(pelvic epithelial hyperplasia and pigmentation of cortical tubules)	
							690 F		
			Endocr	690					
			Bd Wt	30	140	(10% decrease in body weight)			

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)		LOAEL Serious (mg/m**3)		Reference Chemical Form
	Systemic								
10	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d	Resp	140	690	(lesions of olfactory epithelium)			Springer et al. 1987 coal tar aerosol
			Cardio	690					
			Gastro	690					
			Hemato	140	690	(significant decrease in red blood cells, hemoglobin, reticulocytes and volume of packed red cells)			
			Hepatic	29 M 140 F	140 M 690 F	(significant decrease in liver weight)			
			Renal	690					
			Endocr	690					
			Bd Wt	690					
11	Rabbit (New Zealand)	9 mo 5 d/wk 6 hr/d	Bd Wt				10 F	(31% decrease in body weight)	MacEwen et al. 1977 coal tar
	Immuno/lymphoret								
12	Rat (Fischer- 344)	5 wk 5 h/d 6 hr/d		140	690	(decreased number of megakaryocytes in spleen)			Springer et al. 1986b coal tar aerosol
13	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		30	140	(significant reduction in weight of thymus)	690	(atrophy of thymus, hypocellular bone marrow, and decreased number of megakaryocytes in marrow and spleen)	Springer et al. 1986b coal tar aerosol

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)	LOAEL Serious (mg/m**3)	Reference Chemical Form
	Immuno/lymphoret						
14	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d		140 M 29 F	690 M (significant decrease in weight of thymus) 140 F		Springer et al. 1987 coal tar aerosol
	Neurological						
15	Rat (Fischer- 344)	5 wk 5 d/wk 6 hr/d		140 M 690 F	690 M (significant increase in relative brain weight)		Springer et al. 1986b coal tar aerosol
16	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		30	140 (significant increase in relative brain weight)		Springer et al. 1986b coal tar aerosol
17	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d		690			Springer et al. 1987 coal tar aerosol
	Reproductive						
18	Rat (Fischer- 344)	5 wk 5 h/d 6 hr/d		690 M 140 F	690 F (decreased luteal tissue)		Springer et al. 1986b coal tar aerosol
19	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		30 M 140 F	140 M (significant increase in relative weight of testis) 690 F (significant decrease in relative weight of ovary and amount of luteal tissue)		Springer et al. 1986b coal tar aerosol
20	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d		690 M 140 F	690 F (significant decrease in ovary weight)		Springer et al. 1987 coal tar

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)	LOAEL Serious (mg/m**3)	Reference Chemical Form
	Cancer						
21	Rat (Wistar)	10 mo 5 d/wk 17 hr/d				2.6 F (CEL: 39% incidence broncho-alveolar adenomas & adenocarcinomas)	Heinrich et al. 1994a, b coal tar pitch
22	Mouse CAF1- JAX	90 d 24 hr/d				10 F (CEL: 18/43 skin tumor, control = 0/225) (CEL: 27/50 lung tumor, control = 0/225)	MacEwen et al. 1977 coal tar
23	Mouse ICR CF-1	90 d 24 hr/d				2 F (CEL: 14/75 skin tumor, controls = 3/225)	MacEwen et al. 1977 coal tar
	CHRONIC EXPOSURE						
	Death						
24	Rat (Wistar)	20 mo 5 d/wk 17 hr/d				2.6 F (increased mortality)	Heinrich et al. 1994a coal tar pitch
	Systemic						
25	Monkey (Macaca mulatta)	18 mo 5 d/wk 6 hr/d	Bd Wt	10			MacEwen et al. 1977 coal tar
26	Rat (Sprague-Dawley)	18 mo 5 d/wk 6 hr/d	Bd Wt		10 (15% decrease in body weight)		MacEwen et al. 1977 coal tar
	Cancer						
27	Rat (Wistar)	20 mo 5 d/wk 17 hr/d				1.1 F (CEL: 33% incidence broncho-alveolar adenomas & adenocarcinomas)	Heinrich et al. 1994a, b coal tar pitch

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)	LOAEL Serious (mg/m**3)	Reference Chemical Form
28	Rat (Sprague-Dawley)	18 mo 5 d/wk 6 hr/d				10 M (CEL: 38/38 squamous cell carcinoma) 10 F (CEL: 31/38 squamous cell carcinoma and 3/38 mammary fibroadenoma)	MacEwen et al. 1977 coal tar

aThe number corresponds to entries in Figure 3-1.

Differences in levels of health effects and cancer between males and females are not indicated in figure 3-1

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CTPV = coal tar pitch volatiles; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; hr = hour(s); LDH = lactic dehydrogenase; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; SGPT = serum glutamic pyruvic transaminase; wk = week(s)

Figure 3-1 Levels of Significant Exposure to Creosote - Inhalation

Acute (≤14 days)

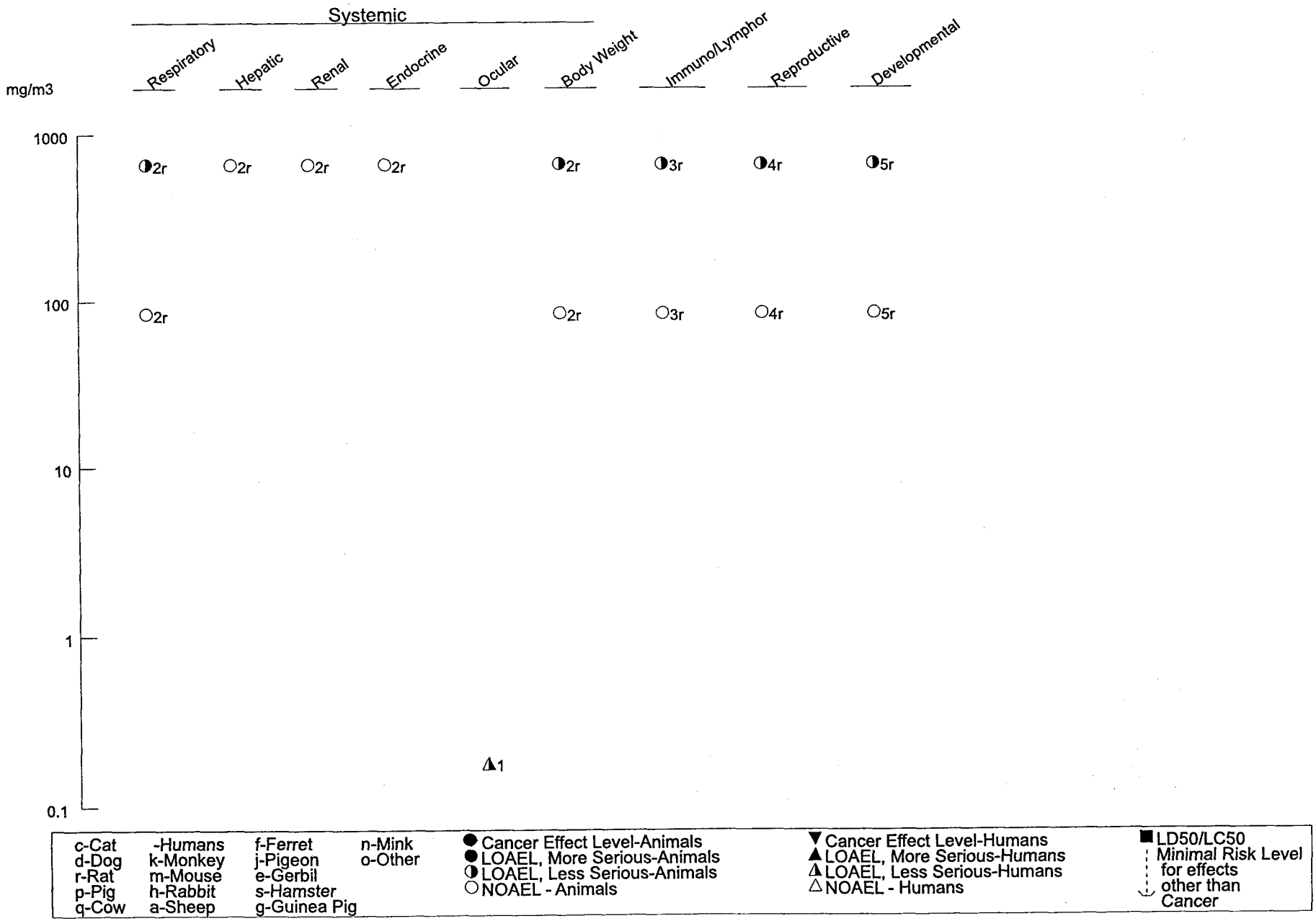


Figure 3-1 Levels of Significant Exposure to Creosote - Inhalation (*Continued*)

Intermediate (15-364 days)

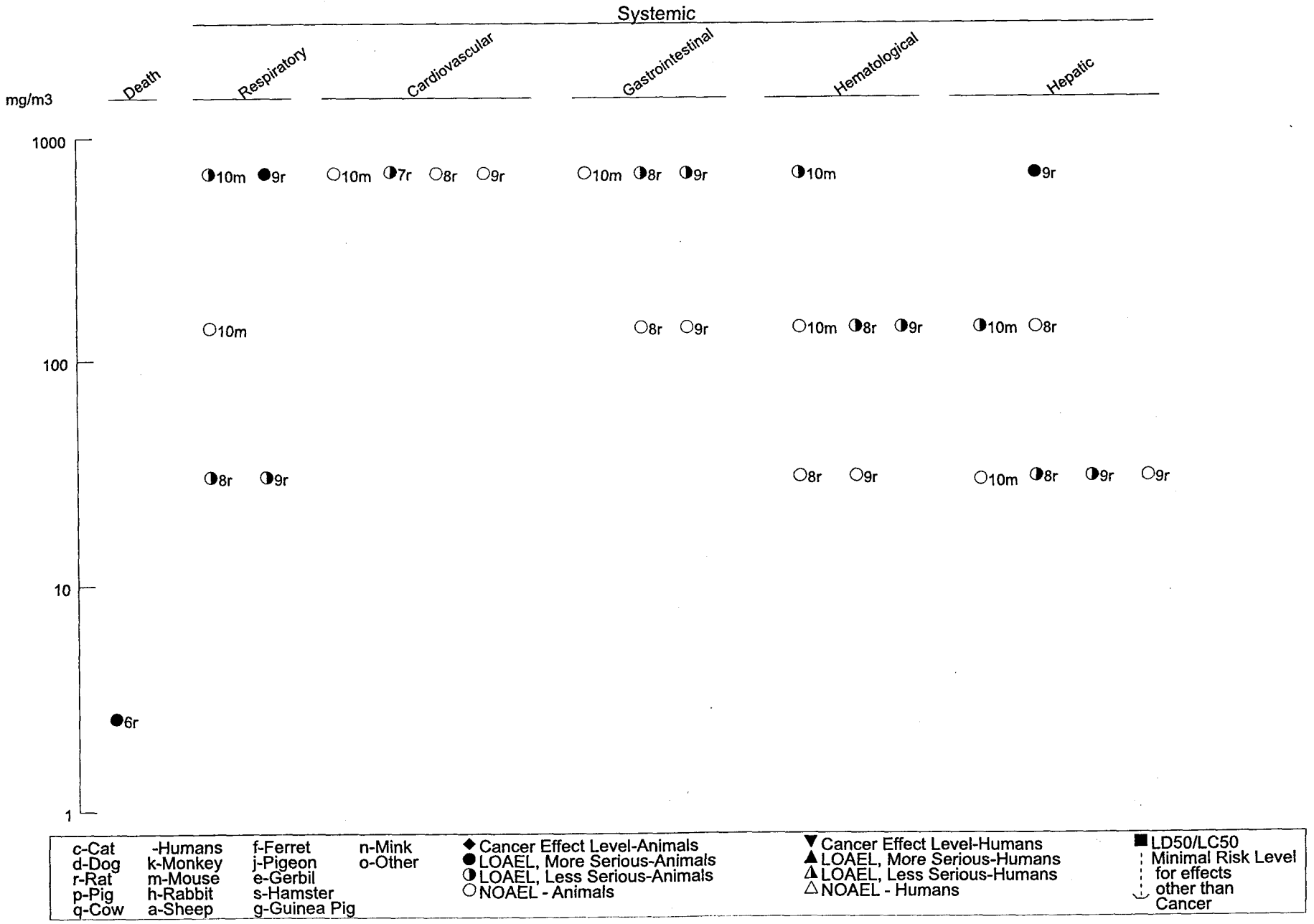


Figure 3-1 Levels of Significant Exposure to Creosote - Inhalation (*Continued*)

Intermediate (15-364 days)

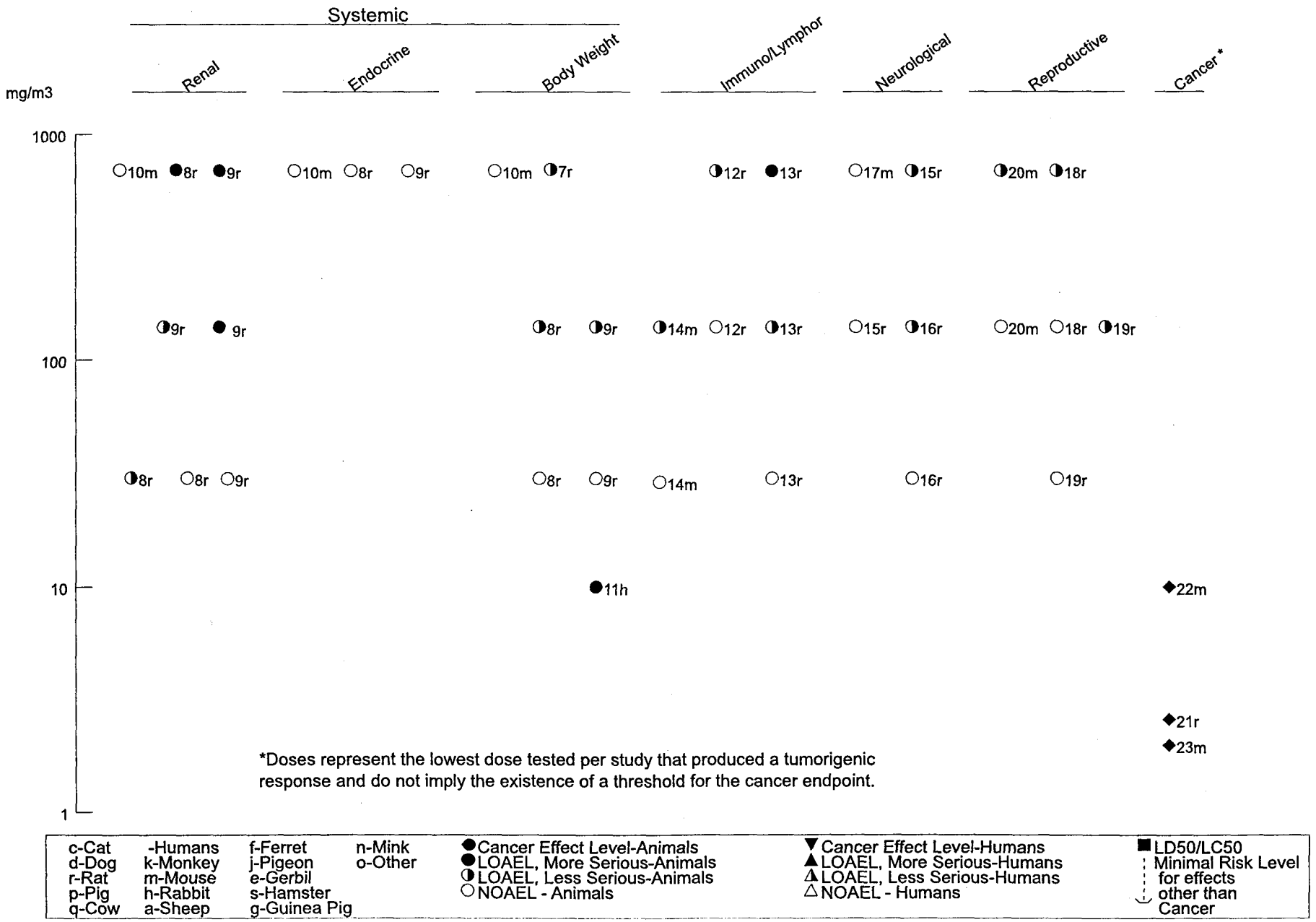
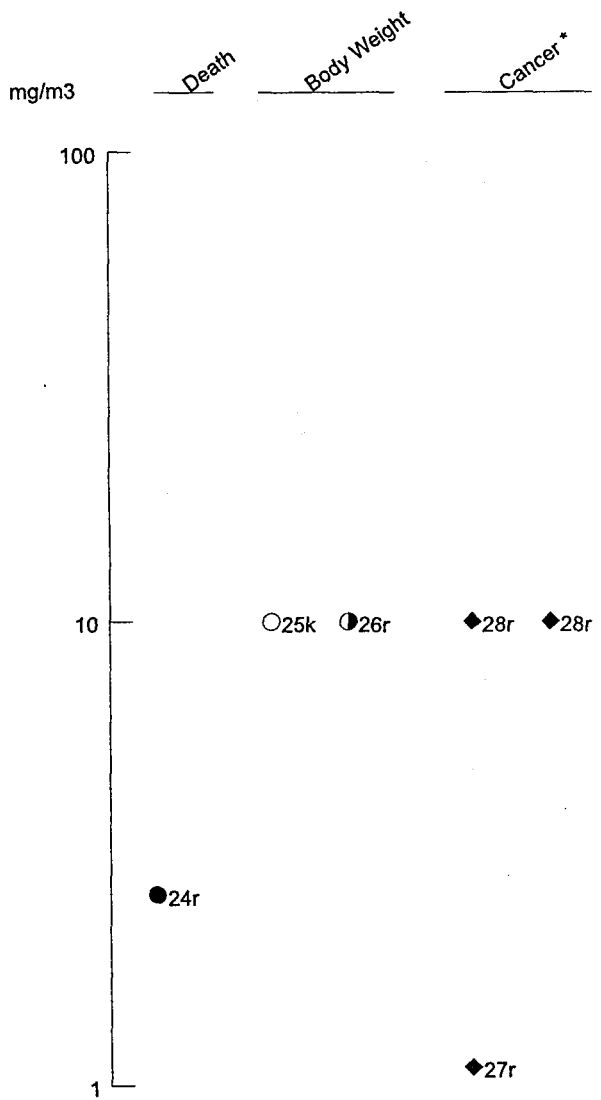


Figure 3-1 Levels of Significant Exposure to Creosote - Inhalation (*Continued*)

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat d-Dog r-Rat p-Pig q-Cow	-Humans k-Monkey m-Mouse h-Rabbit a-Sheep	f-Ferret j-Pigeon e-Gerbil s-Hamster g-Guinea Pig	n-Mink o-Other	◆ Cancer Effect Level-Animals ● LOAEL, More Serious-Animals ◑ LOAEL, Less Serious-Animals ○ NOAEL - Animals	▼ Cancer Effect Level-Humans ▲ LOAEL, More Serious-Humans ◭ LOAEL, Less Serious-Humans △ NOAEL - Humans	■ LD50/LC50 Minimal Risk Level for effects other than Cancer

3.2.1.1 Death

No reports were located of death in humans attributed to inhalation exposure to wood creosote or the creosote bush by inhalation.

Coal Tar Products. No studies were located connecting death in humans following exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles solely by inhalation. A mortality study of human exposure during employment at eight coal tar plants indicated significant increases in cancer-related deaths, compared to the general population (TOMA 1982). No clear relationship between inhalation of coal tar and increased mortality could be established since exposure routes in addition to inhalation (e.g., dermal and oral) were likely and subjects were also exposed to other chemicals and cigarette smoke. Since the study was retrospective, no attempt was made to estimate occupational exposure levels from any source (TOMA 1982). Limitations of the study included absence of data on smoking habits, short cut-off date of 10 days of employment, use of U.S. male mortality rates for comparison as opposed to regional mortality rates, and mixed chemical exposure. The same study population was used as the basis for a nested cancer case-control study (CEOH 1997). Fifty lung-cancer cases were identified and matched with controls from the same cohort. There were three controls per case, and individuals were matched for plant, gender, race, date of hire, and age at hire. Smoking history, work and medical history data were gathered by telephone interviews with the subjects or their next of kin and used to assign workers to various exposure classes. There was no statistically significant increase in lung cancer risk in persons assessed as highly exposed to coal tar compared with those having low or no exposure. The risk associated with working for >20 years in production was lower than that of short-term employees. Controlling for smoking (data analyzed for smokers only) did not change the results, but no nonsmoking cases were identified and therefore, it was not possible to assess the effects of coal tar exposure without concurrent cigarette smoking.

In a mortality study of steelworkers employed in a coke oven plant in 1953, increased mortality from respiratory neoplasms (monitored from 1953 to 1961) was observed in coke oven workers compared to expected mortality rates (Lloyd 1971). Specifically, 20 deaths from respiratory neoplasms were observed, compared to the expected 7.5 deaths. The increase in mortality was linked to an increase in mortality from respiratory neoplasms in nonwhite oven workers who had been employed for $5 years. No increase in deaths from respiratory neoplasms was observed in nonoven workers. In a series of follow up studies of these same coke oven workers in Allegheny County, Pennsylvania, similar associations between coal tar or coal tar pitch volatile exposure and mortality, primarily from lung cancer, were

observed (Redmond 1976; Redmond et al. 1972, 1976). An increase in death due to kidney cancer was observed at the plant, although this was not limited to the coke oven workers at the steel plant (Redmond et al. 1976). Lung cancer mortality was higher in men exposed to coal tar in an aluminum smelter plant for more than 21 years, with a standardized mortality ratio (SMR) of 2.2–2.4 compared to persons not exposed to tar (Gibbs 1985; Gibbs and Horowitz 1979). Increased risk of mortality from pancreatic cancer and leukemia of more than 30% was observed for workers in the potrooms and carbon departments of 14 aluminum reduction plants, who had worked for >5 years (Rockette and Arena 1983).

A study of proportionate mortality among the 11,144 members of the United Union of Roofers, Waterproofers, and Allied Workers (Stern et al. 2000) found a significant excess in mortality due to cancers of the lung, bladder, esophagus, and larynx, and to pneumoconioses and other nonmalignant respiratory diseases in these workers compared with U.S. age-, gender-, and race-specific proportional mortality rates for the years of the study (1950–1996). These workers were occupationally exposed to asphalt fumes and asbestos as well as coal tar pitch volatiles, and cigarette smoking must also be considered as a likely confounding factor.

Spinelli et al. (1991) examined mortality and cancer incidence over a 30-year period among a cohort of 4,213 workers exposed to coal tar pitch volatiles emitted during the production of aluminum. A significant increase in the mortality rate for brain cancer was observed. However, no exposure response was seen for deaths from any form of cancer in direct relation to cumulative coal tar pitch volatile exposure. Mortality in a Norwegian aluminum smelter plant was investigated in a cohort of 1,085–1,137 men who worked between 1922 and 1975 (Rönneberg 1995b; Rönneberg and Andersen 1995). An increase in mortality from atherosclerosis and chronic obstructive lung disease were associated with 40 or more years of exposure or 20–39 years exposure to pot emissions, respectively (Rönneberg 1995b). When cancer incidence was analyzed, associations were found between tar exposure and increases in bladder, prostatic, and lung cancer (Rönneberg and Andersen 1995). In a study of exposure to coal tar pitch volatiles in coke oven plants in France, mortality due to lung cancer was 2.5 times higher in the coke plant workers (534 males) exposed for periods from <5 to >10 years compared to the French national male population (Bertrand et al. 1987). In another study of coal tar pitch volatile exposure in coke oven plants, mortality was monitored in coke oven workers in Pennsylvania who had been employed for >10 years (Mazumdar et al. 1975). An increase in mortality due to lung cancer was positively correlated with coal tar pitch volatile exposure. In a study of coal tar pitch volatile exposure in the aluminum industry, four workers from the same area of the plant died of lung cancer (Bolt and Golka 1993). The duration of exposure to coal tar pitch volatiles ranged from 3.5 to 23 years. Costantino et al.

(1995) carried out an epidemiological study of 5,321 coke oven workers and 10,497 non-oven workers. Statistically significant excess mortality was present among coke workers for several categories of death. The relative risk (RR) for all causes of death was 1.08 ($P<0.01$; 95% confidence interval [CI]=1.02–1.14). The increase in overall mortality was primarily due to increased deaths from cancers. There were highly significant trends ($P<0.001$) for increased cancer risk with increasing duration of employment and increasing exposure. The study did not control for smoking. However, the similar socioeconomic status of the controls and exposed workers suggests that it is unlikely that there was a substantial difference in smoking habits between the two groups. Further discussion of retrospective human cancer/mortality studies can be found in Section 3.2.1.7.

Animal studies were also limited in number for this route of exposure. One study was located in which rats were exposed for 1 hour to saturated vapors of coal tar creosote (Pfitzer et al. 1965). In this study, no specific concentration level was stated and no deaths were observed. In a study in Wistar rats, female rats were exposed to 1.1 or 2.6 mg/m^3 coal tar pitch aerosol for 17 hours/day, 5 days/week for 10 months, followed by exposure to clean air for 20 months (Heinrich et al. 1994a, 1994b). Increased mortality was observed in the high-concentration group, due to lung tumors (no mortality data shown). Increased mortality was also observed in Wistar rats exposed to 1.1 or 2.6 mg/m^3 coal tar pitch aerosol for 17 hours/day, 5 days/week for 20 months, followed by clean air exposure for 10 months (Heinrich et al. 1994a, 1994b). New Zealand white rabbits exposed to 10 mg/m^3 coal tar pitch aerosol in a mixture of benzene, toluene, and xylene for 6 hours/day, 5 days/week for 18 months, exhibited higher mortality than the control animals (89 versus 33%), although the authors attributed death to chronic respiratory infection (MacEwen et al. 1977). Further evaluation of these animals was not provided, so it is not known whether the inhalation exposure affected the susceptibility of the animals to respiratory infection. More importantly, the biological effect of benzene, toluene, and xylene (BTX), which were used as carrier solvents for the coal tar aerosol, was not evaluated in this study. Thus, while these solvents may have played a part in the development of the adverse effects observed in this study, the actual magnitude of the effect, if any, cannot be determined. Kock et al. (1994) reported death of 7 of 20 black rhinoceroses that had been held in creosote-treated holding pens. The animals that died had oral and gastric ulcers, widespread hemorrhages and hematoma, and uniformly swollen intensely green livers, containing excessive intrahepatic bilirubin. However, doses and routes of exposure were not established in this study.

The LOAEL values for death in each species are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding the gastrointestinal, musculoskeletal, hepatic, endocrine, or body weight effects in humans or musculoskeletal effects in animals after inhalation exposure to creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles. The systemic effects that have been observed in humans and animals are discussed below. LOAEL and NOAEL values for systemic effects are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects.

Coal Tar Products. A single case report describes acute bronchoconstriction in an asthmatic patient exposed to coal tar vapor while being treated with coal tar occlusive bandages for a skin condition (Ibbotson et al. 1995). The authors conclude that the effect was probably due to inhalation of coal tar vapor leading to a nonspecific irritant response. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, respiratory effects, including reduced lung function (forced vital capacity [FVC]), were noted in 17% (44 of 257) of the employees examined. Most of these respiratory impairments (35/44) were considered to be mild (reduction in FVC of 66–79%) (TOMA 1979). Reductions in FVC were evident in smoking and nonsmoking workers in similar proportions. Obstructive deficits were observed in 8% of smoking and 5% of nonsmoking workers; these were also generally mild to moderate (reduction in forced expiratory volume of 46–69%), but one smoker did show a severe deficit. Workers in nine coal tar plants had a 33% (150 of 453) incidence of restrictive pulmonary deficits (reduced FVC) (TOMA 1981). The study authors proposed that the elevated abnormal findings could be attributed to factors related to administration of the test and not to a disease state. However, other pulmonary function tests were, according to the authors, within the normal limits. A limitation of this study is that smoking status of the subjects was not reported (TOMA 1981). Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., dermal and oral) were likely. Also, the ability to relate respiratory effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1979, 1981). Additional limitations of the studies included geographical variation in plant locations, lack of past employment history, voluntary participation in the study that could have biased it in favor of healthy

workers, lack of statistical analyses, lack of adequate controls, use of only current employees, and testing confined to a single season (winter). In an industrial health survey of five workers in an electrode manufacturing plant, respiratory symptoms were observed, including pneumonoconiosis, respiratory obstruction, impaired gas exchange, and lung fibrosis with interstitial tissue alveoli filled with black pigment (Petsonk et al. 1988). These workers had been exposed to coke dust, pitch fumes, pitch dust, and other dusts for >15 years, which could be associated with the respiratory symptoms. Increased chronic obstructive lung disease was associated with 20–39 years of exposure to pot emissions in an aluminum smelter (Rönneberg 1995b). Similar increases in respiratory diseases have been noted in other studies of the aluminum industry (Gibbs 1985).

A study of proportionate mortality among the 11,144 members of the United Union of Roofers, Waterproofers, and Allied Workers (Stern et al. 2000) found a significant excess in mortality due to pneumoconioses and other nonmalignant respiratory diseases in these workers compared with U.S. age-, gender-, and race-specific proportional mortality rates for the years of the study (1950–1996). These workers were occupationally exposed to asphalt fumes and asbestos as well as coal tar pitch volatiles. Cigarette smoking is a potential confounding factor that, due to the nature of the study, could not be evaluated.

A site surveillance program was conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant (Agency for Toxic Substances and Disease Registry 1994). The plant had ceased creosoting activities in 1961, after operating for 51 years. A sand and gravel company had operated on part of the abandoned site during the 1970s and 1980s. Because of soil and groundwater contamination with PAHs and other chemicals, the EPA identified this site and placed it on the National Priorities List (NPL) in 1984. Several residential lots were observed to have soil concentrations of benzo[a]pyrene (B[a]P) in excess of 325 mg/kg, or oily-stained areas, and were subject to emergency resodding by the EPA. Contaminated soils were scheduled to be treated for clean-up. A total of 214 residents (123 males, 91 females) of the contaminated residential area (Koppers) were interviewed twice during a period of 2 years, and were compared to 212 residents (122 males, 93 females) from a nearby town. Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. The residents of the Koppers area showed a

significantly higher risk of chronic bronchitis (RR=2.65, 95% CI=1.26–5.57) relative to the comparison population during the first year of the study. During the second year of the study, 11 residents from the Koppers area reported chronic bronchitis, whereas 7 were expected based on the 1990 National Health Interview Survey rates. These study results are seriously limited by the study's reliance on self reporting of health conditions for which diagnosis verification was not always available.

Pfitzer et al. (1965) exposed rats by inhalation to near-saturated vapors generated from coal tar creosote for 1 day. The rats exhibited dyspnea and slight nasal irritation. The actual exposure level was not determined (Pfitzer et al. 1965). A significant increase in lung weight was reported for female Fischer rats exposed to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12–16, but not for females exposed to 84 mg/m^3 (Springer et al. 1982). Lesions of the olfactory epithelium were reported for Fischer rats and CD-1 mice exposed to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but not for animals exposed to 140 mg/m^3 (Springer et al. 1986b, 1987). Rats exposed to concentrations of coal tar $30 mg/m^3 for 5 or 13 weeks also showed histiocytosis of the lung tissue (Springer et al. 1986b). No lesions of the olfactory epithelium were reported for rats exposed to up to 690 mg/m^3 coal tar aerosol for 5 weeks (Springer et al. 1986b). Respiratory symptoms, consisting of extensive chronic fibrosing pneumonitis with peribronchial adenomatosis, were observed in female Bethesda rats and guinea pigs (sex not specified) exposed to coal tar or roofing asphalt vapors (exposure level not specified) for 4 days/week for a total period of 2 years (Hueper and Payne 1960).

Cardiovascular Effects.

Coal Tar Products. In an industrial health survey of employees in a wood preservative plant in which coal tar creosote, coal tar, and pentachlorophenol were the main treatments used, cardiovascular effects, including increased diastolic blood pressure, were noted in 21% (24 of 113) of the employees examined (TOMA 1979). Industrial hygiene surveys of coal tar pitch volatiles at this and three other wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., oral and dermal) were likely. Also, the ability to relate cardiovascular effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals including pentachlorophenol and cigarette smoke (TOMA 1979). Additional limitations of the study are noted above (see "Respiratory Effects"). However, in another industrial study, an increase in mortality from

atherosclerosis was associated with cumulative tar exposure and $40 years of exposure to pot emissions in the aluminum industry (Rönneberg 1995b).

The susceptibility of the rat cardiovascular system to high-boiling coal liquid (heavy distillate, HD) administered by inhalation (700 mg/m^3, for 6 hours/day, 5 days/week for 6 consecutive weeks) was studied in male Fischer 344 rats (Sasser et al. 1989). Ten days after treatment was stopped, the cardiovascular assessments were made. The most striking observation was a 20% increase in arterial blood pressure of HD-exposed rats over that of sham-exposed rats. Heart rate was also elevated in the HD-treated animals. The nature of the causal relationship (i.e., direct or secondary) between HD and the elevation of blood pressure and heart rate is not clear since physiological disturbances of other systems, whose activity influence pressure and rate parameters (e.g., pulmonary and renal systems) might have produced the observed changes in cardiovascular activity. No change in heart weight or the histology of the heart or aorta was found for Fischer rats or CD-1 mice exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for up to 13 weeks (Springer et al. 1986b, 1987).

Gastrointestinal Effects.

Coal Tar Products. No change in histology of the gastrointestinal tract was found in female Fischer rats exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks or in male or female CD-1 mice exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Male rats exposed to exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks and male and female rats exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar for 13 weeks showed epithelial hyperplasia and chronic inflammation of the cecum (Springer et al. 1986b).

Hematological Effects.

Coal Tar Products. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, hematological effects, including increased number of white blood cells (basophils), were noted in 6% (15 of 257) of the employees examined (TOMA 1979). Similarly, 8% of the employees in nine coal tar plants surveyed had increased white blood cells (eosinophils). However, the changes in white blood cell numbers, as well as their morphology, were apparently related to mild infections and allergies. According to the study authors, these results do not indicate any adverse hematologic effects directly related to plant hazards (TOMA

1981). Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). No determination of exposure was made at the nine coal tar plants (TOMA 1981). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., oral and dermal) were likely. Also, the ability to relate hematological effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1981). Other limitations of the studies are noted above (see "Respiratory Effects").

In two studies by Springer et al. (1986b, 1987) Fischer rats appeared to be more sensitive to the effects of inhaled coal tar aerosol than CD-1 mice. Male rats exposed to 140 mg/m^3, but not to 30 mg/m^3, of a coal tar aerosol for 6 hours/day, 5 days/week for 5 or 13 weeks had decreased red blood cell counts, hemoglobin concentration, white blood cells, lymphocytes, eosinophils, monocytes, and increased reticulocytes (Springer et al. 1986b). Female rats also had decreased red blood cell counts, hemoglobin concentration, white blood cells, lymphocytes, eosinophils, monocytes, and increased reticulocytes when exposed to 140 mg/m^3 coal tar for 5 weeks or 690 mg/m^3 for 13 weeks, but there was no significant difference from controls for females exposed to 30 mg/m^3 coal tar for 5 weeks or 140 mg/m^3 coal tar for 13 weeks. Red blood cell counts, hemoglobin concentration, and the volume of packed red cells were also significantly decreased in CD-1 mice exposed to 690 mg/m^3 (but not 140 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but other hematologic parameters such as erythrocyte, leukocyte, and reticulocyte counts were unaffected by exposure (Springer et al. 1987). Kock et al. (1994) reported death of 7 of 20 black rhinoceroses which had been held in creosote-treated holding pens. The animals which died had widespread hemorrhages and anemia which may reflect the effects of hemolysis, but doses and routes of exposure were not established in this study.

Hepatic Effects.

Coal Tar Products. No significant change in liver weight was reported for female CD rats exposed to up to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12–16 (Springer et al. 1982). In two other studies, Fischer rats appeared to be slightly more sensitive to the effects of inhaled coal tar aerosol than CD-1 mice (Springer et al. 1986b, 1987). Relative liver weights were significantly increased in male rats exposed to 690 mg/m^3 (but not 140 mg/m^3) and female rats exposed to $30 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks and in male rats exposed to $30 mg/m^3 and female

rats exposed to $140 mg/m^3 (but not 30 mg/m^3) coal tar aerosol for 13 weeks (Springer et al. 1986b). Subtle changes in liver histology were also noted for males and females exposed to 690 mg/m^3 compared with controls. These included a slight increase in cytoplasmic basophilia, slightly more variability in hepatocellular size, the presence of hepatomegalocytes, increased variability in nuclear size and minimal loss of cording and lobular pattern. Minimal scattered focal necrosis was also observed in liver tissue of some exposed animals, but not in controls. Similar changes in weight and histology were also noted in mice exposed to 690 mg/m^3 (females) or $140 mg/m^3 (males) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1987). No changes in weight or histology were observed for female mice exposed to 140 mg/m^3 or male mice exposed to 29 mg/m^3 for 13 weeks (Springer et al. 1987). Kock et al. (1994) reported death of 7 of 20 black rhinoceroses that had been held in creosote-treated holding pens. The animals that died had uniformly swollen intensely green livers, containing excessive intrahepatic bilirubin. Serum levels of aspartate transaminase (AST) and bilirubin were also elevated. However, doses and routes of exposure were not established in this study.

Renal Effects.

Coal Tar Products. Elevated red and white cell counts in urine were noted in 6–8% (29–34 of 452) of the employees examined in an industrial health survey in nine coal tar plants in which coal tar creosote and coal tar were the main treatments used (TOMA 1981). Some of these cell count elevations were attributed to urinary tract infections resulting from inadequate personal hygiene, and not to industrial exposure to toxic chemicals. However, some of the workers with elevated red and white cell counts in urine had cellular and granular casts and traces of protein, suggesting abnormal renal function. These individuals were referred to their physicians for diagnosis. No determination of exposure was made at the nine coal tar plants (TOMA 1981). Moreover, no clear relationship could be established because exposure routes in addition to inhalation (e.g., oral and dermal) were likely. Also, the ability to relate renal effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke. Additional limitations of the study included seasonal and geographical variation in plant locations, past employment history, voluntary participation in the study that could have biased it in favor of healthy workers, lack of statistical analyses, lack of adequate controls, and use of only current employees.

No change in kidney weight was reported for female CD rats exposed to up to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12–16 (Springer et al. 1982). In another two studies, Fischer rats appeared to be more sensitive to the renal effects of inhaled coal tar aerosol than CD-1 mice (Springer

et al. 1986b, 1987). Relative kidney weights were increased in female rats exposed to $140 mg/m^3 (but not 30 mg/m^3) and in male rats exposed to $30 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks and in male rats and female rats exposed to $140 mg/m^3 (but not 30 mg/m^3) for 13 weeks (Springer et al. 1986b). Male rats exposed to 690 mg/m^3 (but not 140 mg/m^3) for 5 weeks or 140 mg/m^3 (but not 30 mg/m^3) for 13 weeks and female rats exposed to 690 mg/m^3 (but not 140 mg/m^3) for 13 weeks also showed pelvic epithelial hyperplasia and pigmentation of the cortical tubules (Springer et al. 1986b). Relative kidney weights were also increased in mice exposed to 690 mg/m^3 (but not 140 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but the difference between exposed and control animals was not significant and no histological changes were reported (Springer et al. 1987).

Endocrine Effects.

Coal Tar Products. No adverse effect on the adrenal glands was reported for female CD rats exposed to up to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12–16 or on the adrenal, pancreas, parathyroid, pituitary, or thyroid glands in Fischer rats exposed to up to 690 mg/m^3 for 5 or 13 weeks or in CD-1 mice exposed to up to 690 mg/m^3 for 13 weeks (Springer et al. 1982, 1986b, 1987).

Dermal Effects.

Coal Tar Products. In an industrial health survey of 251 employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, 82 instances of dermal effects, including skin irritation, eczema, folliculitis, and benign growths on the skin were noted (TOMA 1979). The incidence of benign growths, eczema, and folliculitis was greater than that observed in the general U.S. population, but the study authors concluded that only the incidence of folliculitis cases met the criterion of a significant skin condition such "that the examiner believes should be seen at least once by a physician for assessment or care". In another industrial health survey (TOMA 1981), workers in nine coal tar plants had a 2% incidence of benign skin growth and a 21% incidence of some other skin condition such as keratosis, eczema, folliculitis, and chloracne, but the study authors concluded that the incidence of skin conditions was less than that seen in the general population. Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). No determination of exposure was made at the nine coal tar plants (TOMA 1981). Moreover, no clear relationship could be established because exposure routes in addition to

inhalation were likely (e.g., dermal contact with coal tar creosote and coal tar vapors and oral exposure). Also, the ability to relate dermal effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals (TOMA 1979, 1981). Additional limitations of the studies are noted above (see "Respiratory Effects"). In other industrial studies, dermal effects were also noted (Bolt and Golka 1993; NIOSH 1982). Four workers in an aluminum reduction plant, who had been exposed to coal tar pitch volatiles for a period of 3.5–23 years showed tar-related skin changes, including hyperkeratosis and telangiectasis (Bolt and Golka 1993). Skin lesions that were possibly pitch-related were observed in four workers involved in the transfer and transport of coal tar pitch, who had been exposed to coal tar pitch and asphalt for 2–8 years (NIOSH 1982). Warts and other lesions on the hands and face were described. Workers transferring coal tar pitch from a river barge to an ocean barge, or from a railroad car to an ocean barge were observed for 2 days to evaluate exposure conditions and health complaints after exposure to coal tar pitch volatiles (NIOSH 1982). Skin irritation, described as redness like a sunburn, lasting 2–3 days, with drying and peeling, and photosensitivity, was described by the workers. Personal air samples from the workers indicated respirable coal tar pitch vapors in concentrations up to 0.18 mg/m^3.

Dermal effects were noted in a site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant (Agency for Toxic Substances and Disease Registry 1994). Because of soil and groundwater contamination with PAHs and other chemicals, the EPA identified this site and placed it on the NPL in 1984. A total of 214 residents of the contaminated residential area (Koppers) were interviewed twice during a period of 2 years, and were compared to 212 residents from a nearby town. Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. Residents living on or near the Koppers area reported a higher prevalence of skin rashes (27.9%) during the first year of the surveillance than the comparison neighborhood (4.9%), with a RR of 5.72 ($P<0.05$; 95% CI=3.01–10.87). During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results, and similar results were obtained, with 34 Koppers residents reporting skin rashes, compared to an expected incidence of 4. Rashes were associated with digging in the yard, having contact with the soil, or wading in or having contact with a creek in the area. Most rashes were associated with itching or burning. The recommendation of the Texas Department of Health was that residents in the Koppers area should wear protective clothing when having contact with the soil, and should wash their

skin thoroughly when contact with the soil occurs. Other dermal effects of coal tar creosote, coal tar, or coal tar pitch exposure are mentioned in Sections 3.2.3 and 3.4.1.3.

Ocular Effects.

Coal Tar Products. Workers transferring coal tar pitch from a river barge to an ocean barge, or from a railroad car to an ocean barge, were observed for 2 days to evaluate exposure conditions and health complaints after exposure to coal tar pitch volatiles (NIOSH 1982). Eye irritation, including burning, redness, swelling, and watering of the eyes lasting about 2 days was described, occasionally associated with photophobia. Personal air samples from the workers indicated respirable coal tar pitch vapors in concentrations up to 0.18 mg/m^3. However, all of the workers were wearing protective equipment, including respirators and therefore, the measurements taken do not represent actual exposures. Conjunctivitis was observed in roofers exposed to coal tar pitch volatiles at levels $0.18 mg/m^3, but no cases of conjunctivitis were observed in workers exposed to levels #0.11 mg/m^3 (Emmett 1986).

Pfitzer et al. (1965) exposed rats by inhalation to near-saturated vapors generated from coal tar creosote for 1 day. The rats exhibited slight eye irritation. The actual exposure level was not determined.

Body Weight Effects.

Coal Tar Products. Body weight changes were monitored in monkeys, rats, and rabbits after inhalation exposure to 10 mg/m^3 coal tar aerosol (MacEwen et al. 1977). No other systemic effects were reported in this article. No change in body weight was observed in male or female *Macaca mulatta* monkeys after exposure for 6 hours/day, 5 days/week for 18 months, but when male and female Sprague-Dawley rats were exposed to the same concentration of coal tar aerosol for the same period of time, a 14–15% decrease in body weight was observed. Female New Zealand white rabbits exhibited a 31% decrease in body weight after exposure to 10 mg/m^3 for 6 hours/day, 5 days/week for 9 months.

Male Fischer 344 rats were exposed to high-boiling coal liquid (heavy distillate, HD) administered by inhalation (700 mg/m^3) for 6 hours/day, 5 days/week for 6 consecutive weeks (Sasser et al. 1989). During the study, the growth of the HD-exposed animals was suppressed significantly relative to the control group. Subsequently, growth was resumed after the treatment was stopped, although HD-treated rats weighed 17.5% less than control rats at necropsy. A significant decrease in body weight was reported for female Sprague-Dawley rats exposed to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational

days 12–16, but not for female Sprague-Dawley rats exposed to 84 mg/m^3 (Springer et al. 1982). In two other studies, Fischer rats appeared to be more sensitive to the effects of inhaled coal tar aerosol than CD-1 mice (Springer et al. 1986b, 1987). Body weights were significantly decreased in rats exposed to $140 mg/m^3 (but not 30 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 5 or 13 weeks, but not in mice exposed to up to 690 mg/m^3 coal tar aerosol for 13 weeks (Springer et al. 1986b, 1987).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals following inhalation exposure to wood creosote or the creosote bush.

Coal Tar Products. No studies were located regarding immunological and lymphoreticular effects in humans or animals following inhalation exposure to coal tar creosote, coal tar pitch, or coal tar pitch volatiles. A significant increase in spleen weight and a significant decrease in thymus weight was reported for female rats exposed to 660 mg/m^3 (but not 84 mg/m^3) of a coal tar aerosol for 6 hours/day on gestational days 12–16 (Springer et al. 1982). In two other already cited studies by Springer et al. (1986b, 1987), Fischer rats appeared more sensitive to the effects of inhaled coal tar aerosol than CD-1 mice. Relative thymus weights were significantly decreased in female rats exposed to 690 mg/m^3 coal tar aerosol 6 hours/day for 5 weeks and both males and females exposed to $140 mg/m^3 for 13 weeks (Springer et al. 1986b). Males exposed to up to 690 mg/m^3 and females exposed to 30 mg/m^3 for 5 weeks, and both sexes exposed to 30 mg/m^3 for 13 weeks, showed no change in thymus weight. The thymus was atrophied in male rats exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar aerosol for 6 hours/day for 5 weeks and in both male and female rats exposed for 13 weeks (Springer et al. 1986b). Examination of bone marrow smears showed that rats exposed to 690 mg/m^3 coal tar aerosol for 13 weeks had hypocellular marrows with a marked decrease in the number of megakaryocytes (Springer et al. 1986b). The number of megakaryocytes in the spleens of animals exposed to 690 mg/m^3 coal tar aerosol for 5 or 13 weeks was also decreased relative to controls. Both absolute and relative thymus weights were also significantly decreased in male mice exposed to 690 mg/m^3 (but not to 140 mg/m^3) or in female mice exposed to $140 mg/m^3 (but not to 29 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but no histological changes were observed (Springer et al. 1987).

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following inhalation exposure to wood creosote or the creosote bush.

Coal Tar Products. No studies were located regarding neurological effects in humans or animals following inhalation exposure to coal tar creosote, coal tar pitch, or coal tar pitch volatiles. Inhalation of up to 690 mg/m^3 coal tar aerosol by CD-1 mice for 13 weeks had no effect on brain weight or histology (Springer et al. 1987). Inhalation of 690 mg/m^3 coal tar aerosol by male Fischer rats for 5 weeks and inhalation of $140 mg/m^3 by male and female rats for 13 weeks produced a significant increase in relative brain weights, but no change in absolute brain weight or histological abnormalities (Springer et al. 1986b). The rats had a significant reduction in body weight compared to controls, so it seems likely that the change in relative brain weight reflects the body weight loss rather than an adverse neurological effect that affected the absolute brain weight. There was no change in relative brain weight for male rats exposed to up to 140 mg/m^3 or for female rats exposed to up to 690 mg/m^3 for 5 weeks or for male and female rats exposed to 30 mg/m^3 for 13 weeks.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in animals following inhalation exposure to wood creosote or the creosote bush.

Coal Tar Products. No studies were located regarding reproductive effects in humans or animals following inhalation exposure to coal tar pitch. No adverse effects on sperm characteristics, including sperm count and morphology, were noted in workers exposed to coal tar pitch volatiles in an aluminum reduction plant (Ward 1988). No adverse reproductive effects were reported for residents at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc. creosote wood treatment plant and was studied as a site surveillance program by the Texas Department of Health (Agency for Toxic Substances and Disease Registry 1994). There was no difference in the overall reproductive outcome of female residents of the Koppers area compared to the comparison neighborhood or the 1990 National Health Interview Survey. In particular, there was no effect on the number of pregnancies, live births, premature births, spontaneous abortions, or still births. Koppers women who reported having problems becoming pregnant during the first year of surveillance had an average of 1.3 pregnancies compared to an average of 3.4 pregnancies for women in the comparison neighborhood

who also reported difficulty in becoming pregnant, but no difference in pregnancy outcome was noted during the second year of surveillance (Agency for Toxic Substances and Disease Registry 1994). It is likely that reports of difficulty in becoming pregnant were confounded by perception of risk and possibly also by the age of the mother as the difference was not significant when the results for the entire group were adjusted for concerns about chemical exposure, or when women over the age of 39 were excluded from the analysis.

A significant increase in the incidence of mid- and late-gestational resorptions was reported for female rats exposed to 660 mg/m^3 (but not to 84 mg/m^3) of a coal tar aerosol for 6 hours/day on gestational days 12–16 (Springer et al. 1982). Animals exposed to 660 mg/m^3 coal tar showed some signs of maternal toxicity. The thymus weight was significantly reduced and the weights of the lungs and spleen were significantly increased, but maternal body weights (without the products of conception) were not significantly reduced compared to controls and the weights of the liver, kidney, and adrenal glands were similar to controls. No change in the relative weights of ovary or testis were recorded for Fischer rats exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks (Springer et al. 1986b). Relative ovary weights were significantly decreased in Fischer rats and CD-1 mice exposed to 690 mg/m^3 (but not to 140 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Testis weight in rats exposed to $140 mg/m^3 (but not to 30 mg/m^3) coal tar for 13 weeks was significantly increased relative to controls, while testis weight in male mice exposed to 690 mg/m^3 (but not to 140 mg/m^3) coal tar was decreased relative to controls, but the difference was not significant. Examination of ovarian sections showed a significant decrease in the amount of luteal tissue in animals exposed to 690 mg/m^3 (but not to 140 mg/m^3) coal tar for 5 or 13 weeks.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to wood creosote or the creosote bush.

Coal Tar Products. No studies were located regarding developmental effects in humans or animals following inhalation exposure to coal tar pitch or coal tar pitch volatiles. As cited above, a site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant on soil contaminated with creosote revealed no adverse developmental

effects on the residents (Agency for Toxic Substances and Disease Registry 1994). Specifically, there was no difference in the number of low birth weight births or in birth defects.

In a study by Springer et al. (1982) mated female rats were exposed to 0, 17, 84, or 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12–16. There was a significant increase in the incidence of mid- and late-gestational resorptions in the 660 mg/m^3 group compared with controls. Crown-rump length, fetal weight, fetal lung weight, and placental weights were significantly reduced, and there was a significantly increased incidence of reduced ossification in the 660 mg/m^3 group and a significant trend for reduced ossification with increased coal tar concentration. Cleft palates were also observed in this group, but the increased incidence was not significant. No significant changes in the number of resorptions, size of fetuses, or incidence of abnormalities were observed for animals exposed to less than 660 mg/m^3. Animals exposed to 660 mg/m^3 coal tar showed some signs of maternal toxicity. The thymus weight was significantly reduced and the weights of the lungs and spleen were significantly increased, but maternal body weights (without the products of conception) were not significantly reduced compared to controls and the weights of the liver, kidney, and adrenal glands were similar to controls.

3.2.1.7 Cancer

No studies were located regarding cancer in humans or animals following inhalation exposure to wood creosote or the creosote bush.

Coal Tar Products. A number of studies have provided evidence of an association between occupational exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles and increased incidence of cancer-related mortalities and cancer in humans (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Kerr et al. 2000; Lloyd 1971; Lloyd et al. 1970; Martin et al. 2000; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg and Andersen 1995; Sakabe et al. 1975; Spinelli et al. 1991; Stern et al. 2000; TOMA 1982; Tremblay et al. 1995), although other industrial chemicals were present. Other studies have not shown a statistically significant association between occupational exposure to coal tar products and increased incidence of specific types of cancer (CEOH 1997; Kromhout et al. 1992; Kunze et al. 1992; Romundstad et al. 2000; Schildt et al. 1999; Siemiatycki et al. 1994; Swaen and Slangen 1997). Interpretation of the data of many of the studies mentioned above is limited by a variety of factors including small study populations, concurrent cigarette smoking, and poor exposure data.

Industrial populations that have been studied include coke oven workers, aluminum smelter workers, steelworkers, and people exposed to creosote through other activities (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; CEOH 1997; Costantino et al. 1995; Gibbs and Horowitz 1979; Kromhout et al. 1992; Kunze et al. 1992; Lloyd 1971; Lloyd et al. 1970; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Romundstad et al. 2000; Rönneberg and Andersen 1995; Sakabe et al. 1975; Siemiatycki et al. 1994; Spinelli et al. 1991; Stern et al. 2000; Swaen and Slangen 1997; TOMA 1982; Tremblay et al. 1995). Following occupational inhalation exposure to coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, cancer was observed involving a number of tissues including the respiratory tract, lips and skin, lung, pancreas, kidney, scrotum, prostate, rectum, bladder, and central nervous system; leukemia and lymphoma were also diagnosed (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Gibbs 1985; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Liu et al. 1997; Lloyd 1971; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg and Andersen 1995; Sakabe et al. 1975; Stern et al. 2000; TOMA 1982; Tremblay et al. 1995). Exposure levels in these studies were not consistently quantified. In addition, there were confounding factors. In all cases of occupational exposure, the workers were not exposed to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles as single agents, but in combination with other chemicals. For instance, some employees exposed themselves to additional carcinogens via cigarette smoking (TOMA 1982). In other studies, exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles was generally combined with other substances. Some studies had significant limitations. For example, TOMA (1982) is a retrospective study and no attempt was made to estimate occupational exposure levels from any source. Additional limitations of the study are the absence of data on smoking habits, short cut-off date of 10 days of employment, use of U.S. male mortality rates for comparison as opposed to regional mortality rates, and mixed chemical exposure.

Spinelli et al. (1991) evaluated the mortality and cancer incidence over a 30-year period among a cohort of workers exposed to coal tar pitch volatiles emitted during production of aluminum. Aluminum is produced by one of two electrolytic processes wherein petroleum and coal tar pitch are baked in pots. These processes result in a continuous generation of coal tar pitch volatiles, which include PAHs. For analysis of these data, the assignment of exposure level was based on data on coal tar pitch volatiles from recent plant monitoring, as well as knowledge of historical operational and engineering changes. Based on the time-weighted average (TWA) for coal tar pitch volatiles of 0.2 mg/m^3 benzene soluble material (BSM), 4 coding systems were adopted:

(1) no exposure to coal tar pitch volatiles (0 mg/m^3 BSM),

(2) low exposure to coal tar pitch volatiles (<0.2 mg/m^3 BSM),

(3) medium exposure to coal tar pitch volatiles (0.2–1.0 mg/m^3 BSM), and

(4) high exposure to coal tar pitch volatiles (>1.0 mg/m^3 BSM).

According to Spinelli et al. (1991), jobs with the highest exposure to coal tar pitch volatiles primarily occurred before 1970 and included jobs located within the potrooms. The primary findings of this study were a significantly elevated incidence of bladder cancer in the cohort and the significant trend toward higher risk with greater lifetime exposure to coal tar pitch volatiles. Also observed was a nonstatistically significant association between lung cancer and coal tar pitch volatiles. Adjusting for smoking did not change the observed association. The authors state that the apparent discrepancy between the results of this study (Spinelli et al. 1991) and those performed previously that found a strong association between lung cancer and exposure to coal tar pitch volatiles (Anderson et al. 1982; Gibbs 1985; Gibbs and Horowitz 1979) might relate to the latency period and the levels of coal tar pitch volatiles, both of which were lower in the Spinelli et al. (1991) study relative to the previous studies.

Costantino et al. (1995) carried out an epidemiological study of 5,321 coke oven workers and 10,497 non-oven workers matched for place of work and socioeconomic status. The average daily exposure to coal tar pitch volatiles was determined in previously published studies as 3.15 mg/m^3 for topside full time jobs, 1.99 mg/m^3 for topside part time jobs and 0.88 mg/m^3 for side jobs. Mortality was assessed by race for 33 categories of cause of death. All RRs were adjusted for age, race, coke plant, and period of follow up as appropriate. Statistically significant excess mortality occurred in coke workers for several categories of death. The RR for all causes of death was 1.08 ($P<0.01$; 95% CI=1.02–1.14). The increase in overall mortality was primarily due to increased deaths from the following cancers: all cancers (RR=1.34; $P<0.001$; 95% CI=1.19–1.50), cancer of the lungs, bronchus, and trachea (RR=1.95; $P<0.001$; 95% CI=1.59–2.33), and prostate cancer (RR=1.57; $P<0.05$; 95% CI=1.09–2.30). These findings were consistent across racial categories, but excess risk was higher among nonwhite than white workers. There were highly significant trends ($P<0.001$) for increased cancer risk with increasing duration of employment and increasing exposure. The study did not control for smoking. However, the similar socioeconomic status of the controls and exposed workers suggests that it is unlikely that there was a substantial difference in smoking habits between the two groups.

Elevated risk of death from cancer and from lung cancer was reported in a retrospective cohort study of 6,635 male workers employed for more than 15 years during the period 1970–1985 in seven factories in China (Liu et al. 1997). The main chemical exposure was to coal tar pitch volatiles. Significantly

elevated SMRs were observed in highly exposed workers for all causes of death (SMR 1.69, P<0.01), all cancers (SMR 2.53, P<0.01), digestive cancer (SMR 1.97, P<0.01), esophageal cancer (SMR 3.97, P<0.05), liver cancer (SMR 2.25, P<0.01), and lung cancer (SMR 4.3, P<0.01). The SMRs for highly exposed nonsmokers were also elevated for all cancers (SMR 2.1, P<0.01) and lung cancer (SMR 3.0, P<0.01), and there was a significant correlation between deaths from lung cancer and exposure to coal tar pitch volatiles.

A cohort study (Karlehagen et al. 1992) that examined cancer incidence among 922 workers exposed to coal tar creosote while impregnating wood (railroad cross ties and telegraph poles) at seven plants in Sweden and six plants in Norway during the period of 1950–1975 reported a significant increase in incidence of nonmelanoma skin cancer (observed=9, standardized incidence ratio (SIR)=2.37, 95% CI=1.08–4.50, P=0.02) for the entire study population and a significant increase in cancer of the lip (observed=5, expected=1.34, 95% CI=1.21–8.7, P=0.01) among individuals exposed over 20 years earlier compared with the national male population. Workers were exposed to creosote vapors when removing wood from the autoclave in which it was pressure-treated, but were also likely to receive dermal exposure while handling the wood. The conclusions that can be drawn from this study are limited by the lack of information about the smoking status or exposure to sunlight of the subjects and the absence of measurements of exposure to creosote.

A study of proportionate mortality among the 11,144 members of the United Union of Roofers, Waterproofers, and Allied Workers (Stern et al. 2000) found a significant excess in mortality due to cancers of the lung, bladder, esophagus, larynx, and to pneumoconioses and other nonmalignant respiratory diseases in these workers compared with U.S. age-, gender-, and race-specific proportional mortality rates for the years of the study (1950–1996). These workers were occupationally exposed to asphalt fumes and asbestos as well as coal tar pitch volatiles, and cigarette smoking must also be considered as a likely confounding factor. Exposure to coal tar pitch volatiles is higher for waterproofers than for roofers, and a comparison of proportional mortality of nine local unions with a large number of waterproofers found that the risk of death due to cancer, lung cancer, esophageal cancer, and pharyngeal cancer were higher in these workers (2,804 deaths) than in the workers (8,334 deaths) who did not do much of waterproofing, but these differences were not analyzed for statistical significance.

A significant association between exposure to coal tar creosotes and lung cancer was reported in a case-control study of a cohort of 1,535 male workers who were active in the French national electricity and gas company (EDF-GDF) between 1978 and 1989 (Martin et al. 2000). Controls (four per case) were

matched to the 310 cases by year of birth. Occupational exposure was estimated using a job exposure matrix, and in the absence of individual data on tobacco consumption, the socioeconomic status of the subjects was used to control for this factor. Since a positive association between exposure to asbestos and lung cancer had been previously established for this study population, an adjustment for asbestos exposure was also included in the analysis. The unadjusted odds ratios (ORs) for workers exposed to coal tar and coal tar creosotes were significantly increased. After adjusting for socioeconomic status and asbestos exposure, the odds ratio for coal tar creosotes was still significant (OR=1.56, 95% CI=1.08–2.27), but the odds ratio for coal tar was not significant. A similar pattern was seen when the data were analyzed by level of exposure. Coal tar showed a significant association with increased lung cancer risk at high exposures, but the odds ratio was no longer significant when the data were adjusted for socioeconomic status and asbestos exposure. High exposure to coal tar creosotes was significantly associated with increased odds ratios for lung cancer, both with and without adjustment for socioeconomic status and asbestos exposure, and there was also a significant exposure-response relationship between coal tar creosotes and lung cancer.

A case-control study conducted with 183 neuroblastoma cases, aged 0–14 years diagnosed among residents of New York state (excluding New York City) between 1976 and 1987, found a significant increase in risk of neuroblastoma associated with self-reported paternal exposure to creosote (21 cases, 20 controls, OR=2.1, 95% CI=1.1–4.3), coal soot (6 cases, 2 controls, OR=5.9, 95% CI=1.0–60.4), or coal tar (10 cases, 7 controls, OR=2.8, 95% CI=1.0–8.4), or maternal exposure (both certain and potential exposure combined) to coal soot (OR=10.4, 95% CI=1.2–495.3) or coal tar (OR=4.1, 95% CI=1.2–15.5) (Kerr et al. 2000). Cases were histologically confirmed and were compared with 372 controls matched by year of birth. Due to the small number of nonwhite cases, both cases and controls were limited to cases born to white mothers. Individuals with amended or sealed (adopted) birth certificates were also excluded from the study. Some specific exposure information was collected (via telephone interviews) for creosote, but in general, exposure was based on job description. Possible sources of uncertainty in this study include poor exposure information, the possibility of interviewer bias (interviewers were not blinded to the disease status of the child), and the possibility of the reported increases in risk being chance findings due to the large number of comparisons made.

In a study of the effects of coal tar pitch exposure on the respiratory system, Wistar rats received 10 weekly intratracheal instillations of 0.648, 13.56, and 20.0 mg of coal tar pitch (equivalent to 5.18, 109.2, and 160.0 mg/kg) or 2 mg charcoal powder (control group) and were sacrificed and examined at 1, 3, 6, 12, and 18 months after treatment (Chang et al. 1992). The treatment produced inflammation,

hyperplastic, and metaplastic changes. All rats with lung cancer were found in the two highest treatment groups. The pathogenesis of coal tar pitch-induced lung carcinomas seems to start from hyperplasia of bronchiole-alveolar epithelium, progressing through squamous metaplasia and/or different stages of dysplasia to carcinomas (Chang et al. 1992). According to Chang et al. (1992), the effects produced with coal tar pitch were consistent with the effects reported after similar treatment with PAHs and tobacco smoke condensate. Although the findings presented by Chang et al. (1992) suggest a correlation between coal tar pitch and lung cancer, the relevance of this relationship to potential human exposures by inhalation is questionable given the animal dosing technique.

In a study by Heinrich et al. (1994a, 1994b), groups of female Wistar rats were exposed to 0, 1.1, or 2.6 mg/m^3 coal tar pitch aerosol for 17 hours/day, 5 days/week for 10 months. This exposure was followed by 20 months of clean air exposure. The lung tumor rates of animals exposed to 1.1 and 2.6 mg/m^3 coal tar pitch aerosol for 10 months were 4.2 and 38.9%, respectively. Most of the tumors were benign and malignant keratinizing squamous cell tumors. Some broncho-alveolar adenomas and adenocarcinomas were also found. No exposure-related tumors were found in other organs. No lung tumors were found in the control animals. Similar results (i.e., increased incidence of benign lung tumors) were also observed in Wistar rats exposed to 1.1 and 2.6 mg/m^3 (increased incidence of tumors 33.3 and 97.2%, respectively) coal tar pitch aerosol for 17 hours/day, 5 days/week for 20 months, followed by clean air exposure for 10 months (Heinrich et al. 1994a, 1994b).

In a study by MacEwen et al. (1977), groups of 40 male and 40 female Sprague-Dawley rats were exposed to 10 mg/m^3 coal tar aerosol 6 hours/day, 5 days/week for 18 months. Control animals were held in a vivarium. After exposures, the animals were returned to the vivarium and held for an additional 6 months of observation prior to necropsy. The tumors found in rats exposed to coal tar aerosol showed 31 of 38 females and all males (38 of 38) with squamous cell carcinoma (lung) and 3 of 38 females with mammary fibroadenoma. Overall tumor incidences for controls were 0% for males and 13% for females. Overall tumor incidences for exposed animals were 100% for males and 82% for females.

MacEwen et al. (1977) indicated that tumor-susceptible ICR CF-1 female mice and tumor-resistant CAF1-JAX female mice exposed to coal tar aerosol-BTX mixture continuously for 90 days at concentrations of 0, 0.2, 2, and 10 mg/m^3 developed skin tumors at 2 and 10 mg/m^3, respectively. In the ICR CF-1 strain mice, tumors continued to develop for as long as 86 weeks postexposure. Skin tumor incidences in ICR CF-1 mice exposed to 0, 0.2, 2, and 10 mg/m^3 coal tar aerosol-BTX mixture for 90 days were 3 of 225 (1%), 1 of 61 (2%), 14 of 75 (19%), and 44 of 55 (80%), respectively. Skin tumor

incidences in CAF1-JAX mice exposed to 0, 0.2, 2, and 10 mg/m^3 coal tar aerosol-BTX mixture for 90 days were 0 of 225 (0%), 0 of 75 (0%), 3 of 65 (5%), and 18 of 43 (42%), respectively. Tumors were confirmed by histological examination. Tumor-susceptible ICR CF-1 female mice and tumor-resistant CAF1-JAX female mice were exposed to 0 or 10 mg/m^3 coal tar aerosol-BTX mixture intermittently for 18 months (MacEwen et al. 1977). For animals exposed intermittently, skin tumor incidences were 5 of 75 in ICR CF-1 mice and 3 of 75 in controls, and 2 of 50 in CAF1-JAX mice as compared to 1 of 50 in controls. Calculation of total exposure indicated the amount of coal tar reaching the skin of the animals was the same as in the 90-day continuous exposure study. However, the intermittent exposure allowed daily normal cleaning of the fur. The incidence of tumors was less in the animals subjected to intermittent exposure. Tumors found in control and exposed mice of both strains included alveolargenic carcinoma, alveolargenic adenoma, bronchogenic carcinoma, squamous cell carcinoma, lymphosarcoma, reticulum cell sarcoma, hemangiosarcoma, hemopoietic tumors, and subcutaneous sarcoma. The effects of the carrier solvents (BTX) used in this study were not evaluated.

Levels of exposure associated with CELs of creosote are indicated in Table 3-1 and plotted in Figure 3-1.

3.2.2 Oral Exposure

This section describes the health effects observed in humans and laboratory animals associated with oral exposure to coal tar and beechwood creosote at varying times and exposure levels. The LSEs by the oral route presented in Tables 3-2 and 3-3 and Figures 3-2 and 3-3 include studies using beechwood creosote, petroleum creosote, coal tar, and coal tar creosote. All reliable exposure levels have been reported.

Although beechwood creosote, creosote bush resin, and coal tar creosote have some components in common, such as phenols, it is not known whether these mixtures will induce the same effects. Furthermore, coal tar creosote contains a complex mixture of animal and human carcinogenic and co-carcinogenic PAHs that probably accounts for the cancer risk associated with chronic exposure to coal tar creosote while wood creosote does not.

3.2.2.1 Death

Wood Creosote. The acute toxicity of beechwood creosote in both rats and mice was studied following single gavage administration of a 10% aqueous solution (Miyazato et al. 1981). The oral LD_{50} values of beechwood creosote in Wistar rats were 885 mg/kg for males and 870 mg/kg for females. The highest dose at which no death occurred was 600 mg/kg. There was no significant difference between male and female rats with respect to mortality, and most animals died within 24 hours. However, no treatment-related deaths were observed when rats were given doses of beechwood creosote in the feed of up to

Table 3-2 Levels of Significant Exposure to Creosote - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (CD)	5 d Gd 12-16 1x/d (G)				740 F (10 of 16 animals died)	Hackett et al. 1984 coal tar
2	Rat (Wistar)	once (G)				1700 M (LD50)	Pfitzer et al. 1965 coal tar
	Systemic						
3	Rat (CD)	5 d Gd 12-16 1x/d (G)	Hepatic	370 F			Hackett et al. 1984 coal tar
			Renal	370 F			
			Endocr		90 F (significant increase in adrenal weight)		
			Bd Wt	140 F	180 F (significant decrease in body weight gain)		
4	Rat (Wistar)	once (G)	Gastro	53 F	106 F (significant decrease in peristaltic movement of intestine)		Ogata et al. 1993 wood creosote
5	Mouse (ICR)	5 d Gd 5-9 1 x/d (G)	Resp	400 F			Iyer et al. 1993 petroleum creosote
			Hepatic	400 F			
			Renal	400 F			
			Endocr	400 F			
			Bd Wt		400 F (16.1% decreased maternal body weight)		

Table 3-2 Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)		LOAEL Serious (mg/kg)		Reference Chemical Form
	Systemic								
6	Mouse (CD-1)	once (G)	Gastro		0.08 M	(significant reduction in propulsive motility of the colon)			Ogata et al. 1999 wood creosote
	Immuno/lymphoret								
7	Rat (CD)	5 d Gd 12-16 1x/d (G)			90 F	(significant increase in adrenal weight and decrease in thymus weight)			Hackett et al. 1984 coal tar
	Reproductive								
8	Rat (CD)	5 d Gd 12-16 1x/d (G)		140	180	(significant increase in the number of resorptions)	370	(significant decrease in number of live fetuses/litter and increase in the number of resorptions)	Hackett et al. 1984 coal tar
9	Rat (Sprague-Dawley)	3 d Gd 12-14 1x/d (G)		740					Springer et al. 1986a coal tar
10	Mouse (ICR)	5 d Gd 5-9 1x/d (G)		400 F					Iyer et al. 1993 creosote
	Developmental								
11	Rat (CD)	5 d Gd 12-16 1x/d (G)		90	140	(significant decrease in relative fetal lung weight and a significant increase in anomalous fetuses)	370	(significant increase in the incidence of cleft palate, syndactyly/ectrodactyly and missing toenails on hind feet)	Hackett et al. 1984 coal tar
12	Rat (Sprague-Dawley)	3 d Gd 12-14 1x/d (G)					740	(significant increase in early mortality, increased incidence of cleft palate and small lungs)	Springer et al. 1986a coal tar

Table 3-2 Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Developmental						
13	Mouse (ICR)	5 d Gd 5-9 1x/d (G)			400	(12% decreased fetal weight, increased incidence of missing sternbrae)	Iyer et al. 1993 creosote
	INTERMEDIATE EXPOSURE						
	Systemic						
14	Rat (Fischer- 344)	3-5 wk 1x/d (GO)	Gastro	50 M			Chadwick et al. 1995 coal tar
			Bd Wt	50 M			
15	Mouse (B6C3F1)	28 d (F)	Bd Wt	410 M	693 M	(approx 16% decreased body weight)	*Culp and Beland 1994* coal tar
			Other	410 M	693 M	(significantly decreased food intake)	
16	Mouse	15 d ad lib (F)	Bd Wt	659 M	1871 M	(12.5% decreased body weight)	Weyand et al. 1991 coal tar
			Other	659 M	1871 M	(decreased food consumption)	

Table 3-2 Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
17	Mouse (B6C3F1)	185 d (F)	Resp	462			Weyand et al. 1994 coal tar
			Cardio	462			
			Gastro	462			
			Hemato	462			
			Hepatic	462			
			Renal	462			
			Endocr	462			
			Bd Wt	462			
18	Mouse (B6C3F1)	94 d (F)	Resp	462			Weyand et al. 1994 coal tar
			Cardio	462			
			Gastro	462			
			Hemato	462			
			Hepatic	462			
			Renal	462			
			Endocr	462			
			Bd Wt	462			

Table 3-2 Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
19	Mouse A/J	260 d (F)	Bd Wt	236 F			Weyand et al. 1995 coal tar
	Immuno/lymphoret						
20	Mouse (B6C3F1)	185 d (F)		462			Weyand et al. 1994 coal tar
21	Mouse (B6C3F1)	94 d (F)		462			Weyand et al. 1994 coal tar
	Reproductive						
22	Mouse (B6C3F1)	185 d (F)		462			Weyand et al. 1994 coal tar
23	Mouse (B6C3F1)	94 d (F)		462			Weyand et al. 1994 coal tar
	Cancer						
24	Mouse A/J	260 d (F)				100 F (significant increase in incidence of lung tumors CEL: 70%/0%)	Weyand et al. 1995 Coal tar
	CHRONIC EXPOSURE						
	Death						
25	Mouse (B6C3F1)	2 yrs (F)				333 F (significantly increased incidence of early mortality)	Culp et al. 1998 Coal tar
	Systemic						
26	Mouse (B6C3F1)	2 yrs (F)	Bd Wt	628 F	1364 F (decrease in body weight)		Culp et al. 1996a coal tar

Table 3-2 Levels of Significant Exposure to Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
27	Mouse (B6C3F1)	2 yrs (F)	Resp	117 F	333 F (significantly decreased lung weight)		Culp et al. 1998 coal tar
			Gastro	1300 F			
			Hepatic	117 F	333 F (40% increase in liver weight)		
			Renal	33 F	117 F (significantly decreased kidney weight)		
			Bd Wt	117 F	333 F (20% decrease in body weight gain)		
			Other	117	346 F (significantly reduced food consumption)		
	Cancer						
28	Mouse (B6C3F1)	2 yrs (F)				200 F (increased incidence of tumors of the forestomach CEL: 61%: 0% in controls)	Culp et al. 1996a Coal tar
29	Mouse (B6C3F1)	2 yrs (F)				333 F (significantly increased incidence of neoplasms of the liver, lung and forestomach and of hemangiosarcomas and histiocytic sarcomas, CEL: 27/47 alveolar/bronchiolar adenomas)	Culp et al. 1998 Coal tar

aThe number corresponds to entries in Figure 3-2.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; Hemtao = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); x = times

Figure 3-2 Levels of Significant Exposure to Creosote - Oral

Acute (≤14 days)

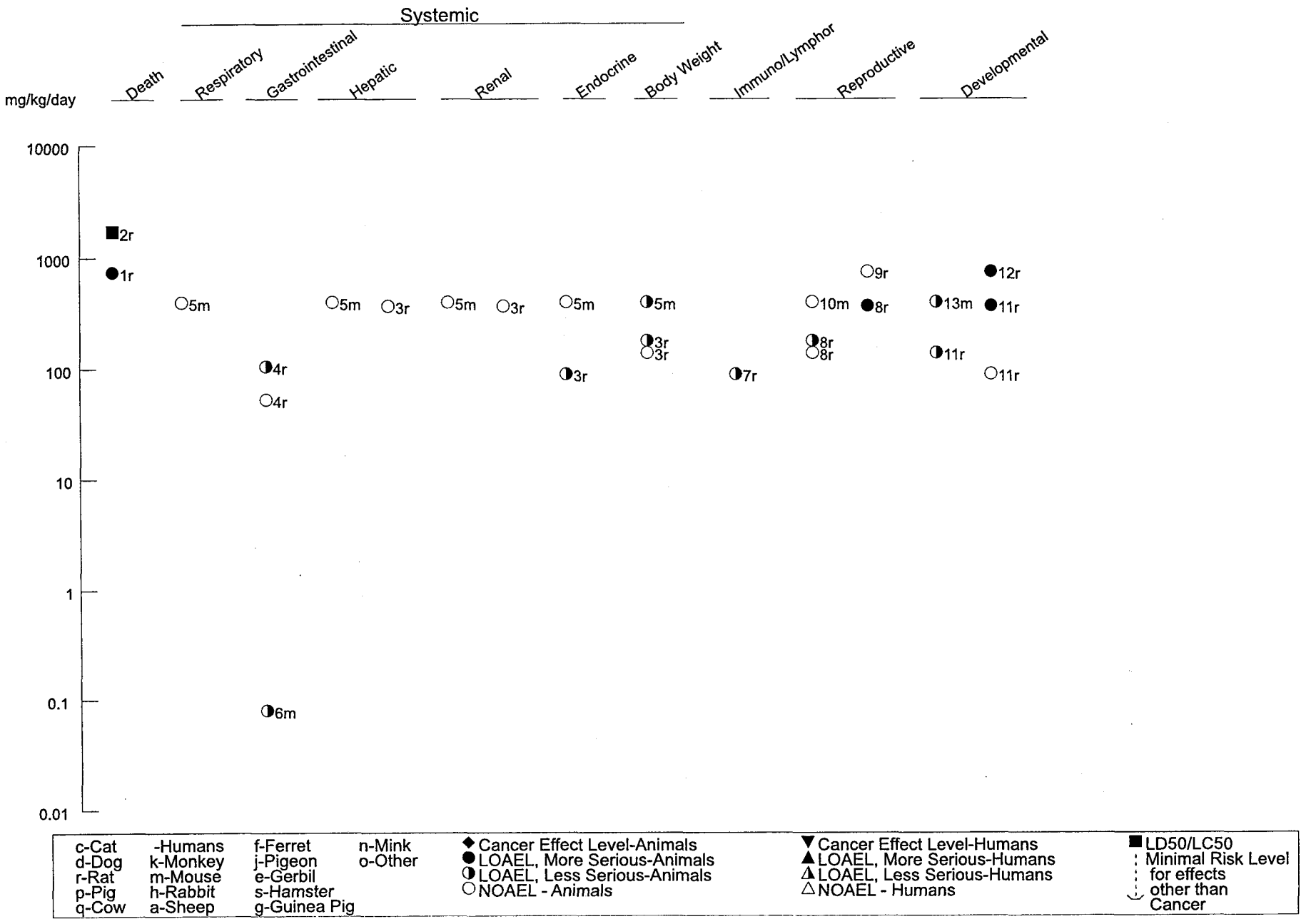


Figure 3-2 Levels of Significant Exposure to Creosote - Oral (*Continued*)

Intermediate (15-364 days)

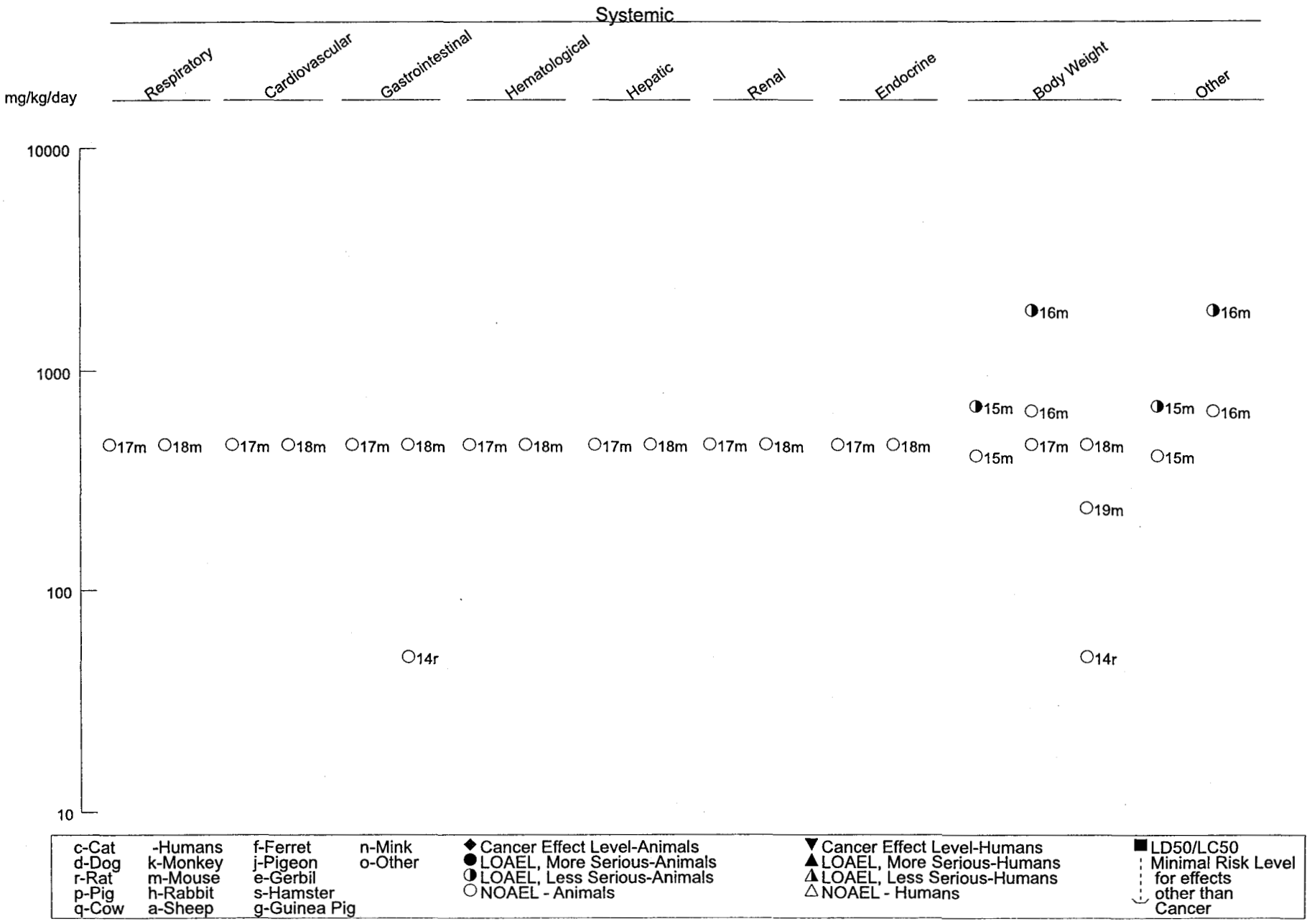
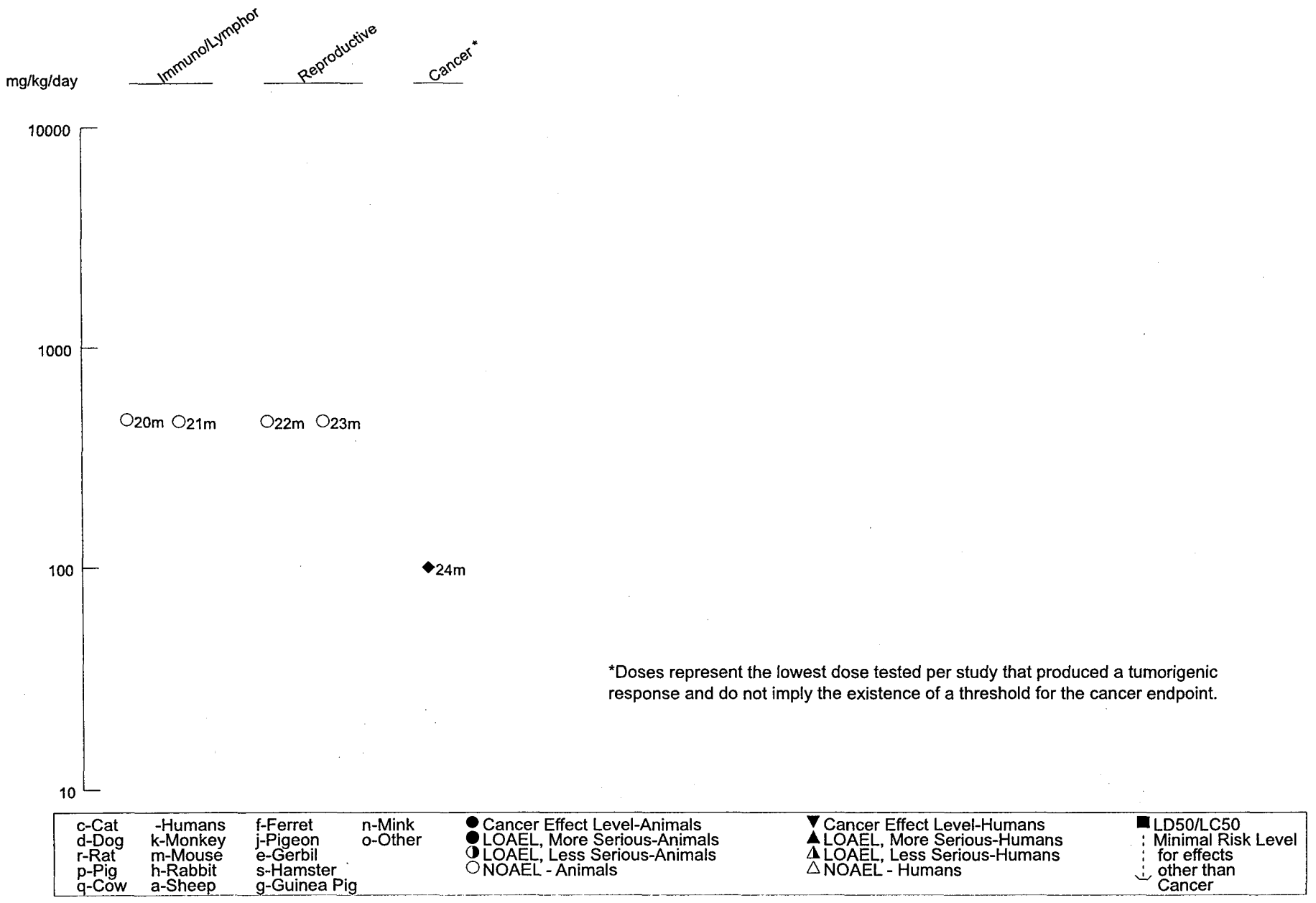


Figure 3-2 Levels of Significant Exposure to Creosote - Oral (*Continued*)

Intermediate (15-364 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

Figure 3-2 Levels of Significant Exposure to Creosote - Oral

Chronic (≥365 days)

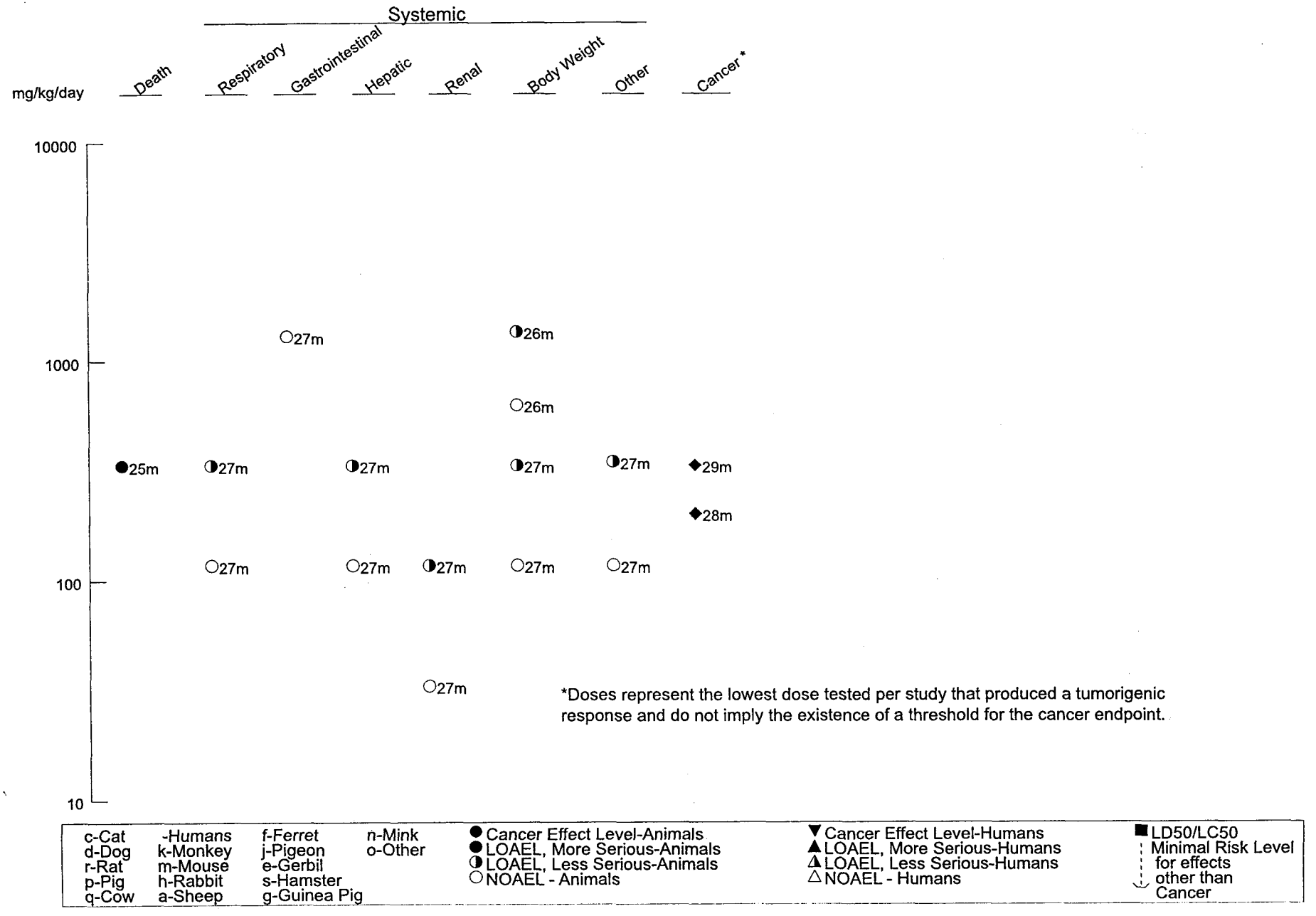


Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	once (G)				885 M (LD50) 870 F	Miyazato et al. 1981 beechwood
2	Mouse (ddY)	once (G)				525 M (LD50) 433 F	Miyazato et al. 1981 beechwood
Neurological							
3	Rat (Wistar)	once (G)				600 (convulsions)	Miyazato et al. 1981 beechwood
4	Mouse (ddY)	once (G)		313 M		376 M (convulsions) 313 F	Miyazato et al. 1981 beechwood

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Systemic						
5	Rat (Wistar)	3 mo (F)	Resp	812			Miyazato et al. 1981 beechwood creosote
			Cardio	812			
			Hemato	812			
			Hepatic	163 F	168 M (increased relative liver weight) 215 F		
			Renal	168 M	210 M (increased relative kidney weight) 163 F		
			Endocr	812			
			Bd Wt	534	768 F (11% decreased body weight)	812 M (22% decreased body weight)	

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
6	Mouse (ddY)	3 mo (F)	Resp	1427			Miyazato et al. 1981 beechwood creosote
			Cardio	1427			
			Hemato	1427			
			Hepatic	768 M 1127 F	1065 M (significant increase in relative liver weight) 314 F		
			Renal	1427			
			Endocr	1427			
			Bd Wt	450 M 1127 F	768 M (16% decreased body weight) 1427 F (11% decreased body weight)		
	Immuno/lymphoret						
7	Rat (Wistar)	3 mo (F)		317 M 768 F	805 M (increased relative spleen weight)		Miyazato et al. 1981 beechwood
8	Mouse (ddY)	3 mo (F)		1810			Miyazato et al. 1981 beechwood
	Neurological						
9	Rat (Wistar)	3 mo (F)		768 F	257 M (increased relative brain weight)		Miyazato et al. 1981 beechwood
10	Mouse (ddY)	3 mo (F)		1810			Miyazato et al. 1981 beechwood

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Reproductive						
11	Rat (Wistar)	3 mo (F)		317 M 768 F	805 M (increased relative testes weight)		Miyazato et al. 1981 beechwood
12	Mouse (ddY)	3 mo (F)		1810			Miyazato et al. 1981 beechwood
	CHRONIC EXPOSURE						
	Death						
13	Rat (Sprague-Dawley)	95 or 102 wk G				200 Significant increase in mortality in male and female rats.	Kuge et al. 2001 Seirogan
14	Rat (Wistar)	96 wk (F)				313 M (30/51 died)	Miyazato et al. 1984b beechwood
	Systemic						
15	Rat (Sprague-Dawley)	95 or 102 wk G	Cardio			200 M Significant reduction in heart weight.	Kuge et al. 2001 Seirogan
			Bd Wt			200 F Significant reduction in mean terminal body weight and body weight change.	

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
16	Rat (Wistar)	96 wk (F)	Cardio	143 M 394 F	313 M (increased relative heart weight)		Miyazato et al. 1984b beechwood creosote
			Hepatic		143 M (increased relative liver weight and serum cholesterol) 179 F (increased serum cholesterol)		
			Renal		143 M (increased relative kidney weight, increased BUN, nephrosis) 179 F		
			Endocr	143 M 394 F	313 M (increased relative weight of adrenal glands) 313 F		
			Bd Wt	394			
17	Mouse (ddY)	52 wk (F)	Resp	532			Miyazato et al. 1984a beechwood creosote
			Hemato	532			
			Hepatic	532			
			Renal	532			
			Bd Wt	532			
	Immuno/lymphoret						
18	Rat (Sprague-Dawley)	95 or 102 wk G			200 M Significant reduction in spleen weight.		Kuge et al. 2001 Seirogan

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Immuno/lymphoret						
19	Rat (Sprague-Dawley)	95 or 102 wk G			200 F Significant reduction in thyroid-parathyroid weight.		Kuge et al. 2001 Seirogan
20	Rat (Wistar)	96 wk (F)		394			Miyazato et al. 1984b beechwood
21	Mouse (ddY)	52 wk (F)		532			Miyazato et al. 1984a beechwood
	Neurological						
22	Rat (Wistar)	96 wk (F)		179 F	143 M (increased relative brain weight) 394 F		Miyazato et al. 1984b beechwood
23	Mouse (ddY)	52 wk (F)			247 M (increased relative brain weight) 297 F		Miyazato et al. 1984a beechwood
	Reproductive						
24	Rat (Sprague-Dawley)	95 or 102 wk G			200 M Significant increase in testis weight		Kuge et al. 2001 Seirogan
25	Rat (Wistar)	96 wk (F)		394			Miyazato et al. 1984b beechwood

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
26	Mouse (ddY)	52 wk (F)		532			Miyazato et al. 1984a beechwood

aThe number corresponds to entries in Figure 3-3.

Differences in levels of health effects and cancer between males and females are not indicated in figure 3-3

Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; Hemtao = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); x = times

Figure 3-3 Levels of Significant Exposure to Wood Creosote - Oral

Acute (≤14 days)

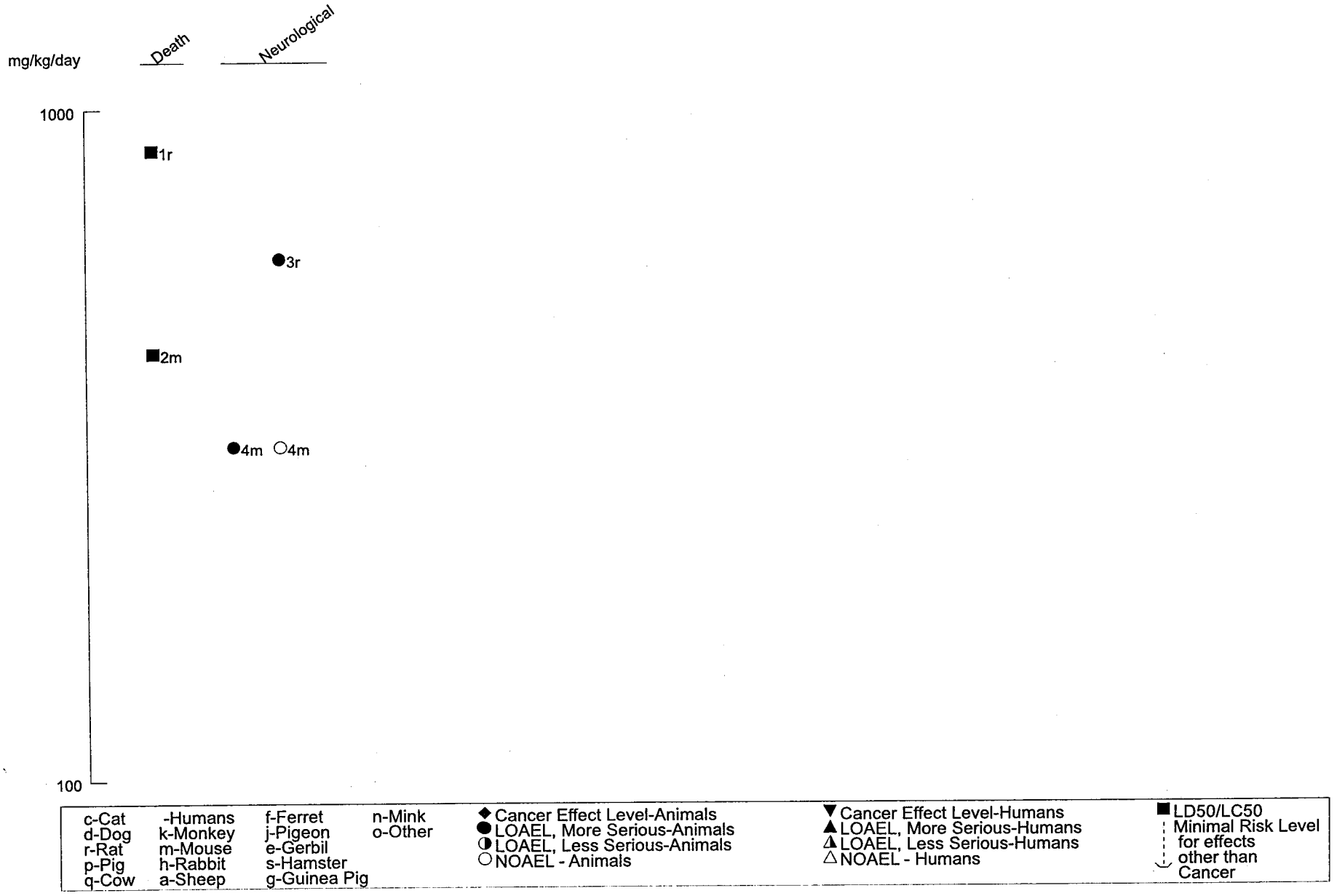


Figure 3-3 Levels of Significant Exposure to Wood Creosote - Oral (*Continued*)

Intermediate (15-364 days)

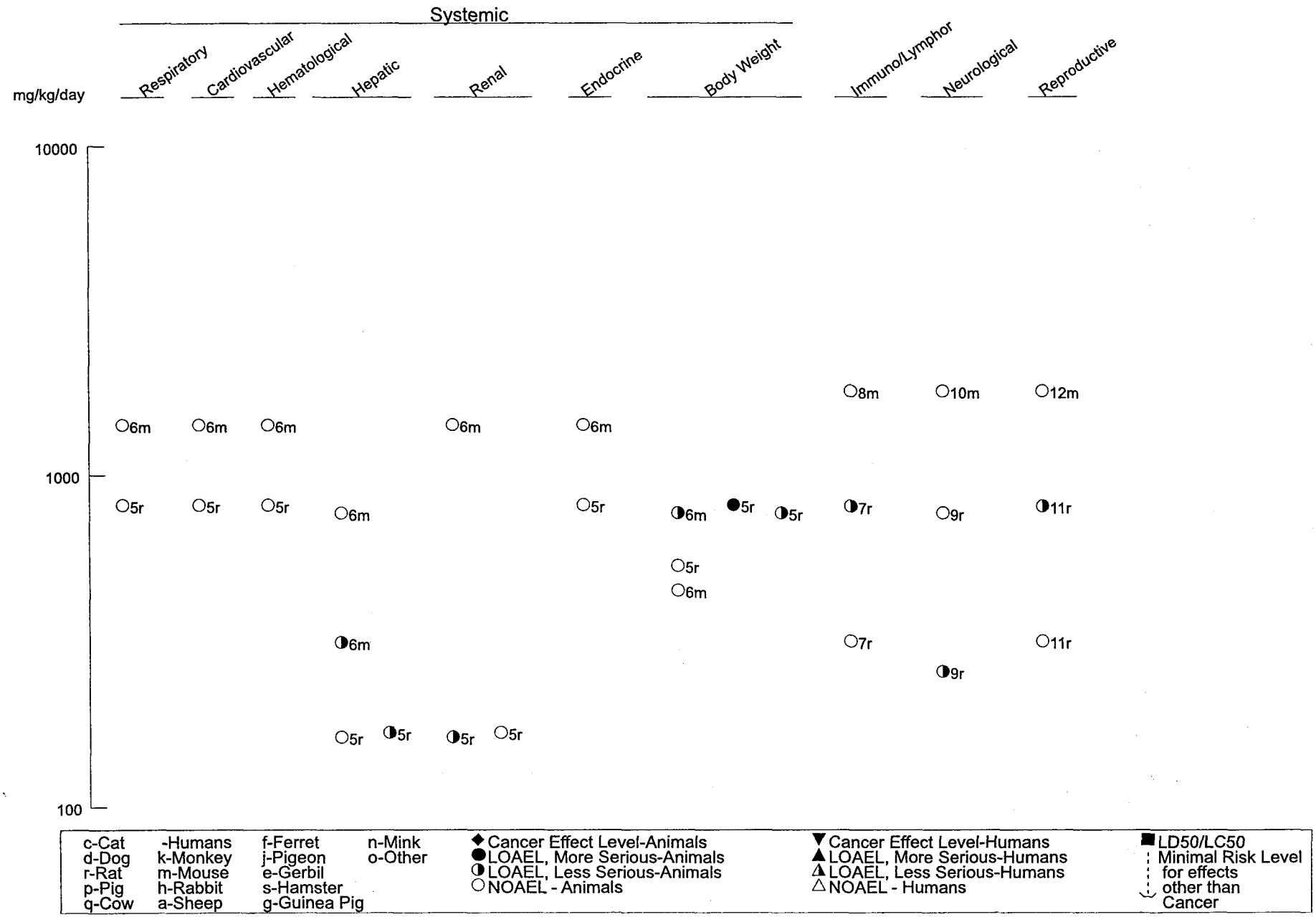
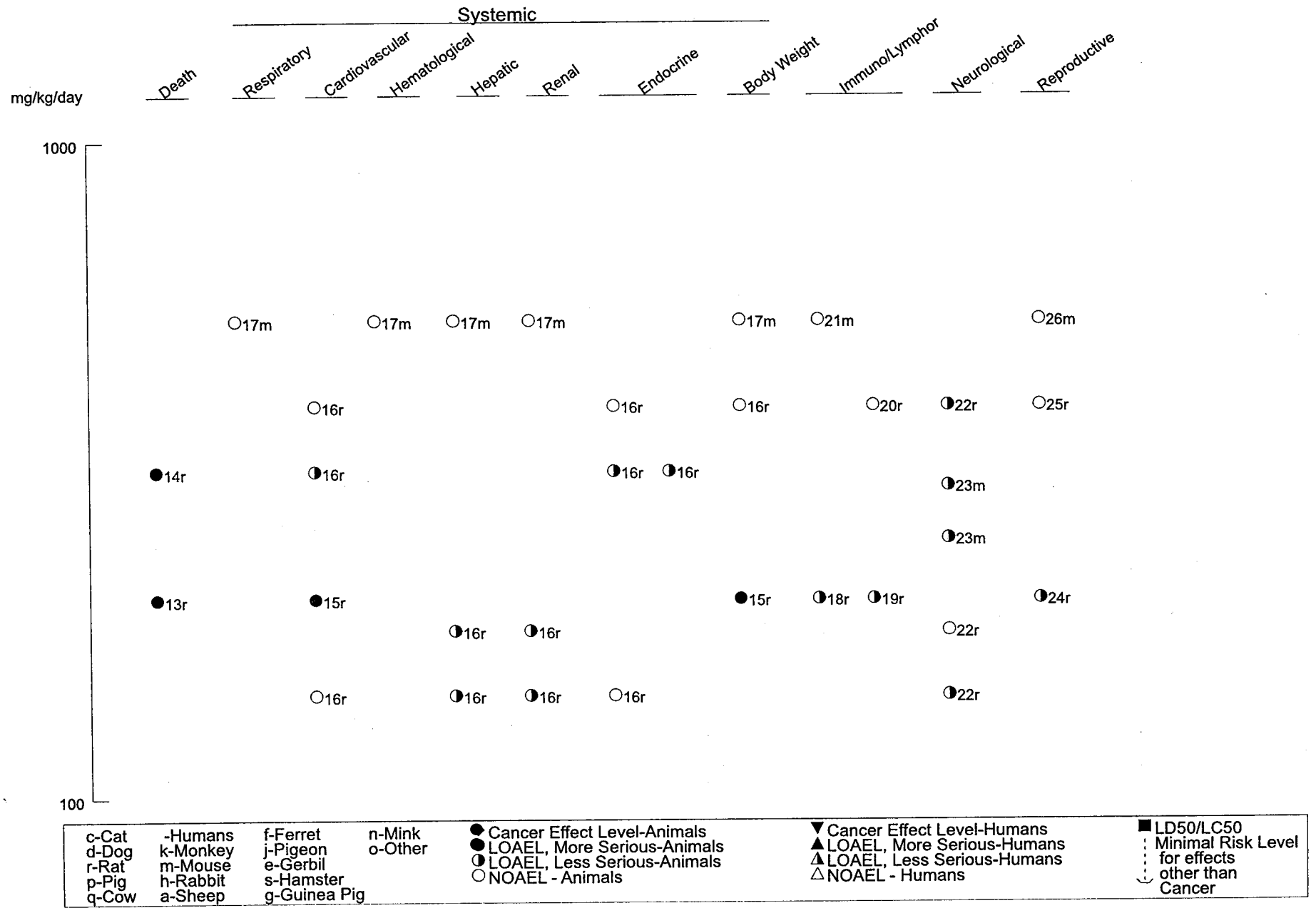


Figure 3-3 Levels of Significant Exposure to Wood Creosote - Oral (*Continued*)

Chronic (≥365 days)



812 mg/kg/day (males) or 768 mg/kg/day (females) for 3 months (Miyazato et al. 1981). Male and female Wistar rats fed diets that contained up to 313 or 394 mg/kg/day beechwood creosote for 96 weeks exhibited deaths in all groups (Miyazato et al. 1984b). There was no treatment-related increase in mortality in the females; the major cause of death in the females including controls was bronchpneumonia and leukemia. The high-dose males had a slightly higher mortality rate than controls and low-dose males; and this was due to chronic progressive nephropathy. Significant increases in mortality were observed in male and female Sprague-Dawley rats administered wood creosote by gavage at 200 mg/kg/day for 40 or 80 weeks, respectively (Kuge et al. 2001). Mortality in groups of rats administered 20 or 50 mg/kg/day did not exceed the mortality rate in the control group. Based on necropsy examinations, it was suggested that mortality in the experimentally exposed animals may have been associated with aspiration of the test material.

Mice appeared to be more susceptible to the lethal effects of beechwood creosote. The oral LD_{50} values in gavaged ddY mice were 525 mg/kg for males and 433 mg/kg for females (Miyazato et al. 1981). The highest dose at which no death occurred was 376 mg/kg (males) and 433 mg/kg (females). The mortality in female mice was significantly higher than in male mice. Most animals died within 5 hours. However, no treatment-related deaths were observed when mice were given doses of beechwood creosote in the feed of up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) for 3 months (Miyazato et al. 1981). These results indicate that the acute oral toxicity of beechwood creosote is relatively low, and is influenced by the method of administration. Some species and sex differences exist.

The LD_{50} values from each reliable study for each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Coal Tar Products. A 70-year-old man died following ingestion of an unspecified amount of "industrial" creosote (presumably coal tar creosote) (Bowman et al. 1984). Death was attributed to multi-organ failure and occurred 30 hours after admission to the hospital. It is not known if this man had a history of prior coal tar creosote ingestion. Death has been reported to occur in adults and children 14–36 hours after the ingestion of about 7 and 1–2 g coal tar creosote, respectively (Lewin 1929). Thus, ingestion of creosote can be fatal to humans, but the dose level required to produce death cannot be accurately estimated from these reports.

The acute oral LD_{50} for coal tar creosote is reported to be 1,700 mg/kg in male Wistar rats (Pfitzer et al. 1965). No deaths were reported in $B6C3F_1$ mice after oral treatment with doses of manufactured gas

plant (MGP) residue, a form of coal tar, up to 462 mg/kg/day (males) or 344 mg/kg/day (females) for 94 or 185 days (Weyand et al. 1994). Cases of lethal poisoning resulting from ingestion of large amounts of coal tar creosote have been reported in larger farm animals (Cribb 1968; Davis and Libke 1968; Giffee 1945; Graham et al. 1940; Harrison 1959; Luke 1954). Some of the reports are anecdotal and do not include quantification of the amount of creosote ingested (Cribb 1968; Giffee 1945; Graham et al. 1940; Luke 1954). Experimental feeding of powdered clay pigeon targets containing an unspecified amount of coal tar pitch (15–30 g of powdered material daily for up to 15 days) caused death in 8 of 9 pigs (Davis and Libke 1968). The acute fatal doses are 4 g/kg for sheep and over 4 g/kg for calves (Harrison 1959). Based on these data, coal tar creosote can be classified as mildly to moderately toxic in acute and intermediate duration studies.

Mated female Sprague-Dawley CD rats (25–36 per group) were gavaged on gestational days 12–16 with 0, 90, 140, 180, 370, or 740 mg/kg/day coal tar (Hackett et al. 1984). Ten of the females receiving 740 mg/kg/day died within 4 days of the initial dose, but no deaths occurred at lower doses. In a feeding study, 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from MGP waste sites for 2 years (Culp et al. 1998). Coal tar 1 was a mixture of samples from seven waste sites and coal tar 2 was a mixture from two of the sites included in coal tar 1 plus a third site with a very high benzo[a]pyrene content. This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day (0.03, 0.1, and 0.3%) of coal tar 2. Dietary levels $0.3% (333 mg/kg/day coal tar 1 or 346 mg/kg/day coal tar 2) coal tar produced a significant increase in early mortality compared with controls, while lower levels did not.

The LD_{50} and LOAEL values for death from each reliable study for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

There is relatively little information available regarding the systemic effects of ingested wood creosote, coal tar creosote, coal tar, or coal tar pitch. The database consists primarily of old anecdotal reports or animal studies that would be considered inadequate by current standards. Some clinical reports describe oral exposure of humans to wood creosote, but the amounts ingested are only estimates (Alderman et al. 1994; Clark and Reed 1992; Gordon et al. 1995). Three studies published by Miyazato et al. (1981, 1984a, 1984b) that evaluated the acute, intermediate, and chronic effects of beechwood creosote in rats and mice and a chronic study in rats by Kuge et al. (2001) comprise the bulk of reliable information on

the systemic effects of ingested beechwood creosote. Based on the results of these studies, the liver, kidney, and central nervous system appear to be target organs of creosote toxicity. Effects have also been observed in the gastrointestinal, respiratory, and cardiovascular systems. No studies were located regarding musculoskeletal, endocrine, ocular, or body weight effects in humans or musculoskeletal or dermal effects in animals after oral exposure to creosote. Studies regarding systemic effects that have been observed in humans and animals after oral exposure to coal tar creosote or coal tar are discussed below. Culp et al. (1996a, 1998), Goldstein et al. (1998), Hackett et al. (1984), Iyer et al. (1993), and Weyand et al. (1994, 1995) comprise the bulk of the data for these compounds. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Tables 3-2 and 3-3 and plotted in Figures 3-2 and 3-3.

Respiratory Effects.

Creosote Bush. A report was found in the literature describing the medical condition of a 60-year-old woman hospitalized after taking 1–2 capsules of chaparral (prepared by grinding leaves of an evergreen desert shrub known as creosote bush or "greasewood;" active ingredient is nordihydroguaiaretic acid [NDGA]) daily for 10 months (Gordon et al. 1995). The patient developed "flulike syndrome" and increased her chaparral intake to six capsules/day 3 weeks before admission. She developed aspiration pneumonia requiring antibiotic therapy and endotracheal intubation.

Wood Creosote. Beechwood creosote has been and continues to be used therapeutically on a limited basis in Asia as an expectorant/cough suppressant based on its presumed ability to increase the flow of respiratory fluids. The efficacy of creosote (type not specified, but presumably beechwood creosote) as an expectorant was studied by measuring the output of respiratory tract fluids in cats given a single oral dose of 0.1 or 5 mL/kg (concentration not specified) (Stevens et al. 1943). Creosote produced a slight increase in the output of respiratory tract fluid under these conditions. This is not considered a toxic effect. Given the limitations of this study (e.g., no dose information, no other respiratory effects evaluated), it provides no useful information on the potential respiratory effects of beechwood creosote after oral exposure.

No adverse effect on lung weight was noted for Wistar rats given up to 812 mg/kg/day (males) or 768 mg/kg/day (females) beechwood creosote or ddY mice given up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) beechwood creosote in the feed for 3 months (Miyazato et al. 1981). In a chronic study, rales were observed in Sprague-Dawley rats administered wood creosote by gavage at

200 mg/kg/day (Kuge et al. 2001). These signs were not seen in rats administered wood creosote at 20 or 50 mg/kg/day. After 95 weeks, reddened lungs were evident in all groups of rats in this study, including the control group, but were more prevalent in rats administered the high dose of wood creosote. The cause of this lung reddening was not determined, but the authors suggested that it may have been associated with aspiration of the test material. There were no increases in lung weight in any of the experimental groups.

A slightly higher incidence of bronchitis or thickening of the tracheal mucous membrane was observed in ddY mice that ingested feed containing 0.3% (equivalent to 247 mg/kg/day for males and 297 mg/kg/day for females) and 0.6% (equivalent to 474 mg/kg/day for males and 532 mg/kg/day for females) beechwood creosote for 52 weeks (Miyazato et al. 1984a). However, the authors attributed this to irritation from long-term inhalation exposure to volatile components of beechwood creosote in the feed, and not to a direct toxic effect on the respiratory tissue from oral exposure.

Coal Tar Products. No adverse effect on lung weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in dimethyl sulfoxide (DMSO) on gestational days 5–9 (Iyer et al. 1993). Five groups of $B6C3F_1$ mice (24 males, 24 females) were fed a control gel diet or adulterated diets containing 0.05, 0.25, or 0.50% MGP residue, a type of coal tar formed as a by-product of coal gasification (Weyand et al. 1994). Consumption was equivalent to 0, 51, 251, or 462 mg/kg/day for males and 0, 42, 196, or 344 mg/kg/day for females. Half of the animals in each group were sacrificed after 94 days of treatment and all organs examined for gross lesions. The remaining animals from each group were maintained on diets for an additional 91 days. After a total of 185 days of treatment, the remaining animals were sacrificed and all organs examined for gross and microscopic lesions. There was no adverse effect of treatment on the lung. In another feeding study 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day (0.03, 0.1, and 0.3%) of coal tar 2. The dietary level of 0.3% coal tar produced a significant decrease in lung weight compared to controls, but lower dietary levels did not (Culp et al. 1998).

Two pigs that died after ingesting an unknown amount of coal tar pitch exhibited pneumonia (Luke 1954). Heavy respiration was observed in a Hereford bull that had accidentally ingested creosote from an open drum; the actual amount ingested could not be estimated (Cribb 1968).

Cardiovascular Effects. The case of a 52-year-old woman who had been taking creosote (type and dose not specified) for 9 years to treat chronic bronchitis was reported by Robinson (1938). The woman was found to be weak, dizzy, light-headed, and hypertensive (blood pressure=206/140 mm Hg). A modified diet and diuretic therapy relieved all of these symptoms. Upon reinstitution of creosote therapy, her blood pressure rose to 235/130. The author concluded that creosote was responsible for the woman's hypertension. This study provides anecdotal evidence of creosote-induced cardiovascular effects, but the limited sample size, lack of detail on exposure, and possibility of confounding factors limit its usefulness.

Wood Creosote. No adverse effect on heart weight was noted for rats given up to 812 mg/kg/day (males) or 768 mg/kg/day (females) beechwood creosote or mice given up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) beechwood creosote in the feed for 3 months (Miyazato et al. 1981), or female rats given up to 394 mg/kg/day and male rats given 143 mg/kg/day beechwood creosote for 96 weeks (Miyazato et al. 1984b) or male or female Sprague-Dawley rats administered 20 or 50 mg/kg/day of wood creosote by gavage for 102 weeks (Kuge et al. 2001). However, male, but not female, rats administered 200 mg/kg/day for 95 weeks showed a significant reduction in heart weight. Male rats given 313 mg/kg/day beechwood creosote for 96 weeks exhibited an increase in heart weight (Miyazato et al. 1984b).

Coal Tar Products. In a feed study of MGP coal tar by Weyand et al. (1994) using $B6C3F_1$ mice, there was no adverse effect of treatment on the aorta after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females). One pig that died after ingesting an unknown amount of coal tar pitch exhibited pericarditis (Luke 1954).

Gastrointestinal Effects.

Wood Creosote. The antidiarrheal effect of beechwood creosote was studied in rats (Ogata et al. 1993, 1999). Female Wistar rats were dosed orally with creosote in concentrations of 0, 7, 13, 27, 53, 107, 213, and 427 mg/kg mixed with 7.7 mg/kg of saline (Ogata et al. 1993). After 1 hour, 5.6 mg/kg castor oil was administered through the stomach cannula to all groups of rats to induce diarrhea. Feces excreted were then observed at 1 hour intervals during the next 7 hours. To assay antimotility effects, female Wistar rats were given creosote at the same concentrations as above. After 1 hour, 0.2 mL of a charcoal meal (12% wet weight [w/w] charcoal powder and 2% [w/w] gum arabic in water) was administered through the stomach cannula and the rats sacrificed 20 minutes later; the small intestine was examined to determine how far the charcoal meal had traveled from the stomach. Creosote administered 1 hour before

the castor oil treatment prevented diarrhea with an ED_{50} of 53 mg/kg. The gastrointestinal transit time of the charcoal meal given to rats was significantly suppressed by 106 and 213 mg/kg (but not by 53 mg/kg) creosote, which showed creosote inhibited peristaltic propulsive movement of the intestine.

In a second study by Ogata et al. (1999), the effect of orally administered wood creosote on propulsive motility of the intestine and the colon were tested in male CD-1 mice using a charcoal meal test and a colonic bead expulsion test. The effect of treatment with wood creosote was compared with untreated mice or mice treated with loperamide (a known antidiarrheal agent). Postdose plasma samples were removed from mice 30 minutes after dosing and tested for the ability to suppress colonic propulsive movement. Wood creosote showed only a slight inhibitory effect on the propulsive motility of the small intestine at administered doses of 0.08 and 0.4 mg/kg, but not at an ordinary human therapeutic dose level (2–10 mg/kg). In the colonic bead expulsion test orally administered wood creosote significantly ($p<0.05$) increased bead expulsion time at doses of 0.08, 0.4, and 2 mg/kg; it was most marked at the dose of 2 mg/kg. The reduction in colonic propulsive motility produced by wood creosote occurred within 15 minutes of dosing. Postdose plasma samples from creosote treated mice produced a significant reduction in colonic propulsive motility when injected into untreated mice. This suggests that the effect is mediated by wood creosote (or its metabolites) in the blood rather than wood creosote from the lumen of the colon as the time period would not be sufficient for creosote to have reached the colon.

Coal Tar Products. Ulceration of the oropharynx and petechial hemorrhages over the gastrointestinal serosal surfaces were noted at autopsy of a 70-year-old man who died following ingestion of an unspecified amount of industrial (presumably coal tar) creosote (Bowman et al. 1984). However, the esophagus and stomach were intact. The authors attributed these effects to acute tissue damage resulting from phenol-induced corrosive effects, since phenol is a component of coal tar creosote.

Wistar rats that died following the administration of single gavage doses of coal tar creosote in an acute range-finding study (doses ranged from 613 to 5,000 mg/kg) exhibited hyperemia and distention of the stomach upon necropsy (Pfitzer et al. 1965). No adverse gastrointestinal effects were noted in male Fischer 344 rats treated with 50 mg/kg/day creosote by gavage for 1–5 weeks, including no change in the weight of the small intestines, large intestines, or caecum (Chadwick et al. 1995). In a feed study of MGP coal tar by Weyand et al. (1994) using $B6C3F_1$ mice, there was no adverse effect of treatment on the glandular stomach or forestomach after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females). In another feeding study, 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from

manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day (0.03, 0.1, and 0.3%) of coal tar 2. No effect on the weight or histology of the stomach or small intestine was observed at any dose (Culp et al. 1998). Pigs that died after ingesting an unknown amount of coal tar pitch exhibited blood-stained fluid in the abdominal cavity (Luke 1954).

Hematological Effects.

Creosote Bush. A report was found in the literature describing a 45-year-old woman who developed painless jaundice, fatigue, anorexia, and pruritus after taking chaparral tablets, 160 mg/day for around 2 months (Alderman et al. 1994). Complete blood count, platelet count, and clotting times were normal. A 60-year-old woman was hospitalized with a 1-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking 1–2 capsules of chaparral daily for the past 10 months. The patient developed "flulike syndrome" and increased her chaparral intake to 6 capsules a day 3 weeks before admission. The patient's prothrombin time increased from 15.9 to 28 seconds (normal values 10.9–13.7 seconds).

Wood Creosote. Various hematological parameters (red blood cell, white blood cell, lymphocyte, and neutrophil counts, hemoglobin concentration, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit) were measured by Miyazato et al. (1981, 1984a, 1984b) in Wistar rats and ddY mice fed beechwood creosote in the daily diet for 3 months, 52 weeks (mice), or 96 weeks (rats). No significant treatment-related changes were noted in mice of either sex fed doses of up to 1,065 mg/kg/day (male) or 1,427 mg/kg/day (female) for 3 months (Miyazato et al. 1981). These doses are considerably higher than the oral LD_{50} values reported for mice by the same authors. One possible explanation for this discrepancy is that the LD_{50} values were determined by bolus gavage and in the intermediate study, the beechwood creosote was administered in the feed. A slight reduction in red blood cells (RBCs) was noted in male and female rats following dietary exposure to doses of 210 (male) or 163 (female) mg/kg/day for 3 months, but this reduction was not observed in mice exposed to higher doses (812 [male] or 768 [female] mg/kg/day), and was therefore not considered to be toxicologically significant (Miyazato et al. 1981). Chronic (52 weeks) dietary exposure of mice to up to 474 mg/kg/day (males) or 532 mg/kg/day (females) beechwood creosote resulted in statistically significant dose-related differences in mean cell volume, mean corpuscular hemoglobin, and absolute lymphocyte and neutrophil counts when compared to the corresponding control values. These changes were not considered by the authors to be toxicologically significant; they claimed

that the values were within normal physiological ranges (Miyazato et al. 1984a). An unspecified set of hematologic parameters were not affected in Sprague-Dawley rats administered wood creosote at 20, 50, or 200 mg/kg/day for up to 102 weeks (Kuge et al. 2001).

Coal Tar Products. In a feed study of MGP coal tar by Weyand et al. (1994) using $B6C3F_1$ mice, there was no adverse effect of treatment on the bone marrow after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females).

Hepatic Effects.

Creosote Bush. Acute toxic hepatitis has been attributed to ingestion of chaparral, an herbal nutritional supplement product derived from the leaves of the creosote bush (Clark and Reed 1992). A 42-year-old man had icterus and jaundice after consuming three 500 mg capsules of chaparral a day for 6 weeks. Serum chemistry tests showed elevated bilirubin, gamma glutamyltranspeptidase (GGT), AST, and lactate dehydrogenase. His illness was diagnosed as hepatic dysfunction secondary to chaparral ingestion. Three weeks after discontinuing the chaparral ingestion, his serum chemistry was normal, and he had no other symptoms. The same article noted the case of a 41-year-old woman who had abdominal pain and jaundice after consuming 150 tablets of chaparral over an 11-week period. Serum chemistry tests revealed elevated bilirubin, AST, alanine aminotransferase (ALT), GGT, and lactate dehydrogenase. Six weeks after discontinuation of chaparral ingestion, serum chemistry tests were normal, and there were no other symptoms reported.

A 45-year-old woman developed painless jaundice, fatigue, anorexia, and pruritus after taking chaparral, 160 mg/day, for about 2 months (Alderman et al. 1994). Physical examination confirmed jaundice and a 14-cm liver with a smooth, nontender border. Serum enzyme levels were elevated; serum ALT was 1,611 IU (normal 0–65 IU); AST was 957 IU (normal 0–50 IU); alkaline phosphatase was 265 IU (normal 35–130 IU); GGT was 993 IU (normal 0–65 IU), and total bilirubin was 11.6 mg/dL (normal <1.4 mg/dL). Tests for anti-hepatitis A IgG and IgM, hepatitis B surface antigen, antibody against hepatitis B surface antigen and hepatitis B core antigen, and acute antibody against hepatitis virus were all negative. Ultrasonography showed no abnormality. Endoscopic retrograde cholangiopancreatigraphy (ERCP) showed sparse, smooth, but severely narrowed biliary ducts without sclerosing cholangitis, distal obstruction, tumor, or stenosis. Specimens from percutaneous liver biopsy showed prominent acute inflammation with neutrophil and lymphoplasmocytic infiltration, diffuse hepatocyte disarray and necrosis, focal acute pericholangitis, some ductal dilatation, and proliferation of bile ductules in portal-

periportal regions. The patient was started on Prednisone at 60 mg/day, tapered to 10 mg/day and discontinued in 7 weeks; the patient remained well with normal laboratory findings. The patient was diagnosed with chaparral-induced toxic hepatitis after reports of two cases of chaparral hepatotoxicity were published. In another report, a 60-year-old woman was hospitalized with a 1-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking 1–2 capsules of chaparral daily for the past 10 months. The patient developed "flulike syndrome" and increased her chaparral intake to 6 capsules a day 3 weeks before admission. Jaundice occurred 2 weeks later. On admission, she was confused and deeply jaundiced. Her total serum bilirubin increased from 212 mmol/L (12.4 mg/dL) to 607 mmol/L (35.5 mg/dL) (normal values 2–20 mmol/L [0.1–1.2 mg/dL]). The patient's liver failure was considered to be chaparral-induced toxic hepatitis. Viral hepatitis was ruled out because antibodies to hepatitis A virus IgM, antibody to hepatitis B core antigen, and hepatitis C virus were undetectable. An exploratory laparotomy performed 1 week after admission showed ascites and a nodular liver. Liver biopsy showed severe acute hepatitis with areas of lobular collapse and nodular regeneration, mixed portal inflammation and marked bile ductular proliferation. Her total serum bilirubin increased to 607 mmol/L. The patient underwent orthotopic liver transplantation. The patient slowly recovered and was discharged.

Serum liver enzymes, blood urea nitrogen, creatinine levels, glucose levels, electrolytes, bilirubin levels, iron levels, ferritin levels, lipid levels, and complete blood count of four patients prescribed an extract of creosote bush in 90% ethanol were within the normal range and were unchanged by exposure to the extract of creosote bush (Heron and Yarnell 2001). The authors also reported that an additional eight patients who had been prescribed an extract of creosote bush had no noticeable adverse effects, but no information as to blood chemistry was available for these patients.

Wood Creosote. Liver-to-body-weight ratios tended to increase in male Wistar rats exposed to doses of beechwood creosote >168 mg/kg/day in the diet for 3 months or in females exposed to $215 mg/kg/day (but not 163 mg/kg/day) (Miyazato et al. 1981). A similar increase in relative liver weight was observed for rats exposed to $143 (male) or 179 (female) mg/kg/day beechwood creosote for 96 weeks (Miyazato et al. 1984b). Increased relative liver weights were observed in female ddY mice fed beechwood creosote at doses $314 mg/kg/day (but not 164 mg/kg/day) and in male mice fed 1,065 mg/kg/day (but not 768 mg/kg/day) for 3 months and in female mice fed $297 mg/kg/day, but not in male mice fed up to 474 mg/kg/day for 52 weeks (Miyazato et al. 1981). Although this response is considered to be of minimal pathologic significance, it may be an early indication of adverse changes since the liver is a known target organ. No treatment-related histopathological alterations were observed. Liver weights

were unaffected in Sprague-Dawley rats administered wood creosote at 20 or 50 mg/kg/day for 102 weeks or 200 mg/kg/day for 95 weeks (Kuge et al. 2001).

A significant increase in serum glutamic-oxaloacetic transferase (GOT, currently known as AST) and glutamic-pyruvic transferase (GPT, currently known as ALT) levels was also observed in the chronically exposed female mice, but these levels were still within normal physiological range (Miyazato et al. 1981). A slight increase in serum cholesterol was noted in male and female rats following dietary exposure to 210 (male) or 578 (female) mg/kg/day beechwood creosote for 3 months (Miyazato et al. 1981). The significance of the serum cholesterol changes is not known. Increases in serum cholesterol were also noted in rats exposed to beechwood creosote in the diet for 96 weeks at doses of 143 (male) and 179 (female) mg/kg/day and above (Miyazato et al. 1984b). There was no effect of treatment on liver weight or serum cholesterol in mice exposed to up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) in the diet for 3 months or for mice exposed to up to 474 mg/kg/day (males) or 532 mg/kg/day (females) beechwood creosote in the diet for 52 weeks (Miyazato et al. 1984a). Taken together, these early changes indicate that if increased doses of beechwood creosote are used, more clear cut hepatotoxic effects would be expected to occur.

Coal Tar Products. Degeneration and necrosis of hepatocytes were observed at autopsy in the case of a 70-year-old man who ingested industrial (coal tar) creosote (Bowman et al. 1984). The actual amount ingested was not specified. Given the lack of comparison data for the condition of the liver in healthy individuals of that age it is not possible to definitively attribute these effects to coal tar creosote ingestion.

No adverse effect on liver weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 (Iyer et al. 1993). In a feed study of MGP coal tar by Weyand et al. (1994), $B6C3F_1$ mice were exposed to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females) in the feed for 94 or 185 days. Plasma clinical chemistry parameters determined were as follows: glucose, creatine, blood urea nitrogen, total protein, ALT, ALT, and alkaline phosphatase activity. Tissues obtained from the animals were examined for microscopic lesions. There was no adverse effect of treatment on liver histopathology or serum enzymes.

Anecdotal reports of mortality in pigs after ingestion of clay pigeons containing coal tar pitch from pastures formerly used for target shooting were found in the literature (Giffee 1945; Graham et al. 1940). Lack of appetite, sluggishness, rough coat, and weakness, followed by death were reported. Autopsy revealed degenerative hepatic changes. Experimental feeding of powdered clay pigeon targets containing

an unspecified amount of coal tar pitch (15–30 g powdered material daily for up to 15 days) caused death in eight of nine pigs (Davis and Libke 1968). Twenty-four to 48 hours prior to death, a decrease in hemoglobin, packed blood cell volume, and blood sugar concentration was noted. Autopsy revealed centrilobular hepatic necrosis and hemorrhage of the liver. Four pigs that ingested an unknown amount of coal tar pitch exhibited, at necropsy, marked enlargement of the liver (Luke 1954). The hepatic surface was pitted, the lobules very prominent and the whole organ extremely friable. Fibrinous strands were found on the liver, the cut surface of which presented a mottled mosaic-like pattern. Three pigs were fed a small quantity of pitch ground up in their feed (Luke 1954). These three pigs received 2 pounds (approximately 0.38 ounces/day) of pitch over a period of 28 days. At the end of the 28th day, the pigs were sacrificed and examined. The addition of pitch did not interfere with their appetite and no marked symptoms were observed. Enlargement of the liver was seen together with a varying degree of liver damage. The liver lesions were extensive and there was a marked excess of peritoneal fluid. Histological examination of the affected liver tissue showed marked central necrosis of the lobules, which, in some cases, had completely destroyed the normal liver cells. These liver changes had a somewhat patchy distribution with badly affected and normal lobules often occurring side by side. The factors in the pitch responsible for the lesions were not identified.

No change in liver weight was observed in female rats gavaged on gestational days 12–16 with up to 370 mg/kg/day coal tar (Hackett et al. 1984). In a feeding study, 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day (0.03, 0.1, and 0.3%) of coal tar 2. The dietary level of 0.3% coal tar produced a significant increase in liver weight (40%) compared with controls, exposure to lower doses had no effect on the liver (Culp et al. 1998).

Renal Effects.

Creosote Bush. No adverse renal effects were noted in a 45-year-old woman who took 160 mg/kg/day chaparral for approximately 2 months (Alderman et al. 1994). A 60-year-old woman was hospitalized with a 1-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking 1–2 capsules of chaparral daily for the past 10 months. The patient increased her chaparral intake to six capsules/day 3 weeks before admission. Renal failure ensued, which required hemodialysis. The patient underwent cadaveric renal transplantation. The patient slowly recovered and was discharged.

Wood Creosote. Kidney-to-body-weight ratios were significantly increased in Wistar rats exposed to $210 (male) or $163 (female) mg/kg/day or more beechwood creosote in the diet for 3 months or to $143 (males) or $179 (females) mg/kg/day or more for 96 weeks (Miyazato et al. 1981, 1984b), although the trend was not strictly dose-related. No effect on the relative weight of the kidney was observed in mice exposed to up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) for 3 months, mice exposed to 474 mg/kg/day (males) or 532 mg/kg/day (females) for 52 weeks, or male rats exposed to 168 mg/kg/day for 3 months (Miyazato et al. 1981). This response is of minimal pathologic significance in the intermediately treated rats of both sexes and the chronically treated female rats since no treatment-related changes were noted at histopathological evaluation. Blood urea nitrogen and serum inorganic phosphorus were elevated in the chronically treated male rats, which is indicative of uremia. Chronic progressive nephropathy, which occurs spontaneously in old male rats, was also observed at a higher incidence in the chronically treated male rats than in the control male rats, and probably accounts for the biochemical changes observed. The authors concluded that long-term exposure to beechwood creosote at the high dose (1.2% in feed or 534 mg/kg/day) accelerated the occurrence of chronic progressive nephropathy in male rats (Miyazato et al. 1984b). These results suggest that beechwood creosote has the potential to induce adverse effects in the kidney. Kidney weights were unaffected in Sprague-Dawley rats administered wood creosote at 20 or 50 mg/kg/day for 102 weeks or 200 mg/kg/day for 95 weeks (Kuge et al. 2001).

Coal Tar Products. A 70-year-old man who ingested a fatal dose of industrial (coal tar) creosote became acidotic and anuric before he died, indicating probable kidney failure (Bowman et al. 1984). The actual amount ingested was not specified. Acute renal tubular necrosis was revealed at necropsy. However, the acute tubular necrosis may have been due to vascular insufficiency rather than a direct toxic effect on the kidney.

No adverse effect on kidney weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 (Iyer et al. 1993). No change in kidney weight was observed in female CD rats gavaged on gestational days 12–16 with up to 370 mg/kg/day coal tar (Hackett et al. 1984). In a feed study of MGP coal tar by Weyand et al. (1994) using $B6C3F_1$ mice, there was no adverse effect of treatment on the kidney or bladder after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females). In another feeding study 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day

(0.03, 0.1, and 0.3%) of coal tar 2. The dietary level of 0.1% coal tar produced a significant decrease in kidney weight compared with controls, but lower dietary levels did not (Culp et al. 1998).

Postmortem examination on 4 pigs that had ingested an unknown amount of pitch, showed cystic kidneys (Luke 1954).

Endocrine Effects.

Wood Creosote. No adverse effect on adrenal weight was noted for Wistar rats given up to 812 (males) or 768 mg/kg/day (females) beechwood creosote or ddY mice given up to 1,065 (males) or 1,427 mg/kg/day (females) beechwood creosote in the feed for 3 months (Miyazato et al. 1981). Male rats given 313 mg/kg/day beechwood creosote for 96 weeks exhibited an increase in relative adrenal weight, but males receiving 143 mg/kg/day and females receiving up to 394 mg/kg/day did not (Miyazato et al. 1984b). Significant reductions in thyroid-parathyroid weight were observed in female Sprague-Dawley rats administered wood creosote by gavage at 200 mg/kg/day for 95 weeks, but not in female rats administered 20 or 50 mg/kg/day for 102 weeks (Kuge et al. 2001). There were no dose-related changes in adrenal or pituitary weights in male or female rats in any dose group.

Coal Tar Products. Adrenal weights were significantly increased in pregnant rats gavaged with $90 mg/kg/day coal tar on gestational days 12–16 (Hackett et al. 1984). No adverse effect on adrenal weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 (Iyer et al. 1993). Weyand et al. (1994) conducted a feed study of MGP coal tar using $B6C3F_1$ mice. There was no adverse effect of treatment on the salivary glands, pancreas, thymus, parathyroid, or adrenal glands after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day for males and 0, 42, 196, or 344 mg/kg/day for females.

Dermal Effects.

Creosote Bush. A 45-year-old woman developed pruritus, probably secondary to chaparral-induced toxic hepatitis, after taking 160 mg/kg/day chaparral for around 2 months (Alderman et al. 1994).

Body Weight Effects.

Wood Creosote. Body weight gain was decreased 11–22% in Wistar rats given 768 (males) or 812 (females) mg/kg/day beechwood creosote, and 11–16% in ddY mice given 768 (males) or 1,427 (females) mg/kg/day beechwood creosote in the feed for 3 months (Miyazato et al. 1981). No effect on body weight was observed in rats or mice exposed to lower doses (534 mg/kg/day, male rat; 578 mg/kg/day, female rat; 450 mg/kg/day, male mouse; 1,127 mg/kg/day, female mouse) of beechwood creosote for 3 months. No effect on body weight was observed in rats or mice exposed to up to 313 (males) or 394 (females) mg/kg/day for 96 weeks, or to 474 (males) or 532 (females) mg/kg/day for 52 weeks (Miyazato et al. 1984a, 1984b). Significant body weight reductions were observed in male (7% weight reduction) and female (15% weight reduction) Sprague-Dawley rats administered wood creosote by gavage at 200 mg/kg/day for 95 weeks (Kuge et al. 2001). Terminal body weights were unaffected in rats administered 20 or 50 mg wood creosote/kg/day for 102 weeks.

Coal Tar Products. No adverse effect on body weight was noted in male Fischer 344 rats treated with 50 mg/kg/day coal tar creosote by gavage for 3–5 weeks (Chadwick et al. 1995). However, body weight was significantly decreased in female CD rats gavaged on gestational days 12–16 with 180 mg/kg/day (but not 140 mg/kg/day) coal tar (Hackett et al. 1984). A 16% decrease in body weight gain was also observed in female ICR mice after gavage treatment with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9; however, a similar reduction in weight gain was seen in the group treated with DMSO only (Iyer et al. 1993). In another study, male $B6C3F_1$ mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar in feed for 28 days (Culp and Beland 1994). Food consumption and change in body weights were monitored for the coal-tar-fed animals. Dose-related decreases in body weight were observed in all dose groups. Animals treated with 693 and 1,067 mg/kg/day coal tar showed average body weights significantly decreased by approximately 16% from controls. Body weights for other treated groups were not significantly different from those of controls.

The relationship between ingestion of MGP residue and systemic availability of coal tar components in male mice was evaluated by measuring whole animal body weight, DNA adduct formation binding in several soft tissues, and urinary excretion of PAH metabolites (Weyand et al. 1991). Coal tar samples collected from four different coal gasification sites were incorporated separately at varying concentrations into the diet and fed to the mice for 15 days. Animal body weight was not affected in groups fed up to 0.2% (659 mg/kg/day) coal tar, but body weight was significantly reduced in animals fed diets containing 0.5% (1,871 mg/kg/day) coal tar because the animals refused to eat the higher concentration of coal tar.

Five groups of B6C3F$_1$ mice (24 males, 24 females) were fed a control gel diet or adulterated diets containing 0.05, 0.25, or 0.50% MGP (Weyand et al. 1994). Consumption was equivalent to 0, 51, 251, or 462 mg/kg/day for males and 0, 42, 196, or 344 mg/kg/day for females. Half the animals in each group were sacrificed after 94 days of treatment and all organs examined for gross lesions. The remaining animals from each group were maintained on diets for an additional 91 days. After a total of 185 days of treatment, the remaining animals were sacrificed and all organs examined for gross and microscopic lesions. Differences in weight gain did not show any clear dose response. Control and treated males ingesting 51 mg/kg/day feed had the highest weight gain. Body weight gains in the 251 and 462 mg/kg/day groups were considerably lower (statistical analysis not performed). Females exposed to 42 mg/kg/day diets had the highest body weight gains, while females on the 196 mg/kg/day diets had the lowest. In a similar study Weyand et al. (1995) fed female A/J mice with a control diet or a diet containing 0.1 or 0.25% coal tar samples from manufactured gas plant waste sites for 260 days. This diet provided approximately 100 or 236 mg/kg/day coal tar. Consumption of coal tar did not significantly alter body weight gain since mice fed the control and 0.25% coal tar diets had equally low body weight gain compared to mice fed the 0.1% coal tar diet.

Culp et al. (1996a) fed diets containing 0, 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar to female B6C3F$_1$ mice for 2 years and noted a decrease in body weight (data not shown) at the two highest doses (1,364 and 2,000 mg/kg/day) compared with controls. No decrease was noted for animals exposed to #0.3% (628 mg/kg/day) compared with controls. In another feeding study, 5-week-old female B6C3F$_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day (0.03, 0.1, and 0.3%) of coal tar 2. The dietary level of 0.3% coal tar (333 mg/kg/day coal tar 1 or 346 mg/kg/day coal tar 2) produced a significant decrease in body weight gain (20%) compared with controls, but lower dietary levels did not (Culp et al. 1998).

Other Systemic Effects.

Wood Creosote. Dose-related clinical signs consisting of salivation, decreased activity, signs of apparent abdominal discomfort, and significant reductions in food consumption and food efficiency (food consumption divided by body weight gain) were observed in Sprague-Dawley rats administered 200 mg wood creosote/kg/day by gavage for 95 weeks, but not in rats administered 20 or 50 mg/kg/day for 102 weeks (Kuge et al. 2001).

Coal Tar Products. Consumption of food containing MGP residue was evaluated in male $B6C3F_1$ mice by measuring whole animal body weight and food consumption (Weyand et al. 1991). Coal tar samples collected from four different coal gasification sites were incorporated separately at varying concentrations into the diet and fed to the mice for 15 days. Food consumption was not affected in groups fed up to 0.2% (659 mg/kg/day) coal tar. However, animals fed diets containing 0.5% (1,871 mg/kg/day) or 1.0% (3,125 mg/kg/day) coal tar refused to eat for 2 or 4 days, respectively, while animals fed 2% or more coal tar continued to refuse to eat for the duration of the experiment. In another feeding experiment, male $B6C3F_1$ mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar in feed for 28 days (Culp and Beland 1994). Dose-related decreases in food consumption were observed in all treated groups. Animals treated with 693 and 1,067 mg/kg/day coal tar showed significantly decreased food consumption compared to controls over a period of 28 days, animals receiving lower doses did not. Similar reductions in food consumption were seen in another study of female $B6C3F_1$ mice fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day (0.03, 0.1, and 0.3%) of coal tar 2. Mice fed coal tar 1 ate significantly less food than controls. The reduction in food consumption was approximately 30% for mice fed 1% coal tar 1 and 25% for mice fed 0.6% coal tar 1. Mice fed 0.3% coal tar 2 also ate significantly less food than controls and had approximately a 20% reduction in food consumption.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunologic/lymphoreticular effects in humans after oral exposure to wood creosote, coal tar creosote, coal tar, or coal tar pitch.

Wood Creosote. In rats, the spleen may be affected by beechwood creosote exposure, although the data are not conclusive (Miyazato et al. 1981). In particular, exposure to beechwood creosote at 805 mg/kg/day in the diet for 3 months resulted in increased relative spleen weight of male Wistar rats. Spleen weights of male rats exposed to lower levels of beechwood creosote in the diet and female rats at doses up to 768 mg/kg/day indicated no consistent trend of either increase or decrease (Miyazato et al. 1981). In companion experiments using ddY mice, no effect on relative spleen weight was seen at doses up to 1,810 (male) or 1,570 (female) mg/kg/day, in the feed (Miyazato et al. 1981). No effect on spleen weight was observed in rats exposed to doses up to 394 mg/kg/day for 96 weeks, or mice exposed to doses of 532 mg/kg/day for 52 weeks (Miyazato et al. 1984a, 1984b). Spleen weight was unaffected in male and female Sprague-Dawley rats administered 20 or 50 mg wood creosote/kg/day by gavage for 102 weeks. Spleen weight in female rats administered 200 mg/kg/day for 95 weeks was similarly unaffected, but male rats at the latter dose and duration showed a significant reduction in spleen weight (Kuge et al. 2001).

All reliable NOAEL and LOAEL values for immunological and lymphoreticular effects for each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Coal Tar Products. Coal tar may affect the spleen and thymus in rats, but not in mice. A significant decrease in thymus weight and endocrine weight was observed in female CD rats gavaged on gestational days 12–16 with 90 mg/kg/day coal tar (Hackett et al. 1984). B6C3F$_1$ mice fed a control gel diet or diets containing 0, 51, 251, or 462 mg/kg/day MGP coal tar (males) and 0, 42, 196, or 344 mg/kg/day (females) MGP coal tar, exhibited no adverse gross or histopathological effects for the spleen, thymus, or bone marrow after treatment for 94 or 185 days (Weyand et al. 1994).

All reliable NOAEL and LOAEL values for immunological and lymphoreticular effects for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to coal tar creosote, coal tar, or coal tar pitch.

Creosote Bush. A 45-year-old woman developed fatigue and anorexia after taking 160 mg/kg/day chaparral for around 2 months (Alderman et al. 1994). The patient was diagnosed with chaparral-induced toxic hepatitis. In another report, a 60-year-old woman was hospitalized with a 1-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking 1–2 capsules of chaparral daily for the past 10 months. The patient developed "flulike syndrome" and increased her chaparral intake to 6 capsules per day 3 weeks before admission. On admission, she was confused; her encephalopathy worsened, and she developed seizure activity. The patient was diagnosed with toxic hepatitis secondary to chaparral ingestion.

Wood Creosote. In rats and mice, the first sign of poisoning following the gavage administration of single high doses (600 mg/kg in Wistar rats; 378 [male] or 313 [female] mg/kg in ddY mice) of beechwood creosote was muscle twitching followed by convulsions within 1–2 minutes. This was followed by asphyxiation, coma, and death (Miyazato et al. 1981). These effects were not observed in male mice gavaged once with 313 mg/kg beechwood creosote (Miyazato et al. 1981). Dose-related increased brain-to-body-weight ratios were observed in male rats exposed to doses of $257 mg/kg/day beechwood creosote in the diet for 3 months, but not female rats exposed up to 768 mg/kg/day or male and female mice exposed to up to 1,810 (male) or 1,570 (female) mg/kg/day (Miyazato et al. 1981). Increased relative brain weights were observed in male and female mice exposed to doses up to 247 (male) or 297 (female) mg/kg/day for 52 weeks in the diet, and in male rats exposed to 143 mg/kg/day and female rats exposed to 394 mg/kg/day (but not 179 mg/kg/day) for 96 weeks in the diet (Miyazato et al. 1984b). This response is of questionable toxicological significance because of the lack of a dose-response trend and/or the lack of treatment-related pathological findings at necropsy.

All reliable NOAEL and LOAEL values for neurological effects for each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Coal Tar Products. Several cases of acute poisoning in cattle have been attributed to ingestion of coal tar creosote. Six cattle believed to have licked creosote-treated electrical light poles as evidenced by burning over the mucosa of the mouth, tongue, and lips showed the following signs: extremely rapid respiration,

contracted pupils, cold skin, apparent severe pain, and coma (Hanlon 1938). However, it is probable that some of these effects may have been due to ingestion of pentachlorophenol. Pentachlorophenol, like creosote, is an oil-borne wood preservative with extensive use in the public utility industry for treatment of utility poles. Some of the effects observed by Hanlon (1938) are more compatible with the metabolic effects (i.e., uncoupling of phosphorylative oxidation) associated with pentachlorophenol. For more information on the effects of pentachlorophenol, please refer to the ATSDR *Toxicological Profile for Pentachlorophenol* (Agency for Toxic Substances and Disease Registry 1999). Thus, it is not possible to determine conclusively whether coal tar creosote is toxic to the central nervous system of animals based on this report. In another report, one of two bulls that had ingested an unknown amount of creosote died and the second one was observed to be walking stiffly (Cribb 1968). The surviving animal recovered fully several days after being removed from the creosote.

All reliable NOAEL and LOAEL values for neurological effects for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to creosotes, coal tar, or coal tar pitch.

Wood Creosote. An increase in relative testis weight was observed in Wistar rats administered 805 mg/kg/day beechwood creosote in the diet for 3 months, but not in rats receiving 317 mg/kg/day or in mice treated with up to 1,810 mg/kg/day beechwood creosote for 3 months (Miyazato et al. 1981). There were no accompanying gross or histopathological lesions of the testes in these animals. No adverse effects on ovary weight were noted in female rats (768 mg/kg/day) or mice (1,570 mg/kg/day) in the same study. No effect on testis or ovary weight was observed in rats exposed to doses up to 394 mg/kg/day for 96 weeks, or mice exposed to doses of up to 532 mg/kg/day beechwood creosote for 52 weeks (Miyazato et al. 1984a, 1984b). Ovary weights were unaffected in female Sprague-Dawley rats administered 20 or 50 mg wood creosote/kg/day for 102 weeks or 200 mg wood creosote/kg/day by gavage for 95 weeks (Kuge et al. 2001). Testis weight was significantly increased in male rats administered 200 mg wood creosote/kg/day for 95 weeks, but not in male rats administered 20 or 50 mg/kg/day for 102 weeks.

All reliable NOAEL and LOAEL values for reproductive effects for each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Coal Tar Products. A significant decrease in both the number of live fetuses/litter and the number of resorptions was observed in female Sprague-Dawley CD rats gavaged with 370 mg/kg/day coal tar on gestational days 12–16 (Hackett et al. 1984). A significant increase in resorptions was also observed in rats treated with 180 mg/kg/day (but not 140 mg/kg/day) coal tar, but there was no decrease in the number of live fetuses/litter. Some maternal toxicity was observed in the body weight (minus the products of gestation) of the dams was significantly reduced for the three highest dose groups and the weight of the adrenal glands was significantly increased. However, the weights of the spleen, liver, kidneys, and ovaries of all dosed groups were similar to controls.

No significant difference in the number of live births was observed in female Sprague-Dawley rats gavaged with 740 mg/kg/day coal tar on gestational days 12–14 (Springer et al. 1986a). Only moderate maternal toxicity was observed. Body weight gain was significantly reduced in treated dams, but the estimated weights of the products of conception were similar for control and treated animals, and no significant reduction in litter size was observed. No adverse effects on reproductive indices, including the number of live fetuses, dead fetuses, and resorptions were observed in female ICR mice dosed by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 (Iyer et al. 1993). Moderate maternal toxicity in the form of reduced body weight gain was observed for both creosote-treated and vehicle control mice compared with untreated controls, but no differences in organ weights were observed for any group. $B6C3F_1$ mice fed a control gel diet or adulterated diets containing 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females) MGP residue as a by-product of coal gasification, exhibited no adverse effect on the epididymides, preputial gland, ovaries, uterus, or clitoral gland after treatment for 94 or 185 days (Weyand et al. 1994).

Coal tar creosote was tested for estrogenic activity using an assay in ovariectomized (OVX) ICR and DBA/2 mice (Fielden et al. 2000). Immature OVX mice were used to assess the ability of creosote to induce an increase in uterine weight, and mature OVX mice were used to assess the ability of creosote to induce both increased uterine weight and vaginal cell cornification. OVX mice were gavaged with 0, 10, 50, or 100 mg/kg creosote in sesame oil or 0.1 mg/kg 17α-ethynylestradiol (positive control) once a day for 4 days beginning when mice were 30 (OVX ICR immature), 32 (OVX DBA/2 immature), 77 (OVX ICR mature), or 85 (OVX DBA/2 mature) days old. Mice were sacrificed 24 hours after the last treatment; body and uterine weights were recorded for all mice and vaginal smears were taken from the mature mice. Treatment with 17α-ethynylestradiol produced a significant increase in uterine weight and vaginal cell cornification compared with animals receiving only sesame oil, but no significant increase in uterine weight or vaginal cell cornification was observed in animals treated with creosote.

All reliable NOAEL and LOAEL values for reproductive effects for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding the developmental effects in humans following oral exposure to wood creosote, coal tar, or coal tar pitch.

Coal Tar Products. A significant decrease in relative fetal lung weight and a significant increase in anomalous fetuses was observed in female CD rats gavaged with 140 mg/kg/day (but not 90 mg/kg/day) coal tar on gestational days 12–16 (Hackett et al. 1984). Further abnormalities, a significant increase in the incidence of cleft palate, syndactyly/ectrodactyly and missing toenails on hind feet, were observed in offspring of females treated with 370 mg/kg/day coal tar. In this study, maternal body weight gain was significantly reduced at the three highest dose groups and the weight of the adrenal glands was significantly increased. However, the weights of the spleen, liver, kidneys, and ovaries of all dose groups were similar to controls. Maternal body weight gain, excluding uterine weight, was significantly reduced at all doses. These findings suggest that maternal toxicity may have played a role in the development of teratogenic effects in this study.

In another developmental study, female Sprague-Dawley rats were gavaged with 740 mg/kg/day coal tar on gestational days 12–14 and allowed to deliver their pups (Springer et al. 1986a). Only moderate maternal toxicity was observed. Body weight gain was significantly reduced in treated dams, but the estimated weights of the products of conception were similar for control and treated animals, and no significant reduction in litter size was observed. Pup development was followed for 21 days after birth. Early mortality was significantly increased in treated pups; within the first 3 days after birth, 54% of the treated pups died compared with 9% of the untreated pups. Body and lung weights of treated pups that died or were sacrificed at 1 or 3 days postdelivery were significantly reduced compared with controls. Body weight gain was significantly reduced (15%) for treated pups compared with controls at all time points. Treated pups that died showed signs of severe dehydration and this became more pronounced as the time to death increased. Thymus and lung weights in treated animals were significantly lower than in the corresponding control animals. Lungs were defined as "small lungs" if their size was more than two standard deviations below the mean of the control group. No controls had small lungs or cleft palates. In treated pups that died, the incidence of small lungs was 27% (in 90% of litters), 10% (in 80% of litters) had cleft palates, and 33% of pups (in 80% of litters) had both small lungs and cleft palates. Median

survival times for pups with cleft palate, both cleft palate and small lungs, and only small lungs were 2, 2, and 10 hours, respectively. No malformations were detected in 30% of the treated pups that died and microscopic examination of fetal lung tissue revealed no overt histological differences between treated and control animals. The data from this study suggest that coal tar is a teratogen in Sprague-Dawley rats; however, given the moderate, yet statistically significant, maternal toxicity, the possibility of fetal effects secondary to maternal toxicity cannot be excluded.

A 12% decrease in mean fetal body weight was observed in the offspring of female ICR mice dosed by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 compared to the solvent control group (Iyer et al. 1993). An increase in the incidence of a skeletal anomaly (i.e., missing sternebrae) was also observed in the creosote-treated litters, but the difference in the frequency of occurrence was not significant compared to the control group. Moderate maternal toxicity in the form of reduced body weight gain was observed for both creosote-treated and vehicle control mice compared with untreated controls, but no differences in organ weights were observed for any group. The authors suggest that creosote is embryotoxic but not teratogenic; however, interpretation of the results of this study is complicated by the apparent toxicity of the carrier solvent (DMSO).

Four sows were confined to wooden farrowing crates for 2–10 days before delivery. The platforms of the crates were coated with 3 brush applications of a commercial wood preservative containing 98.5% coal tar creosote (Schipper 1961). Following contact with creosote, 24 of the 41 pigs delivered were dead at birth, and 11 pigs died by day 3 postfarrowing. The surviving pigs had rough skin and suffered from dehydration and severe diarrhea. The pigs failed to gain weight until they were 5–6 weeks old. No toxic effects on the sows were reported. However, 4 sows confined to untreated lumber crates at least 24 hours before farrowing delivered 36 pigs; 1 died within 24 hours and 3 died postfarrowing. No toxic effects were noted in mothers or baby pigs. These findings suggest that creosote was fetotoxic. The fetal effects were observed in the absence of maternal toxicity.

Although some teratogenic effects were observed in the studies discussed in this section, it is not clear that they were directly induced by creosote. In some studies, the observed fetal deformities appeared to be related to maternal toxicity. If creosote is a teratogen, it would be a weak one. Some of the studies suggest that creosote is fetotoxic. In particular, the study by Schipper (1961) showed an increase in fetal mortality without apparent maternal toxicity.

The LOAEL and NOAEL values for developmental effects in mice and rats after oral exposure to creosote are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located that dealt directly with an association between cancer and ingested coal tar or coal tar pitch in humans.

Creosote Bush. A 56-year-old woman who had been consuming 3–4 cups daily of chaparral tea (an infusion of the leaves of the creosote bush) for a period of 3 months approximately 1.5 years prior to surgery was found to have cystic renal disease and cystic adenocarcinoma of the kidney (Smith et al. 1994). One of the components of chaparral tea is nordihydroguaiaretic acid. This chemical has been shown to produce cystic nephropathy in rats fed a 2% concentration for 6 weeks (Evan and Gardner 1979; Goodman et al. 1970). The concentration of nordihydroguaiaretic acid in chaparral tea is considerably higher than that used to cause cystic nephropathy in animals and the authors conclude that the renal disease seen in their patient was most likely to have been due to consumption of chaparral tea.

Wood Creosote. Wood creosote is a common Japanese folk remedy under the generic name "seirogan" and its relationship to stomach cancer is reported in a study by Weiner (1986). This preparation was used as a treatment for stomach aches, taken 3 times/day and the dose was equivalent to 260 mg creosote daily. The cancer distribution in Japan shows the highest incidence of stomach cancer reported in Toyoma where seirogan was produced and in prefectures close to Toyoma. However, the author notes that there may be other factors in addition to seirogan. At the time of the report, 35 different digestive remedies contained creosote.

Dietary exposure of male and female ddY mice to beechwood creosote at concentrations up to 532 mg/kg/day (which induced signs of toxicity) for 52 weeks induced no treatment-related increase in the incidence of tumors (Miyazato et al. 1984a). This study is limited, in that 52 weeks may not be a sufficient treatment duration to observe an increase in the incidence of tumors in mice. However, these same authors reported that dietary exposure of male and female rats to 394 mg/kg/day beechwood creosote (which induced signs of toxicity) for 96 weeks also failed to result in any treatment-related increase in the incidence of tumors (Miyazato et al. 1984b). Kuge et al. (2001) conducted a chronic study of the carcinogenicity of wood creosote using 20, 50, or 200 mg wood creosote/kg/day administered by gavage to Sprague-Dawley rats for up to 102 weeks. There was a significant increase in mortality in the

200 mg/kg/day group. Significant increases in the incidence of mammary gland adenocarcinoma, adenoma, and fibroadenoma were observed in some groups of female rats, but the increases did not appear to be dose-related. In male rats, there was an increase in pituitary gland adenoma in the animals administered 20 mg wood creosote/kg/day, but not 50 mg wood creosote/kg/day. There was a high incidence of neoplastic changes in the control group of rats that was were not administered wood creosote. Based on the lack of dose-related increases in neoplasms in these studies, there is no clear evidence that ingested beechwood creosote is carcinogenic to mice or rats.

Coal Tar Products. Excess cases of breast cancer have been observed in St. Louis Park, Minnesota, that were tentatively associated with coal tar creosote contamination of the water supply (Dean et al. 1988). Coal tar creosote-derived PAHs were first detected in the water supply of St. Louis Park in November 1978, but may have been there for decades. A 100-acre plot of coal tar creosote-contaminated soil on which stood a plant that used coal tar creosote and operated from 1917 to 1972 is believed to be the source of contamination. The levels of coal tar creosote or creosote-derived PAHs in the contaminated drinking water of St. Louis Park were not specified. There were 113 cases per 100,000 of breast cancer in St. Louis Park compared to 78 cases per 100,000 in the metropolitan Minneapolis-St. Paul area during 1969–1971. An attempt was made to demonstrate that these excess cases could be explained by known risk factors for breast cancer, such as age at first birth, parity, age at menarche and menopause, body mass index, history of benign breast disease, and familial history, and thus had no association with environmental exposure variables (Dean et al. 1988). The authors presented a method to adjust the breast cancer morbidity in St. Louis Park using data from a larger population with documented risk factors for breast cancer ("standard population"). These more stable rates based on breast cancer risk factors were determined in a larger study conducted by Helmrich et al. (1983). Dean et al. (1988) determined that the attributable risk due to the risk factors was higher for the breast cancer cases in St. Louis Park (0.598) than in the metropolitan Minneapolis-St. Paul area (0.311). They then used these attributable risks to calculate an adjusted morbidity ratio to estimate expected numbers of breast cancer cases in the community. After this adjustment, there appeared to be a higher expected number of breast cancer cases (n=134 per 100,000) than the observed number (113 per 100,000) in St. Louis Park, thereby negating any association with creosote in the water supply. It is necessary when using any standardization method in adjusting rates to ensure comparability among the groups in the study population that are being compared and between the study population and the standard population. It would appear that differences do exist between women in St. Louis Park, the metropolitan Minneapolis-St. Paul area, and the larger cohort studied by Helmrich et al. (1983). These differences were not thoroughly examined by Dean et al. (1988) and could include differences in demographic, economic, and/or environmental factors. However, Dean

et al. (1988) did note a difference in religious backgrounds between the study population described by Helmrich et al. (1983) and that of the St. Louis Park area. These dissimilarities indicate that the populations were not directly comparable and, therefore, adjustment of rates was not appropriate. The authors did not attempt to incorporate coal tar creosote contamination of water as an independent variable in their analysis.

The Minnesota Department of Health (1985) also reviewed the St. Louis Park data and concluded that this study did not provide adequate evidence to associate breast cancer with coal tar creosote-contaminated ground water. They supported this conclusion with the following observations. It is not possible to classify individuals or residences within St. Louis Park according to their relative degree of historical exposure to PAH contaminants in drinking water because the pattern and history of municipal well contamination are not known; contaminant levels were measured at the well head and not at the tap; water treatment, storage, and distribution effects on contaminant concentration are not known; and much of the water distribution system is lined with coatings made of coal tar or asphalt. Furthermore, given the ubiquitous nature of PAHs, it is probable that exposures to PAHs from food would significantly exceed exposures from contaminated St. Louis Park well water. In addition, it was found that the specific PAHs (e.g., 3-methyl-cholanthrene) that have been shown to induce mammary tumors in rats (Dao 1964; Dao and Sunderland 1959) were either not present in contaminated wells or were detected very rarely even in the most highly contaminated wells. Furthermore, the many published case-control and cohort studies of breast cancer have not demonstrated clear-cut evidence of an association between breast cancer and smoking, which is a significant source of exposure to PAHs. These studies have also identified a number of risk factors that account for some of the observed variations in rates among different groups of women, and the women of St. Louis Park differ from those in the general Metro area with respect to several of the factors that are known to influence breast cancer rates.

In another analysis of the St. Louis Park data, cancer incidence rates in St. Louis Park were compared with those in Edina and Richfield and in the entire Minneapolis-St. Paul Standard Metropolitan Statistical Area (SMSA), using data from the Third Cancer Survey for 3 years, 1969–1971 (Dusich et al. 1980). Richfield was selected because it was a SMSA suburb similar to St. Louis Park in social and economic characteristics such as median school years completed, percentage high school graduates, occupation and median family income. Edina was selected because the creosote contamination was believed at that time to be moving toward Edina. The entire SMSA was used as a major comparison area. For males, no cancer rates in St. Louis Park were statistically significant from those in the three comparison areas. Among females, age-adjusted rates for all cancers, cancers of the gastrointestinal tracts, and breast cancer

were higher in the St. Louis Park than in Edina, Richfield, and the SMSA. The excess in gastrointestinal cancer rates for females was only slightly significant, but all cancer combined and breast cancer had differences with a high degree of statistical significance.

A feeding study in female A/J mice examined tumor induction after 260 days exposure to MGP residue (Weyand et al. 1995). Treated mice ate diets to which had been added 0.25% MGP coal tar (236 mg/kg/day) or 0.1% MGP coal tar (100 mg/kg/day), while controls received either unadulterated food (negative control) or a diet containing benzo[a]pyrene (positive control). Mice that ingested coal tar had a significant increase in the incidence of lung tumors (70%) compared with controls (0%), but ingestion of coal tar did not produce any tumors of the forestomach. This is in contrast to ingestion of benzo[a]pyrene, which produced a significant increase in incidence of tumors of the forestomach (but not lung tumors) compared with controls.

The most extensive studies of coal tar carcinogenicity to date are 2-year cancer bioassays carried out by Culp et al. (1996a, 1998) using MGP residue. In the earlier of these two studies, female $B6C3F_1$ mice (5 weeks of age) were allocated to 14 dose groups consisting of 48 mice per group (Culp et al. 1996a). Coal tar was added to the animals' feed at the following concentrations; 0, 0.01, 0.03, 0.1, 0.3, 0.6 (15 mg coal tar/day), and 1% (22 mg coal tar/day). Three groups of mice received feed with the following concentrations of benzo[a]pyrene; 5, 25, and 100 ppm. The coal tar was a mixture of samples from seven waste sites and corresponds to coal tar 1 in the later study (Culp et al. 1998). Feeding was continued for 2 years. All mice, including those that died during the experiment were examined grossly at necropsy. Forestomach tumors were found in all groups of mice fed coal tar or benzo[a]pyrene and incidence increased with dose. Tumors of the small intestine were only seen in mice fed 0.6 or 1.0% coal tar.

In the later study, coal tar samples from manufactured gas plant waste sites were added to the feed of 5-week-old female $B6C3F_1$ mice at the following concentrations; 0.01, 0.03, 0.1, 0.3, 0.6, and 1% (12, 33, 117, 333, 739, and 1,300 mg/kg/day) coal tar 1 and 0.03, 0.1, and 0.3% (40, 120, or 346 mg/kg/day) coal tar 2 (Culp et al. 1998). Coal tar 1 was a mixture of samples from seven waste sites and coal tar 2 was a mixture from two of the sites included in coal tar 1 plus a third site with a very high benzo[a]pyrene content. Control mice received either unadulterated feed (negative control) or feed containing 5, 25, or 100 ppm benzo[a]pyrene. Mice fed coal tar 1 or 2 showed a significant concentration-related increase in incidence of neoplasms of the liver, lung, and forestomach and of hemangiosarcomas, histiocytic sarcomas, and sarcomas. Mice treated with coal tar 1 also showed a significant concentration-related increase in incidence of neoplasms of the small intestine. In contrast mice treated with benzo[a]pyrene

showed a significant concentration-related increase in incidence of neoplasms of the forestomach, esophagus, tongue, and larynx. The authors concluded that the forestomach neoplasms produced by coal tar treatment may be due to the presence of benzo[a]pyrene, but that the other tumors produced by coal tar are likely to be due to the presence of genotoxic compounds other than benzo[a]pyrene. The small intestine-tumors produced by coal tar 1 may be due to chemically-induced cell proliferation that occurred at high doses of coal tar.

A risk assessment based on the data from Culp et al. (1998) discussed the validity of using the concentration of a single component of coal tar (benzo[a]pyrene) to estimate the relative cancer risk for coal tar (Gaylor et al. 2000). In this experiment, benzo[a]pyrene dominated the cancer risk for coal tar when it was present at concentrations >6,300 ppm in the coal tar mixture, and in this case, the forestomach was the most sensitive tissue site. However, when benzo[a]pyrene was present in concentrations <6,300 ppm, the lung was the most sensitive site and benzo[a]pyrene did not contribute to the risk. The authors conclude that, in general, the concentration of benzo[a]pyrene in coal tar is unlikely to be as high as 6,300 ppm and, therefore, it probably should not be used as a measure of the cancer risk for coal tar.

Levels of exposure associated with CELs of creosote are indicated in Table 3-2 and Figure 3-2.

3.2.3 Dermal Exposure

This section describes the health effects observed in humans and laboratory animals associated with dermal exposure to coal tar creosote. All reliable exposure levels have been reported. Several reports were found that describe the occurrence of dermal and ocular irritation, burns, and "warts" (i.e., squamous papillomas) following acute or prolonged skin contact with coal tar creosote. Coal tar creosote also induces phototoxicity of the skin, and has been demonstrated to be a skin carcinogen in animals. Conclusions that can be drawn from the results of animal studies are limited by the possibility of concurrent oral ingestion of creosote from the skin via normal preening behavior and by the fact that few studies reported accurate doses. Details of these reports are given below.

3.2.3.1 Death

No studies were located regarding death in humans following dermal or skin contact with creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles solely by this route.

Coal Tar Products. Evaluations of human exposure during employment in coal tar plants indicated significant increases in cancer-related deaths (TOMA 1982). No specific type of cancer was predominant. Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate death to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1982). Additional limitations were identified in this study, including absence of data on smoking habits, short cut-off date of 10 days of employment, unknown race classification for 20 of participants, use of U.S. male mortality rates for comparison as opposed to regional mortality rates, and the relationship between the cohort and production history was not explored.

In test animals, a dermal LD_{50} in rabbits of >7,950 mg/kg was estimated following a 24-hour application of coal tar creosote to both intact and abraded skin; two of four rabbits died at the high dose of 15,800 mg/kg (Pfitzer et al. 1965). This LOAEL value is recorded in Table 3-4. Additional reports of deaths in test animals, after dermal application of coal tar or coal tar pitch volatiles, can be found in the literature, although specific details of the studies are missing (Bonser and Manch 1932; Deelman 1962). Wallcave et al. (1971) treated groups of Swiss albino mice topically with 9% benzene solutions of two coal tar pitches of known PAH content. An additional group of 15 male and female mice were painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of coal tar pitch were painted in this area 2 times/week with 25 mL of solution (approximately 1.7 mg coal tar pitch per treatment). Mean survival time for animals painted with coal tar pitch and control animals was 31 and 82 weeks, respectively. The effect, if any, of benzene on the dermal absorption of asphalt components was not evaluated in this study. Asphalt (500 mg/mL) and coal tar pitch (30–84 mg/mL) were the materials used in assessing skin carcinogenesis in nonpigmented Swiss CD-1 and pigmented C3H/HeJ male mice (Niemeier et al. 1988). The mean survival time for treated C3H/HeJ ranged from 44.3 to 68.7 weeks compared to 65.6–73.9 for the controls. The mean survival time for the treated CD-1 mice ranged from 52.6 to 67.8 weeks compared to 63.9–67.8 weeks for controls.

3.2.3.2 Systemic Effects

No studies were located regarding the musculoskeletal, endocrine, or body weight effects in humans or respiratory, musculoskeletal, or endocrine effects in animals after dermal exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles. Studies regarding the systemic effects that have been observed in humans and animals after dermal exposure to creosotes are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Tables 3-4 and 3-5.

Respiratory Effects.

Coal Tar Products. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, decreased pulmonary function was noted (TOMA 1979). Restrictive deficits in pulmonary function, as indicated by decreases in FVC, were noted in 44 of 257 employees (10 of 47 nonsmokers). Obstructive deficits, as indicated by decreases in percentage forced expiratory volume in one second (FEV1) were noted in 19 of 257 employees (3 of 54 nonsmokers). Nevertheless, no clear relationship could be established because exposure routes in

Table 3-4 Levels of Significant Exposure to Creosote - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
ACUTE EXPOSURE								
Death								
Rabbit	once					15800 mg/kg/day	(2/4 died)	Pfitzer et al. 1965 coal
Systemic								
Rat (Sprague- Dawley)	4 d Gd 11-15 1x/d	Hepatic		500 F mg/kg/day	(significant increase in relative liver weight)			Zangar et al. 1989 coal tar
		Renal		500 F mg/kg/day	(significant increase in relative kidney weight)			
		Endocr	1500 F mg/kg/day					
		Bd Wt		500 F mg/kg/day	(15% decrease in body weight)	1500 F mg/kg/day	(30% decrease in body weight)	
Mouse (t.o.)	1-3 wk 7 d/wk 1 x/d	Dermal		5 M Percent (%)	(irritation)			Wrench and Britten 1975 coal tar
Mouse (CD-1)	4 d Gd 11-15 1x/d	Hepatic		500 F mg/kg/day	(significant increase in relative liver weight)			Zangar et al. 1989 coal tar
		Renal		500 F mg/kg/day	(significant increase in relative kidney weight)			
		Endocr	1500 F mg/kg/day					
		Bd Wt	1500 F mg/kg/day					
Rabbit (New Zealand White)	once	Ocular		0.1 M ml	(conjunctival redness)			Pfitzer et al. 1965 coal tar

Table 3-4 Levels of Significant Exposure to Creosote - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
Systemic								
Rabbit (New Zealand White)	once	Gastro	7950 M mg/kg/day	15800 M mg/kg/day	(intestinal hyperemia)			Pfitzer et al. 1965 coal tar
Immuno/lymphoret								
Rat (Sprague- Dawley)	4 d Gd 11-15 1x/d			500 F mg/kg/day	(significant decrease in relative weight of thymus)			Zangar et al. 1989 coal tar
Mouse (CD-1)	4 d Gd 11-15 1x/d			500 F mg/kg/day	(significant increase in relative weight of spleen)			Zangar et al. 1989 coal tar
Reproductive								
Rat (Sprague- Dawley)	4 d Gd 11-15 1x/d					500 F mg/kg/day	(significant increase in resorptions and decrease in uterine weight)	Zangar et al. 1989 coal tar
Mouse (CD-1)	4 d Gd 11-15 1x/d			500 mg/kg/day	(significant decrease in uterine weight)	1500 F mg/kg/day	(significant increase in resorptions)	Zangar et al. 1989 coal tar
Developmental								
Rat (Sprague- Dawley)	4 d Gd 11-15 1x/d					500 mg/kg/day	(significantly increased incidence of small lungs, cleft palate, edema, midcranial lesion and reduced cranial ossification)	Zangar et al. 1989 coal tar
Mouse (CD-1)	4 d Gd 11-15 1x/d					500 mg/kg/day	(significantly increased incidence of cleft palate, dilated ureter and renal pelvic cavitation).	Zangar et al. 1989 coal tar

Table 3-4 Levels of Significant Exposure to Creosote - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
Cancer								
Mouse (CD-1)	once					5555 M mg/kg	(initiation of skin tumors)	Mahlum 1983 coal tar
Mouse (CD-1)	once					203 F mg/kg	(initiation of skin tumors)	Springer et al. 1989 coal tar
INTERMEDIATE EXPOSURE								
Systemic								
Rabbit (Australian albino)	3 wk 5 d/wk	Dermal	0.01 M Percent (%)	0.1 M Percent (%)	(comedogenicity)			Kligman and Kligman 1994 coal tar
Cancer								
Mouse (Sutter)	4-28 wk 2 x/wk					0.025 F ml	(CEL: papillomas and carcinomas)	Boutwell and Bosch 1958 coal tar
Mouse (Swiss- albino)	31 wk 2 x/wk					1.7 mg	(CEL: squamous cell carcinoma and papillomas in 53/58)	Wallcave et al. 1971 coal tar pitch volatiles
Rabbit (Australian albino)	15 wk 3 x/wk					10 M Percent (%)	(CEL: papillomas, squamous cell carcinoma,s keratoacanthomas & cutaneous horns)	Kligman and Kligman 1994 coal tar

Table 3-4 Levels of Significant Exposure to Creosote - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious		Reference Chemical Form
CHRONIC EXPOSURE							
Death							
Mouse (Swiss CD-1; C3H/HeJ)	78 wk 2 x/wk				30 M - 84 mg/ml	(mean survival time for C3H/HeJ; treated = 44.3-68.7 wks, control = 65.6-73.9 wks; for CD-1; treated = 52.6-67.8 wks, control = 63.9-67.8 wks)	Niemeier et al. 1988 CTPV
Mouse (Swiss CD-1; C3H/HeJ)	78 wk 2 x/wk				500 M mg/ml	(mean survival time for C3H/HeJ; treated = 44.3-68.7 wks, control = 65.6-73.9 wks; for CD-1; treated = 52.6-67.8 wks, control = 63.9-67.8 wks)	Niemeier et al. 1988 CTPV
Mouse (Swiss CD-1; C3H/HeJ)	78 wk 2 x/wk				500 M mg/kg/day	mg/mL asphalt + 30-84 mg/mL coal tar pitch (deaths)	Niemeier et al. 1988 CTPV
Systemic							
Mouse (Swiss CD-1; C3H/HeJ)	78 wk 2x/wk	Bd Wt	30 M - 84 mg/ml				Niemeier et al. 1988 CTPV
Mouse (Swiss CD-1; C3H/HeJ)	78 wk 2x/wk	Bd Wt	500 M mg/ml				Niemeier et al. 1988 CTPV
Cancer							
Mouse (Swiss CD-1; C3H/HeJ)	78 wk 2 x/wk				30 M - 84 mg/ml	(CEL: skin tumors)	Niemeier et al. 1988 CTPV

Table 3-4 Levels of Significant Exposure to Creosote - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious		Reference Chemical Form
Cancer							
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2 x/wk				500 M mg/ml	(CEL: skin tumors)	Niemeier et al. 1988 CTPV
Mouse (Swiss CD-1; C3H/ HeJ)	78 wk 2 x/wk				500 M mg/kg/day	mg/mL asphalt + 30-84 mg/mL coal tar pitch (CEL: tumors)	Niemeier et al. 1988 CTPV
Mouse (C57L)	lifetime 3 x/wk				20 F Percent (%)	(CEL: papillomas 100% incidence)	Poel and Kammer 1957 coal tar

Bd Wt = body weight; CEL = cancer effect level; CTPV = coal tar pitch volatiles; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; wk = week(s); x = times

Table 3-5 Levels of Significant Exposure to Wood Creosote - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
INTERMEDIATE EXPOSURE						
Systemic						
Rabbit (Australian albino)	10 wk 5 d/wk	Dermal		10 M Percent (%) (small visible comedones in 2 wks)		Kligman and Kligman 1994 birch tar

d = days(s); LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; wk = week(s)

addition to dermal were likely, such as inhalation and oral. Also, the ability to relate respiratory effects to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1979). Additional limitations of the studies included seasonal and geographical variation in plant locations, past employment history, voluntary participation in the study that could have biased it in favor of healthy workers, lack of statistical analyses, lack of adequate controls, and use of only current employees.

A site surveillance program was conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant (Agency for Toxic Substances and Disease Registry 1994). The plant had ceased creosoting activities in 1961, after operating for 51 years. A sand and gravel company had operated on part of the abandoned site during the 1970s and 1980s. Because of soil and groundwater contamination with PAHs and other chemicals, the EPA identified this site and placed it on the NPL in 1984. Several residential lots were observed to have soil concentrations of benzo[a]pyrene in excess of 325 mg/kg, or oily-stained areas, and were subject to emergency resodding by the EPA. Contaminated soils were scheduled to be treated for clean-up. A total of 214 residents (123 males, 91 females) of the contaminated residential area (Koppers) were interviewed twice during a period of 2 years, and were compared to 212 residents (122 males, 93 females) from a nearby town. Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results. Residents of the Koppers area showed a significantly higher risk of chronic bronchitis (RR=2.65, 95% CI=1.26–5.57) relative to the comparison population during the first year of the study. During the second year of the study, 11 residents of the Koppers area reported chronic bronchitis, whereas 7 were expected based on the 1990 National Health Interview Survey rates. These study results are seriously limited by the study's reliance on self reporting of health conditions for which diagnosis verification was not always available.

Cardiovascular Effects.

Coal Tar Products. In an industrial health survey of employees in a wood preservative plant in which coal tar creosote, coal tar, and pentachlorophenol were the main treatments used, cardiovascular effects, including increased diastolic blood pressure, were noted in 21% (24/113) of the employees examined

(TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate cardiovascular effects to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals such as pentachlorophenol and cigarette smoke (TOMA 1979). Additional limitations of the study are listed above under Respiratory Effects.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to creosotes, coal tar, or coal tar pitch.

Coal Tar Products. In an acute animal study, New Zealand white rabbits that died following single dermal applications of undiluted coal tar creosote (15,800 mg/kg) exhibited hyperemia of the intestines, but animals treated with 7,950 mg/kg did not (Pfitzer et al. 1965).

Hematological Effects.

Coal Tar Products. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, hematological effects, including increased number of white blood cells (basophils), were noted in 6% (15 of 257) of the employees examined (TOMA 1979). Similarly, 8% of the employees in eight of nine coal tar plants surveyed had increased white blood cells (eosinophils) (TOMA 1981). Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that in 94% of the samples, airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). No determination of exposure was made at the nine coal tar plants (TOMA 1981). Furthermore, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate hematological effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1979, 1981). Additional limitations of the studies are noted above (see "Respiratory Effects").

In a clinical study, 15 patients (Group A) with chronic plaque psoriasis were treated with increasing concentrations (1–4%) of topical coal tar paste (Gilmour et al. 1993). These patients did not receive ultraviolet (UV) therapy and served as controls. Seventeen subjects (Group B) received UV-B phototherapy and four subjects (Group C) received psoralen photochemotherapy (PUVA). Another

control group (Group D) consisted of 4 nonpsoriatic subjects who were receiving UV-B as part of another study. Samples of blood were collected before irradiation and 48 hours after irradiation, and full blood counts were determined. Samples taken from Group A were taken before treatment and again 4 weeks later. Samples taken from Group B and C were taken before treatment, 4 weeks after treatment (48 hours after irradiation), and finally 4 weeks after irradiation. The blood counts were all normal. A similar lack of adverse effect on the hematological system was observed by Tham et al. (1994) in psoriasis patients who applied a total of 120 g of coal tar over a period of 2–6 weeks to the skin of one side of their body.

Hepatic Effects.

Coal Tar Products. Fifteen patients (Group A) with chronic plaque psoriasis were treated with increasing concentrations (1–4%) of topical coal tar paste (Gilmour et al. 1993). An additional 17 subjects (Group B) received UV-B phototherapy and 4 subjects (Group C) received psoralen photochemotherapy (PUVA). Another control group (Group D) consisted of 4 nonpsoriatic subjects who were receiving UV-B as part of another study. Liver function was determined. Samples taken from Group A were taken before treatment and again 4 weeks later. Samples taken from Group B and C were taken before treatment, 4 weeks after treatment (48 hours after irradiation), and finally 4 weeks after irradiation. Liver function was within normal limits. A similar lack of adverse effect on liver function was observed by Tham et al. (1994) in psoriasis patients applying 120 g of coal tar to their skin twice daily for 2–6 weeks.

In a developmental study of Sprague-Dawley rats and CD-1 mice, exposure to 500 or 1,500 mg/kg coal tar on gestational days 11–15 resulted in significant increases in maternal liver to body weight ratios for treated animals from both species compared with controls (Zangar et al. 1989).

Renal Effects.

Coal Tar Products. In an industrial health survey of employees in nine coal tar plants in which coal tar creosote and coal tar were the main treatments used, renal effects, including protein and cells in the urine, were noted in 1–8% (3–34 of 452) of the employees examined (TOMA 1981). Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate renal effects to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1981). A study performed by Wright et al. (1992b) evaluated the nephrotoxic effects of commercial coal tar preparation for the scalp. The preparation was applied to healthy human subjects either for 15 minutes,

twice a week, for 8 weeks to uncovered skin, or for 30 minutes, every second day for 4 weeks under occlusive bandage. The preparations tested contained 5 or 10% beechwood tar. The concentration of coal tar in the preparation was not specified. Renal function and urinary phenol levels were assayed before, during, and after treatment. No impairment of renal function was detected, nor was urinary phenol content found to be related to the coal tar treatment (Wright et al. 1992b). No adverse effect on urinalysis was observed for 15 patients with chronic plaque psoriasis were treated with increasing concentrations (1–4%) of topical coal tar paste in urine samples taken before treatment and 4 weeks after treatment (Gilmour et al. 1993).

In a developmental study of Sprague-Dawley rats and CD-1 mice applied 500 or 1,500 mg/kg coal tar on gestational days 11–15, there were significant increases in maternal kidney to body weight ratios for treated animals compared with controls (Zangar et al. 1989).

Renal effects were also noted in a study conducted by Deelman (1962), in which mice were exposed dermally to an unspecified amount of tar applied 6–18 times over 6–7 weeks. "Seriously affected" kidneys were noted, although no details or data were presented. Ten groups of Swiss albino mice received topical applications of 10% benzene solutions of eight petroleum asphalts of known polynuclear aromatic hydrocarbon content (Wallcave et al. 1971). An additional group of 15 males and females were painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of asphalt were painted in this area 2 times/week with 25 mL of solution (approximately 2.5 mg asphalt per treatment). Amyloidosis was frequently observed in animals receiving asphalt, particularly in the kidney. The potential effect of benzene on the dermal absorption of asphalt components was not evaluated in this study.

Endocrine Effects.

Coal Tar Products. In a developmental study of Sprague-Dawley rats and CD-1 mice, exposure to 500 or 1,500 mg/kg coal tar on gestational days 11–15 produced no change in weight of the adrenal glands of treated animals from both species compared with controls (Zangar et al. 1989).

Dermal Effects.

Creosote Bush. Leonforte (1986) reported six confirmed cases of acute allergic dermatitis subsequent to contact with the creosote bush. Two cases were the result of "casual occupations," two were the result of household remedies, and two were the result of burning the bush. Based on his findings, the author concluded that the allergens are probably contained in the plant's perfume, are volatile, and are not destroyed by heat. In contrast, no adverse treatment-related effects were reported for 23 patients treated topically with an extract of creosote bush (concentration not stated) in castor oil (Heron and Yarnell 2001).

Wood Creosote. Beechwood creosote has been found to irritate tissue other than skin. The effects of beechwood creosote (dose not specified) on the periapical tissue (the connective tissue surrounding the apex of the tooth) were studied in 10 teeth from 4 different dogs 7 days after its application following root canal surgery (Attalla 1968). Beechwood creosote application resulted in localized inflammatory changes and occasional abscess formation in the periapical region, presumably due to tissue damage caused by coagulation of proteins. Bone resorption was observed in the alveolar process. The authors concluded that beneficial disinfectant properties of beechwood creosote may be outweighed by irritant effects following root canal surgery. Birch tar (10%) was applied to the ear of male Australian albino rabbits 5 days/week for 3 weeks (Kligman and Kligman 1994). Comedones were visible on the ear after 2 weeks of treatment.

Coal Tar Products. Burns and irritation of the skin are the most frequent manifestations of coal tar creosote toxicity following dermal exposure. According to a review by EPA (1978b), burns from hot pitch are relatively common in occupational settings. Burn scars and other sites of epidermal atrophy may later be sites for skin cancer. Creosote chemical burns were observed in construction workers who handled wood treated with creosote (presumably coal tar creosote) (Jonas 1943). Exposure levels were not specified. It was found that 70% of the burn cases were mild and were characterized by erythema of the face. These symptoms were more marked on the cheeks, nose, forehead, and posterior part of the neck. The remainder of the burn cases (30%) were more severe and were characterized by intense burning, itching, and considerable subsequent pigmentation followed by desquamation. There is no way to determine, given the information provided, whether this response was due to primary irritation or an allergenic response.

Other reports of skin irritation after contact with coal tar (Cusano et al. 1992) were found. Patients admitted over a 4-month period to the dermatology wards of Manchester Skin Hospital for the treatment of psoriasis were patch tested with 3% coal tar (Burden et al. 1994). A positive reaction to coal tar was followed by dilution series testing down to a 0.1% concentration of coal tar. Patients were asked about previous psoriasis treatment and adverse reactions from topical preparations. Mean duration of psoriasis was 20 years and many patients had been treated as inpatients previously on numerous occasions; 91% of patients recalled previous treatment with coal tar. Thirteen patients showed clinical intolerance to coal tar and two had positive patch test reaction to coal tar confirmed by serial dilutions.

In another study, 5% crude coal tar (CCT) was applied to the backs of eight subjects in six distinct sites for 15, 30, 60, 90, 120, and 180 minutes (Diette et al. 1983). Tar was then vigorously removed with a washcloth, Ivory® soap, and water. Immediately following tar removal, the minimal phototoxic dose (MPD) of UV-A was determined at each site using 1-cm diameter apertures. In all subjects, the minimal erythema dose (MED) and MPD were defined as the minimal dose of UV-A causing 1+ erythema with distinct borders read at 24 hours after exposure. In addition, 5% CCT was applied to four separate sites on the backs of 13 subjects for 1 hour. The following methods of tar removal were compared: (1) water, (2) Ivory® soap and water, (3) mineral oil, and (4) Ivory® soap and water followed by mineral oil. Immediately after tar removal, all sites were exposed to UV-A and the MPD of UV-A was determined. UV-A exposure doses were identical to those used above. A 5% CCT ointment was applied to the backs of 19 subjects and removed 1 hour later with a washcloth, Ivory® soap, and water. The subjects were informed prior to testing about the photosensitizing effect of tar plus UV-A in producing a burning, stinging, or smarting reaction at an unspecified time during UV-A exposure. These subjects would signal the onset of symptoms and were encouraged not to wait until the burning sensation became unbearable. Subjects were tested immediately and at 0.5, 2, 4, 6, 24, and 30 hours following tar removal. At least 8 subjects were tested at each time; only at 24 and 30 hours were <10 subjects tested. Using the same UV-A exposure times, the MED of UV-A was determined in those eight subjects tested at 24 and 30 hours. The minimal UV-A dose required to induce delayed erythema (the MPD) and the minimal UV-A dose required to induce an immediate smarting reaction (minimal smarting dose or MSD) were recorded. The effects of the following variables on MPD were noted: (1) interval of time tar is left on the skin (TA); (2) methods of tar removal; and (3) time between removal of tar and UV-A irradiation. Tar application for 30 minutes was photosensitizing in all eight subjects; six of the subjects showed photosensitization after only 15 minutes of tar application. The photosensitizing effect of tar increased rapidly up to 60 minutes of application. MPD increased from 3.77±1.55 to 6.1±4.0 J/cm^2 after 30 minutes of application. Longer time intervals between tar removal and UV-A exposure were accompanied by more

gradual, but consistent, increases in MPD. The MSD also significantly increased with increasing intervals between tar removal and UV-A exposure. At times, the smarting reaction was associated with an immediate erythema, which faded in several hours; this was not a consistent finding with 1 MSD of UV-A. No urticarial response was noted at this dose level.

Other studies confirm that coal tar creosote is capable of increasing skin sensitivity to sunlight. Phototoxicity is an exaggerated response to sun exposure characterized by excessive sunburn. The usual sunburn is produced by UV-B light, whereas a phototoxic skin response occurs following absorption of UV-A light by chemicals in or on the skin (NIOSH 1981a). Coal tar creosote exposure was evaluated in six male dock builders of Scandinavian descent with fair skin. These builders had worked on this particular construction site for 5 months, but had an average of 16.6 years of work as pile-drivers (NIOSH 1981a). The dermal burning and irritation experienced by these workers upon dermal contact with wood treated with coal tar creosote was exacerbated on hot or sunny days. Skin examinations of these dermally exposed workers revealed erythema and dry peeling skin on the face and neck with irritation and folliculitis on the forearms. These symptoms were worse on hot or sunny days, at which time red, swollen, and puffy eyes were observed. Thus, phototoxicity compounds the irritative response of the skin to coal tar creosote. No skin tumors were observed in this study, but it is not clear if the exposure duration in the group of workers was sufficient to allow development of skin tumors. Nevertheless, some studies have reported latency periods for the development of dermatoses, such as squamous papillomas, ranging from several months to 16 years or more (Cookson 1924; Henry 1946, 1947; O'Donovan 1920; Shambaugh 1935). Effects similar to those seen in the NIOSH (1981a) study were noted in workers transferring coal tar pitch from a river barge to an ocean barge (NIOSH 1982). Exposure levels of coal tar pitch volatiles measured were considered to represent the minimum ambient air exposure in the barge area because of unusual environmental sampling conditions. These levels ranged from below the detectable limit to 0.06 mg/m^3 for breathing zone samples and from below the detectable limit to 0.02 mg/m^3 for area samples. Other studies have been published that describe similar effects of coal tar exposure, although exposure levels are not specified (Emmett 1986).

Coal tar creosote has been reported to produce types of noncancerous skin lesions other than burns and irritation following dermal exposure (Haldin-Davis 1935; NIOSH 1982; Schwartz 1942; Shambaugh 1935). Haldin-Davis (1935) described the case of a man employed in the activity of dipping wood in creosote tanks who received "heavy" dermal exposure to coal tar creosote (level not determined) on the face, trunk, and thighs. He subsequently developed a number of lesions on the hands, forearms, and thighs. One of these lesions was excised and examined, and classified as a benign squamous cell

papilloma. A study was made of the cases of cancer of the lip at various New England hospitals (Shambaugh 1935). Men who were constantly exposed to tars were those who worked in "net lofts" where the fishing nets are repaired and tarred. It was common practice to hold the large wooden shuttle-like needle in the mouth while the tarred nets are being mended. The needle soon becomes smeared with the tar, which is thus carried to the lip. It was found that the older workers who had been exposed to the tar for many years showed typical tar warts on the hands and forearms. An irritative condition on the forearms, which they call "pinginitis," evidently a pustular folliculitis (not cancerous), was observed. Three workers in factories erected for manufacturing armaments developed symptoms 1–2 weeks after beginning work which were attributed to the creosote that evaporated off the wooden floors (Schwartz 1942). It was likely that the fresh creosote on the blocks came in contact with the ends of the trousers and rubbed against the ankles. These employees noticed that their ankles began to itch above the shoe tops and later an erythematous, papular, and vesicular eruption appeared. The lesion extended 4 or 5 inches above the shoe tops, and when seen, presented the appearance of a scratched eczematoid dermatitis. Their condition improved over the weekend. One patient, before the etiology of the condition was discovered, had been treated with a coal tar ointment and the dermatitis became worse. Patch tests were not performed with scrapings from the wooden blocks. It has been reported that chronic hyperpigmentation, a darkening of the skin also known as pitch melanosis, may develop after $5 years of exposure to coal tar pitch (EPA 1978b). Even unexposed areas may be affected.

In an industrial health survey of 251 employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, 82 cases of dermal effects, including skin irritation, eczema, folliculitis, and benign growths on the skin were reported. It is not stated in the report whether multiple conditions were evident in any of the workers examined (TOMA 1979). Workers in nine coal tar plants had a 20% incidence of dermal effects including keratosis, eczema, folliculitis, and chloracne (TOMA 1981). The incidence of benign growths, eczema, and folliculitis was greater than that observed in the general U.S. population, although the authors concluded that only the cases of folliculitis were sufficiently severe to be significant. However, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate dermal effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1979, 1981). Additional study limitations are noted above under “Respiratory Effects.”

The National Institute for Occupational Safety and Health (NIOSH) has investigated potential employee-related health effects in mixers and laborers exposed to coal tar/coal tar creosote/clay products in a

refractory cement factory (NIOSH 1980a). Six of seven environmental samples collected exceeded the Permissible Exposure Limit (PEL) for coal tar products (cyclohexane solubles, which include creosote) of 0.1 mg/m^3. Exposures were reported to be as high as 1.42 mg/m^3. Because environmental levels significantly exceeded the PEL, it is likely that considerable dermal exposure occurred. One worker reported the need for medical treatment when coal tar creosote splashed in his eye, and another claimed that he was hospitalized for 3 days after experiencing convulsions following an incident where he was splashed with coal tar creosote. The medical records for these two men were not reviewed.

A site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant revealed dermal effects of creosote exposure in the residents (Agency for Toxic Substances and Disease Registry 1994). Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. Residents living in or near the Koppers area reported a higher prevalence of skin rashes (27.9%) during the first year of the surveillance than the comparison neighborhood (4.9%), with a RR of 5.72 ($P<0.05$; 95% CI=3.01–10.87). During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results, and similar results were obtained, with 34 Koppers residents reporting skin rashes, compared to an expected incidence of 4. Rashes were associated with digging in the yard, having contact with the soil, or wading in or having contact with a creek in the area. Most rashes were associated with itching or burning. The recommendation was that residents in the Koppers area should wear protective clothing when having contact with the soil, and should wash their skin thoroughly when contact with the soil occurs.

Skin irritation is also observed in laboratory animals following dermal exposure to coal tar creosote. The effects of dermally applied coal tar fractions, derived from creosote and anthracene oils by high-temperature boiling, were studied in mouse tail skin at concentrations of 5 and 10% (acids) in paraffin by Wrench and Britten (1975). Several of the fractions caused irritation, and some caused peeling and epidermal thickening. The authors concluded that the acids that boiled in the range from 280 to 340 EC have a more specific action in inducing granular layers than the parent tars, oils, or whole acids at similar concentrations. This study is of limited value because the chemical composition of the acid fractions was not defined, and no dose levels could be quantified. It can only be concluded that certain fractions of coal tar creosote irritate mouse skin.

Three samples of Scottish blast-furnace tar (I, II, and III), one sample of English tar, and an ether extract of English tar were applied in a clipped area of skin in the region between the shoulder blades of 60 mice (Bonser and Manch 1932). Tar was applied biweekly for the first 14 weeks, and thereafter once weekly. This change in the frequency of the tar applications was necessitated by the rather marked tendency to ulceration of the skin exhibited by many of the mice. This experiment was continued for 56 weeks, by which time all mice had died. At 30 weeks, 35 of 60 mice applied with ether extract of English tar died and among the 25 survivors, 50% bore tumors. The first appearances of warts in mice applied with Scottish tar (samples I, II, and III), English tar sample, and ether extract of English tar was in 16 (7 of 60 animals), 21 (8 of 60 animals), and 12 (24 of 60 animals) weeks, respectively. Warts were confirmed histologically in 4, 3, and 16 mice (per sample), treated with Scottish tar (samples I, II, and III), English tar, and ether extract of English tar, respectively.

The skin of 10 groups of Swiss albino mice was treated with 9% benzene solutions of two coal tar pitches of known PAH content (Wallcave et al. 1971). An additional group of 15 males and females were painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of coal tar pitch were painted in this area 2 times/week with 25 mL of solution (approximately 1.7 mg coal tar pitch per treatment). Animals exhibited hyperplasia of the epidermis as a general phenomenon, frequently accompanied by inflammatory infiltration of the dermis and on several occasions ulceration with formation of small abscesses. This effect was also seen after application of a 10% solution of petroleum asphalts (Wallcave et al. 1971). The effect, if any, of benzene on the dermal absorption of asphalt components was not evaluated in this study.

Guinea pigs also exhibited phototoxicity after dermal treatment with coal tar pitch distillates and UV light (Emmett 1986). In addition, the histological effects of coal and birch tar on guinea pig teat epidermis treated over a period of 22 days have been investigated (Schweikert and Schnyder 1972a, 1972b). Preparations of both coal and birch tar induced a proliferate acanthosis.

Rabbits given single dermal applications of undiluted coal tar creosote exhibited slight to moderate erythema and moderate edema followed by severe hyperkeratosis (Pfitzer et al. 1965).

Coal tar was applied to the ear of male Australian albino rabbits 5 days/week for 3 weeks (Kligman and Kligman 1994). Comedones were visible on the ear after 3 weeks of treatment with 0.1 or 1.0% coal tar.

In summary, dermal application of either coal tar or beechwood creosote results in mild-to-severe irritation of the skin, and other exposed tissues, as well as benign skin lesions in both humans and animals. Coal tar creosote also induces phototoxicity, so that exposure to the sun exacerbates its irritant effects.

Ocular Effects.

Coal Tar Products. Direct exposure of the eye to coal tar creosote is irritating to the superficial tissues. Factory and construction workers, roofers, and other workers who handle coal tar, or wood treated with coal tar creosote have experienced conjunctiva burns and irritation resulting from accidental exposure (Birdwood 1938; Emmett 1986; Jonas 1943; NIOSH 1980a, 1981a). Exposure to the sun exacerbated eye irritation from exposure to creosote or coal tar fumes. It was reported in a review by EPA (1978b) that acute episodes involving the eyes usually begin 2–4 hours after initial exposure to pitch fumes or pitch dust. Symptoms may include reddening of the eyelids and conjunctiva. Discontinuation of exposure will not always result in cessation of symptoms, but in mild cases, the symptoms disappear within 3 days. Chronic exposures may lead to damage to the cornea, chronic conjunctivitis, and restriction of the visual field. The likelihood of adverse effects on the eye may be reduced by maintaining the levels of coal tar pitch volatiles in air below 0.2 mg cyclohexane solubles per cubic meter. In one study, conjunctivitis was not observed at coal tar pitch levels below 0.11 mg cyclohexane solubles per cubic meter (EPA 1978b).

Similar effects (tearing, phototoxicity, and keratoconjunctivitis) have been observed in animals, including C3H/HeJ mice and New Zealand rabbits (Emmett 1986). Instillation of 0.1 mL undiluted coal tar creosote in the eyes of New Zealand white rabbits produced a redness of the conjunctiva with congested vessels that resolved within 7 days (Pfitzer et al. 1965).

Body Weight Effects.

Coal Tar Products. In a developmental study of Sprague-Dawley rats and CD-1 mice exposed to 0, 500, or 1,500 mg/kg coal tar on gestational days 11–15, rats had significant decreases in extragestational body weight compared with controls, while mice had no significant change in extragestational body weight compared with controls (Zangar et al. 1989). Body weight effects were noted in a study conducted by Deelman (1962), in which mice were exposed dermally to an unspecified amount of tar applied 6–18 times over 6–7 weeks. "Diminished weight" was noted, although no details or data were presented. Asphalt (50 μL of a 500 mg/mL solution) and coal tar pitch (50 μL of a 30–84 mg/mL solution) applied

to an unspecified area of the skin of Swiss CD-1 and pigmented C3H/HeJ male mice 2 times/week for 78 weeks had no adverse effect on body weight (Niemeier et al. 1988).

3.2.3.3 Immunological and Lymphoreticular Effects

Creosote Bush. Several cases of acute allergic dermatitis have been reported following contact with the creosote bush. Smith (1937) described the case of a patient who presented with erythematous and vesicular dermatitis of the face, the upper part of the neck, and the backs of the hands after collecting creosote bush. Patch tests confirmed the existence of an allergy to this plant. Leonforte (1986) reported six cases of acute allergic dermatitis subsequent to contact with a creosote bush and confirmed by a patch test. Two cases were a result of "casual occupations," two were a result of household remedies, and two were a result of burning the bush. Based on his findings, the author concluded that the allergens are probably contained in the plant's perfume, are volatile, and are not destroyed by heat. The relevance of these findings to individuals who live in areas surrounding hazardous waste sites and who will most likely be exposed to coal tar creosote is questionable. Creosote bush resin differs from creosote extracted from coal and wood tar, but all contain phenolic derivatives. It is not known whether these derivatives are the allergens in creosote bush resin.

Coal Tar Products. Contact dermatitis has also been reported after short-term contact with coal tar (Cusano et al. 1992). No adverse immunological effects were observed in patients with chronic plaque psoriasis who were treated with increasing concentrations (1–4%) of topical coal tar paste (Gilmour et al. 1993). Autoantibodies, serum immunoglobulin and complement levels were measured; two patients with psoriasis had slightly elevated IgE levels and several had slightly raised concentrations of serum immunoglobulin isotopes and complement components, but these were within normal ranges in most psoriasis patients. Percentages of subsets of peripheral blood mononuclear cells (PBMC) were normal and were not altered by treatment. Lymphocytic infiltration was noted in the pathological evaluation of a tar carcinoma excised from the eyelid of a tar and pitch worker (Goulden and Stallard 1933).

There is very little information describing immunological and lymphoreticular effects of coal tar products in animals after dermal exposure. In a developmental study of Sprague-Dawley rats and CD-1 mice, exposure of rats to 500 or 1,500 mg/kg coal tar on gestational days 11–15 resulted in significant decreases in maternal thymus to body weight ratios for treated animals compared with controls, while spleen weights were similar in control and treated animals (Zangar et al. 1989). Exposure of mice to coal tar produced a significant increase in maternal spleen to body weight ratios for treated animals compared

with controls, while thymus weights were similar in control and treated animals (Zangar et al. 1989). Amyloidosis of the spleen and inflammatory infiltration of the dermis were observed in Swiss mice after topical application of 2.5 mg asphalt in 10% benzene solutions twice weekly for 81–82 weeks (Wallcave et al. 1971). The effect, if any, of benzene on the dermal absorption of asphalt components was not evaluated in this study.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in animals following dermal exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles.

Coal Tar Products. A worker who was splashed with coal tar creosote in a refinery claimed that he was hospitalized for 3 days after experiencing convulsions (NIOSH 1980b). The medical records for this man were not reviewed, so it cannot be concluded that creosote exposure was responsible for his convulsions. No additional information was provided. Observations were made of the effect of coal tar creosote on workers constructing buildings with treated wood (Jonas 1943). Complications observed in 2.4% of the workers included neurological symptoms including headache, weakness, confusion, vertigo, and nausea.

3.2.3.5 Reproductive Effects

No studies on the reproductive effects produced by dermal exposure to wood creosote, coal tar pitch, or coal tar pitch volatiles in human or animals were located.

Coal Tar Products. One retrospective human study of dermal exposure to coal tar was located in which 64 women who had been treated with coal tar for psoriasis or dermatitis were issued questionnaires (Franssen et al. 1999). Fifty-six of the women returned the questionnaires. The ratio of dermatitis to psoriasis was 1:2 with a mean percentage treated body area of 78–90%, and the women were between 18 and 35 years of age for the period of the study (1981–1985). In total the women had been pregnant 103 times. In 59 out of 103 pregnancies, no coal tar had been used; in 21 pregnancies, it was unclear whether coal tar had been used or not, and in the remainder, coal tar had been used at some point during pregnancy. Untreated pregnancies resulted in 19% spontaneous abortion while treated pregnancies resulted in 26% spontaneous abortion. The authors did not consider this to be a significant increase in spontaneous abortion compared with the general population, but pointed out that their sample size was small and this study probably did not have sufficient resolution to detect a modest increase in risk.

A site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant revealed no adverse reproductive effects in the residents (Agency for Toxic Substances and Disease Registry 1994). There was no difference in the reproductive outcome of female residents of the Koppers area compared to the comparison neighborhood or the 1990 National Health Interview Survey. In particular, there was no effect on number of pregnancies, live births, premature births, spontaneous abortions, or still births. Koppers women who reported having problems becoming pregnant during the first year of surveillance had an average of 1.3 pregnancies compared to an average of 3.4 pregnancies from women in the comparison neighborhood who also reported difficulty in becoming pregnant. No difference in pregnancy outcome was noted during the second year of surveillance, and rates of stillbirth, low weight birth, or spontaneous abortions were similar to those of unexposed populations (Agency for Toxic Substances and Disease Registry 1994). It is likely that reports of difficulty in becoming pregnant were confounded by perception of risk and possibly also by the age of the mother as the difference was not significant when the results for the entire group were adjusted for concerns about chemical exposure, or when women over the age of 39 were excluded from the analysis. A retrospective study of dermal exposure to coal tar found no increased risk of spontaneous abortion associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

In a developmental study of Sprague-Dawley rats and CD-1 mice, exposure to 500 or 1,500 mg/kg coal tar on gestational days 11–15 resulted in significant decreases in uterine weight (Zangar et al. 1989). No difference in extragestational body weight gain of the mouse dams was observed, but some maternal toxicity in the form of significantly increased weights of the liver, kidney, and spleen was seen. The extragestational body weights of treated rats were significantly decreased compared to controls and the relative weights of maternal liver and kidney were significantly increased while those of the thymus were significantly decreased. The relative weights of the spleen and adrenal glands were unaffected by treatment. Resorptions were significantly increased for all exposed rats and high dose mice compared to controls. Early resorptions (occurred before dosing) were similar in all groups, but middle resorptions (which corresponded to the dosing period) were significantly increased in exposed rats and high dose mice. Late resorptions were also significantly increased in exposed rats.

3.2.3.6 Developmental Effects

No studies on the developmental effects produced by dermal exposure to wood creosote, coal tar, coal tar pitch, or coal tar pitch volatiles in humans were located.

Coal Tar Products. A site surveillance program was conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc. creosote wood treatment plant (Agency for Toxic Substances and Disease Registry 1994). There was no difference in the number of low birth weight births or birth defects. One retrospective human study of dermal exposure to coal tar was located in which 64 women who had been treated with coal tar for psoriasis or dermatitis were issued questionnaires (Franssen et al. 1999). Fifty-six of the women returned the questionnaires. The ratio of dermatitis to psoriasis was 1:2 with a mean percentage treated body area of 78–90%, and the women were between 18 and 35 years of age for the period of the study (1981–1985). In total, the women had been pregnant 103 times. In 59 out of 103 pregnancies no coal tar had been used, in 21 pregnancies it was unclear whether coal tar had been used or not and in the remainder coal tar had been used at some point during pregnancy. Untreated pregnancies resulted in 5% congenital disorders while treated pregnancies resulted in 4% congenital disorders. The authors pointed out that their sample size was small and this study probably did not have sufficient resolution to detect a small increase in risk.

In a developmental study of Sprague-Dawley rats and CD-1 mice, exposure of 0, 500, or 1,500 mg/kg coal tar on gestational days 11–15 resulted in significant increases in developmental defects (Zangar et al. 1989). Both rats and mice exposed to coal tar showed a significant decrease in uterine weight compared with controls. No difference in extragestational body weight gain of the mouse dams was observed, but some maternal toxicity in the form of significantly increased weights of the liver, kidney, and spleen was seen. The extragestational body weights of treated rats were significantly decreased compared to controls and the relative weights of maternal liver and kidney were significantly increased while those of the thymus were significantly decreased. The relative weights of the spleen and adrenal glands were unaffected by treatment. Fetal and placental weights and crown-rump lengths decreased in a dose dependant manner and fetal lung weights were decreased on absolute and relative weight basis for both low and high dose rat groups. There was no significant difference between fetal weight, placental weight, and fetal lung weights and crown-rump lengths in control and exposed mouse fetuses. A significantly increased incidence of small lungs, cleft palate, edema, midcranial lesion, and reduced cranial ossification

was observed in exposed rat fetuses and a significantly increased incidence of cleft palate, dilated ureter, and renal pelvic cavitation was observed in exposed mouse fetuses.

Another animal study reported that dermal contact with coal tar creosote-treated wood produced fetotoxic effects in pregnant sows (Schipper 1961). Four sows were confined to wooden farrowing crates for 2–10 days before delivery. The platforms of the crates were coated with three brush applications of a commercial wood preservative containing 98.5% coal tar creosote. Following contact with creosote, 24 of the 41 pigs delivered were dead at birth, and 11 pigs died by day 3 postfarrowing. The surviving pigs had rough skin and suffered from dehydration and severe diarrhea. The pigs failed to gain weight until they were 5–6 weeks old. No toxic effects on the sows were reported. However, 4 sows confined to untreated lumber crates at least 24 hours before farrowing delivered 36 pigs; 1 died within 24 hours and 3 died postfarrowing. No toxic effects were noted in mothers or baby pigs.

3.2.3.7 Cancer

Coal Tar Products. Various case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote (coal tar) exposure with the development of skin cancer (Cookson 1924; Goulden and Stallard 1933; Henry 1947; Lenson 1956; Mackenzie 1898; O'Donovan 1920; Shambaugh 1935; Shimauchi et al. 2000). These papers reported similar neoplastic skin lesions for different groups of workers exposed to creosote. Lesions included the development of dermatoses (e.g., squamous papillomas), which progressed to carcinoma, usually squamous-cell carcinoma. Tumor locations included regions of the face, head and neck, and upper limb. Cancer of the scrotum has also been associated with prolonged exposure to coal tar creosote (Henry 1946). The latency period for the development of dermatoses, such as squamous papillomas, was varied, ranging from several months to 16 years or more (Cookson 1924; Henry 1946, 1947; O'Donovan 1920; Shambaugh 1935). Worker exposure in the past was much greater than it is now because of less-sophisticated industrial practices, the lack of knowledge concerning occupational hygiene, and the current recognition of the dangers of excessive exposure to the health of workers. For example, chimney sweeps had a lower incidence of scrotal cancer after limiting their exposure to coal tar creosote by regular washing of their skin. Other factors that should be considered when extrapolating the findings of this older literature to present conditions are the role of exposure to UV radiation in the form of sunshine in these workers (UV radiation is now known to be a major cause of skin cancer), the composition of the creosote products, and other health factors that differ in Great Britain prior to 1940 and the present. Although these studies lack information concerning specific exposures and do not consider other risk factors for the development of skin cancer, when taken

as a group, they suggest a relationship between chronic dermal coal tar creosote exposure, phototoxicity, and the development of skin carcinoma in humans.

The effect of treatment with tar and/or artificial UV radiation on the risk of developing cutaneous carcinoma was evaluated on skin cancer patients (59 cases) with severe psoriasis (Stern et al. 1980); 924 subjects without skin cancer were selected as unmatched controls. A matched group (58 cases and 126 matched controls) was also selected from the same group of controls. Patients were categorized according to amount of tar use (<30, 30–90, or >90 months) and levels of radiation exposures (low, moderate, or high). The relationship between tar exposure and UV radiation treatment and the development of skin cancer both before and after 8-methoxypsoralen photochemotherapy (PUVA) were evaluated. The estimated crude relative rate of cutaneous carcinoma for all patients with high exposure to tar or UV radiation, or both, was 2.4, compared with patients without high exposure. The reported relative rates were 1.8 for high-exposure groups of the prevalence cases and 3.0 for incidence cases. For the matched set of cases and controls, the estimated relative rate for all cases was 4.7. Prevalence and incidence cases in matched sets showed significantly increased risk. However, the conclusions that can be drawn from this study regarding the association of coal tar exposure and skin cancer are limited by the fact that the association of cancer risk and coal tar or UV radiation exposure was not examined separately for each agent.

Bhate et al. (1993) reported that incidence of cancer (total, skin, breast, cervix, genitourinary tract, bronchus, gastrointestinal tract, lynphoma, or other) was not significantly greater in 2,247 patients with psoriasis than in 4,494 age-matched controls without psoriasis. However, they noted that there was a statistically significant increase in skin cancer in the subgroup of 1,252 female psoriasis patients (24/1,228 psoriasis, 25/2,479 controls, P=0.032) and postulated that this might be associated with the fact that women were generally exposed to more treatments for psoriasis than men. The numbers of patients exposed to particular treatments (1,641 psoriasis patients had received coal tar treatment, but many patients had received more than one form of treatment) was too small to allow a statistical analysis of therapeutic risk factors. The authors calculated that although their study population was large, cancer incidence in psoriasis patients would have to be increased to 163% of control levels to be statistically significant at the P=0.05 level.

Fisher (1953) examined a group of 241 tar workers who had not been previously exposed to other carcinogens and found an increase in the number of “tar warts” (defined by the author as early squamous-celled epitheliomas) with duration of exposure. The percentage of workers with warts rose from 5% in

men with <5 years of exposure to 50% in men with 20–25 years exposure and 100% in men with more than 40 years exposure. The author stated that age on starting exposure also influenced susceptibility to tar warts, but did not present the data supporting this statement. No statistical analysis of the data was performed.

Other investigators who have examined the possibility of increased skin cancer incidence in psoriasis patients (Jones et al.1985; Menter and Cram 1983; Torinuki and Tagami 1988) have concluded that coal tar treatment did not produce an increase in cancer incidence, but all of these studies are limited in scope and it is not likely that they would be sufficiently sensitive to detect a small increase in risk. Jones et al. (1985) reported no increase in cancer incidence in 719 tar-treated psoriasis patients compared with the general population. Torinuki and Tagami (1988) reported no effect of tar on cancer rates in patients treated with coal tar and UV light, but only 5 of 43 patients had a follow-up duration of >6 years and this is likely to be insufficient to detect a possible cancer effect. Menter and Cram (1983) reported their opinion that there was no increase in incidence of skin cancer in patients treated with UV light and coal tar, but this was a study of the efficacy of the treatment regime and thus, no untreated controls were included for comparison and no statistical analysis was performed.

Several other studies are available that suggest that there is no association between exposure to coal tar creosote or other coal tar products and cancer in humans. Data from a population-based case-control interview study of 1,867 white men (622 cases and 1,245 controls) in Iowa and Minnesota conducted during 1980–83 were examined (Blair et al. 1993). Interviews were conducted with individuals or their next of kin to obtain information on agricultural exposures, residential history, medical history, family history of cancer, and a detailed occupational history. White men without hematopoietic or lymphatic malignancy were selected as controls. Risks of non-Hodgkin's lymphoma (NHL) were evaluated by intensity or probability of exposure to specific substances. No increased risk was noted with exposure to creosote or asphalt. No increased incidence of nonmelanoma skin cancer was observed in 426 patients 25 years after they had undergone 4 years of coal tar medicinal therapy in combination with UV light for the treatment of atopic dermatitis and neurodermatitis (Maugham et al. 1980). This study is limited in that follow up occurred in only 72% of the patients, and there was no discussion of recall bias or of the effects of mobility (i.e., relocation of the study participants) on the results. In a 25-year retrospective study of 280 psoriatic patients treated with crude coal tar in combination with UV radiation at the Mayo clinic, it was found that the incidence of skin cancer in these patients was not significantly increased above the expected incidence for the general population (Pittelkow et al. 1981). Chemical and biological analysis of coal tar-based therapeutic agents and industrial grade coal tar indicated that the therapeutic

agents and the industrial materials were similar (Wright et al. 1985). The authors suggest that the lack of carcinogenic effects after therapeutic exposure may be due to the presence of solvents and surfactants in the preparations, which may alter deposition and absorption by the skin. Reducing the contact with the therapeutic agents by regular washing may also be a factor (Wright et al. 1985). A case-control study was carried out on 24 PUVA-treated patients with squamous cell cancer of the skin and 96 PUVA-treated patients as matched controls (Lindelof and Sigurgeirsson 1993). Information on past therapies was obtained by questionnaire designed to determine if previous therapy was a risk factor for skin cancer in PUVA-treated patients. For subjects using previous tar therapy, there were 17 of 24 cases of skin cancer (70% exposed) with an estimated RR of 1.3 (95% CI=0.5–3.5); control subjects reported 62 of 96 cases (64% exposed). Prior treatment with tar was not considered to be a risk factor for skin cancer in PUVA-treated patients.

Another study was located that reported that there was no increase in the risk of skin, bladder, or lung cancer in wood treatment plant workers, where coal tar creosote and coal tar pitch were the chemicals used (TOMA 1980). Nevertheless, these findings are of limited value since the study population was limited to those currently working at the plant, was small, and comprised of 46.5% blacks, who experience a very low incidence of skin cancer compared to whites. In addition, the exposure and follow up periods did not allow a long enough latency period for tumor development and there was no verification provided that those studied were actually exposed to coal tar creosote or coal tar. No association was found between bladder cancer and occupational exposures to coal tar and pitch or creosote in a case-control study of 484 persons with confirmed bladder cancer (Siemiatycki et al. 1994).

A large body of evidence exists to show that coal tar is carcinogenic when applied to the skin of laboratory animals. Many of the early studies are limited in that they lack appropriate negative control data, the dose of creosote and the chemical composition of the fractions studied were not quantified, and no other tissues were generally examined (Deelman 1962; Hueper and Payne 1960; Watson and Mellanby 1930). The results from later studies that include appropriate control groups are consistent with the earlier studies that found that coal tar is carcinogenic following dermal application to rodent skin. The more detailed dermal carcinogenicity studies are reviewed below, and the relevant CELs are presented in Table 3-4.

The tumor-promoting potential of coal tar creosote was evaluated by applying various fractions (e.g., basic, phenolic, and neutral) to the skin of albino mice in conjunction with benzo[a]pyrene (Cabot et al. 1940). The various fractions of creosote oil were prepared by distillation and separation; 90% of the

creosote oil distilled between 160 and 300 EC. The basic fraction was removed with aqueous hydrochloric acid. The phenolic fraction was removed with aqueous sodium hydroxide. The remaining neutral fraction was then steam distilled. The composition of the various fractions was not specified. The tumorigenic effect of benzo[a]pyrene was retarded by the creosote oil, neutral distillate, neutral residue, and phenolic fractions. However, in three instances this effect was apparently related to skin damage associated with the treatments rather to a specific inhibitory effect. Only the phenolic fraction seemed to exhibit a primary antagonistic effect. Three other fractions (basic, neutral, and a low concentration of neutral distillate) exhibited apparent tumor promoting effects.

Ten groups of Swiss albino mice were exposed topically with 9% benzene solutions of two coal tar pitches of known PAH content (Wallcave et al. 1971). An additional group of 15 males and females was painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of coal tar pitch were painted in this area 2 times/week with 25 mL of solution (approximately 1.7 mg coal tar pitch per treatment). Animals were weighed once a week (no data shown) and all tumors arising in the skin were charted. Animals were sacrificed when moribund or when they developed highly advanced tumors on the skin. A complete autopsy was performed on all animals, and sections of the skin as well as all grossly pathological organs were studied histologically. Coal tar-painted animals developed squamous cell carcinomas and benign tumors in the form of squamous cell papillomas and keratoacanthomata; 91.4% of animals bore some kind of skin tumor. The potential effects of benzene on the dermal absorption of asphalt components were not evaluated in this study.

Weanling C3H/HeJ mice were exposed to 50 mg solutions containing 25 mg of roofing materials (traditional coal tar pitch, coal tar bitumen, standard asphalt from roofing operation, coal tar bitumen from roofing operation, or roofing dust) 2 times/week for 80 weeks, or until a skin lesion was diagnosed as a papilloma (Emmett et al. 1981). The material was dissolved or suspended in redistilled toluene in a 1:1 ratio (w/w) and applied to the intrascapular region of their backs, where hair had been previously removed. A vehicle control group received 50 mg of toluene 2 times/week, and a positive control group received 50 mg of 0.1% solution of benzo[a]pyrene in toluene 2 times/week. When the papilloma progressed and was diagnosed grossly as a carcinoma, the mouse was sacrificed and autopsied. Selected histopathologic examination of tumors was made to confirm the gross diagnosis. It was found that traditional coal tar pitch and dust from removal of an old roof were significantly more carcinogenic than coal-derived roofing bitumen, but all were strongly carcinogenic. The average times of the appearance of papillomas (and percentage of mice developing tumors) were at 18 (98%), 21.5 (98%), 20.5 (93%),

16.5 (86%), and 31.8 (79%) weeks for traditional coal tar pitch, coal tar bitumen, coal tar bitumen from roofing operation, roofing dust, and positive control, respectively. No tumors were caused by standard roofing asphalt or toluene. The percentage of benzo[a]pyrene in the materials was as follows: traditional coal tar pitch, 0.064%; coal tar bitumen, 0.072%; standard asphalt, <0.004%; coal tar bitumen from roofing operation, 0.064%; roofing dust 0.08%; toluene, 0%; and positive control, 0.1%.

Asphalt and coal tar pitch were the materials used in assessing skin carcinogenesis in nonpigmented Swiss CD-1 and pigmented C3H/HeJ male mice (Niemeier et al. 1988). Animals were divided into 48 experimental groups and treated as follows: (a) 32 groups treated for the primary factorial experiment (i.e., 2 strains x 4 materials x 2 generation temperatures [232 and 316 EC] x 2 light exposure conditions [presence or absence of simulated sunlight]); each animal dosed 2 times/week with 50 μm of the appropriate test material; (b) 4 groups for the solvent control (i.e., 2 strains x 2 light exposure conditions; each animal dosed 2 times/week with 50 μL of cyclohexane/acetone [1:1] vehicle); (c) 2 groups for cage control (i.e., 2 strains x 2 light exposure conditions, dosed 2 times/week with 50 mL solvent and not sham irradiated but always maintained in their individual cages); (d) 4 groups for the positive control (i.e., 2 strains x 2 light exposure conditions, dosed 2 times/week with 50 μL of the solution of 0.01% benzo[a]pyrene in cyclohexane:acetone [1:1]); (e) 4 groups for a combination treatment of asphalt and coal tar pitch fume condensate (i.e., 2 strains x 2 light exposure conditions; each animal dosed 2 times/week with the high temperature condensate from Type III asphalt and Type I coal tar pitch, on alternate weeks); and (f) 2 groups (i.e., 2 strains, for light exposure 2 times/week with no skin painting treatment). Mice were observed daily for systemic toxicity and gross appearance of tumors. Mice found dead were necropsied and those that were moribund were sacrificed and necropsied. Surviving mice at the end of 78 weeks were also necropsied. Tissues were examined and skin lesions excised and prepared for microscopic examination. The theoretical air concentrations of PAH from coal tar pitch at 232 and 316 EC were 5.0×10^6 and 55.1×10^6 mg/m^3, respectively. The theoretical air concentrations of benzo[a]pyrene from coal tar pitch at 232 and 316 EC were 55.6×10^3 and 366.7×10^3 mg/m^3, respectively. The theoretical air concentrations of PAH from asphalt at 232 and 316 EC were 3,300 and 15,000 mg/m^3, respectively. The theoretical air concentrations of benzo[a]pyrene from asphalt at 232 and 316 EC were 21 and 122 mg/m^3, respectively.

Administration of condensed fumes from both types of coal tar pitches and both types of asphalt resulted in benign tumors (papillomas, kerato-acanthomas, fibromas, and unclassified benign epitheliomas) and malignant tumors such as squamous cell carcinoma and fibrosarcomas (seen more often in C3H/HeJ mice) (Niemeier et al. 1988). CD-1 mice had a much lower incidence of malignant tumors than C3H/HeJ

mice (about 5 versus 60%). The average latent period ranged from 39.5 to 56.1 weeks among C3H/HeJ groups and from 47.4 to 76.5 weeks among the CD-1 groups. The tumorigenic response of C3H/HeJ in the coal tar pitch Type III group with concomitant exposure to light increased with high temperature. Both strains when exposed to condensed coal tar pitch fumes or benzo[a]pyrene in the presence of simulated sunlight had inhibited tumorigenic responses; C3H/HeJ strain treated with 0.01% benzo[a]pyrene and coal tar pitch showed increased tumorigenic response. In the CD-1 strain, only the solar exposed pitch fume groups showed significantly increased tumorigenic response when compared to the positive control. The tumorigenic response of C3H/HeJ to the condensed asphalt fumes increased with high temperature, but no significant change in tumorigenic response was observed for CD-1 mice exposed to fumes at the higher temperature. Simulated sunlight significantly inhibited tumorigenic response in C3H/HeJ mice to both types of asphalt fumes collected at the lower temperature and no overall significant effects were noted in the CD-1 strain. Both strains when exposed to benzo[a]pyrene in the presence of simulated sunlight had inhibited tumorigenic responses; C3H/HeJ strain treated with 0.01% benzo[a]pyrene and those exposed to the high temperature asphalt fumes showed increased tumorigenic response. In the CD-1 strain, only the nonsolar exposed asphalt fume exposed groups showed significantly increased tumorigenic response when compared to the positive control. In comparing the combination group to their respective controls, the C3H/HeJ strain showed no differences in latency, but the combination group showed a significantly increased response by the onset rate analysis method as compared to the asphalt group (Type III-316 EC) without light. The responses in CD-1 mice were similar, in that the nonsolar exposed combination group had a significantly increased tumor response, as assessed by the onset rate method, compared with the asphalt group. They also died earlier (no data shown) and developed tumors at a significantly earlier time than the asphalt group. When the combination groups were compared to the responses of the pitch groups, onset rate analysis showed that the sham irradiated pitch group (Type I-316 EC) had a significantly greater tumor response than the combination group. No other differences were noted. Both strains when exposed to benzo[a]pyrene or combination of pitch and asphalt in the presence of simulated sunlight showed inhibited tumorigenic responses; C3H/HeJ strain treated with 0.01% benzo[a]pyrene and the combination groups and those exposed to the high temperature asphalt fumes showed increased tumorigenic response.

In conclusion, both coal tar pitch and asphalt produced benign and malignant skin tumors in mice (Niemeier et al. 1988), but C3H/HeJ mice were more susceptible to the formation of malignant tumors than CD-1 mice. Concomitant exposure to sunlight reduced tumor production by coal tar pitch, or asphalt, or the combination of coal tar pitch and asphalt compared with nonsolar exposed animals. The

combination of exposure to both asphalt and coal tar pitch increased tumor formation compared with asphalt alone, but was reduced compared with coal tar pitch alone.

The potential of basic fractions of coal tar creosote to accelerate tumor induction by known carcinogens was evaluated by Sall and Shear (1940). A 1% solution of the basic fraction of creosote oil in benzene was dermally applied to female strain A mice alone or in conjunction with 0.05 or 0.02% benzo[a]pyrene. The basic fraction alone did not induce skin tumors, but when applied in conjunction with either concentration of benzo[a]pyrene, skin tumors appeared more rapidly than when benzo[a]pyrene alone was applied. Maximum tumor induction was seen between 28 and 42 weeks; 19 of 20 mice developed tumors.

This is in contrast to the results of a tumor initiation study by Springer et al. (1989) in which Charles River CD-1 female mice (30 per group) were treated with crude coal tar and a variety of coal tar fractions in an initiation assay. The backs of the mice were shaved and the skin treated with 50 μL of an acetone solution of the various test materials. Two weeks after initiation, the animals were promoted with twice-weekly applications of 5 μg of 12-O-tetradecanoylphorbol-13-acetate (TPA) (also known as phorbol myristate acetate or PMA) in 50 μL of acetone for 24 weeks. Tumors were identified visually and were not characterized further by histopathology. The time of tumor appearance and the number of tumors were recorded as measures of response. Test materials included: 5 mg (approximately 203 mg/kg body weight) crude coal tar (boiling point: 300–850 EF); coal tar temperature fractions (boiling points: 300–700, 700–750, 750–800, 800–850, or >850 EF); chemical fractions of the 750–800 EF temperature fraction (aliphatics and olefins, neutral PAH, nitrogen-containing polycyclic aromatic compounds, hydroxy-PAH); 25 μg benzo[a]pyrene; 5 mg crude coal tar +25 μg benzo[a]pyrene; coal tar temperature fractions +25 μg benzo[a]pyrene; chemical fractions +25 μg benzo[a]pyrene. The three lower temperature coal tar fractions did not contain benzo[a]pyrene, while the other two contributed 8.5 μg benzo[a]pyrene towards the total dose. Mice initiated with benzo[a]pyrene alone showed the greatest tumor response. Administration of the lowest boiling point coal tar fraction did not produce significantly more tumors than controls. Exposure to the crude coal tar or the 700–750 and 750–800 EF fractions produced a small, but significant increase in tumors compared with controls. The two highest temperature fractions showed substantial initiating activity. The aliphatic fraction did not have tumor initiating activity, the other chemical fractions had some activity, with that of the PAH fraction being the highest and similar to that of crude coal tar. Co-administration of benzo[a]pyrene and coal tar or coal tar fractions resulted in a decrease in the initiation of tumors compared with benzo[a]pyrene alone. The authors suggest that the reduction in benzo[a]pyrene tumor initiation by coal tar fractions may be caused

by altered rates or routes of metabolism of benzo[a]pyrene due to the presence of various components of the coal tar.

The ability of coal tar creosote to induce lung tumors after dermal application to mice was studied when it was observed that mice housed in coal tar creosote-treated wooden cages had a high incidence of lung tumors (Roe et al. 1958). Dermally applied coal tar creosote (0.25 mL undiluted twice weekly for 8 months) induced 5.8 lung adenomas/mouse in mice that were reared in stainless steel cages. Creosote treatment following the same regimen in mice reared in creosote-treated cages induced 10.8 lung adenomas per mouse. Untreated controls reared in untreated cages exhibited 0.5 lung adenomas per mouse. A high incidence of skin tumors was also observed in the creosote-treated mice reared in either type of cage. In a second experiment, topical application of "one drop" of coal tar creosote twice a week for only 4 weeks induced lung adenomas, but not skin tumors in mice reared in stainless steel cages. This study demonstrated that coal tar creosote induces tumors in the lungs and skin of mice when dermally applied. Rearing animals in coal tar creosote-treated wooden cages exacerbated the tumorigenic effect of dermally applied coal tar creosote. Based on this study, lung tumors may be a more sensitive end point of creosote tumorigenic activity than skin tumors after skin contact and inhalation exposure. However, this study did not take into account possible oral exposure due to normal preening behavior.

Seven groups of 30 female Sutter mice each were treated with 75 μL dimethylbenzanthracene (DMBA) and 25 μL coal tar creosote (undiluted creosote oil), alone and in combinations of the two to evaluate the carcinogenic, initiating, and promoting activity of coal tar creosote on mouse skin (Boutwell and Bosch 1958). Coal tar creosote alone, DMBA and coal tar creosote, and coal tar creosote with 25 μL croton oil (0.5% in benzene) all induced the development of papillomas and carcinomas. Tumors first appeared at 10–20 weeks of application. DMBA pretreatment shortened the latent period and increased the tumor yield of coal tar creosote treatment, but since a nearly maximal tumor induction response (i.e., percentage of mice with papillomas just below 100) was seen with coal tar creosote alone, tumor-promoting activity of coal tar creosote could not be definitely proven. The initiating activity of coal tar creosote was demonstrated by its ability to induce tumors when applied prior to croton oil treatment (croton oil alone was without effect). Coal tar creosote alone or in combination with DMBA or croton oil induced papilloma formation more slowly, and carcinomas appeared by 14 weeks and accumulated more rapidly than in the DMBA plus croton oil group. Thus, this study demonstrated the carcinogenic and tumor-initiating activity of coal tar creosote on Sutter mouse skin.

The complete carcinogenic and tumor-promoting activity of undiluted coal tar creosote, a 10% solution of creosote oil, and 2% solution of the basic fraction of coal tar creosote was studied when dermally applied to mice (Lijinsky et al. 1957). Undiluted creosote alone induced 23 skin tumors (16 malignant) in 13 of 26 treated mice with a latent period of 50 weeks. The authors concluded that creosote alone has a carcinogenic activity comparable to a 0.01% solution of DMBA. When applied as a promoter following a single application of DMBA, 32 skin tumors (26 malignant) were observed in 17 of 30 mice with a latent period of 39 weeks. The basic fraction did not act as a tumor promoter when administered after a single application of DMBA. Thus, coal tar creosote appeared to enhance the carcinogenic activity of DMBA, but the promoting effect was not strong, when the results were compared to DMBA positive controls.

Three-month-old Charles River CD-1 male mice (30 per group) were treated with a variety of coal derived complex mixtures in an initiation/promotion assay (Mahlum 1983). The backs of the mice were shaved and the skin was treated with 50 μL of the various test materials. Groups of animals initiated with DMBA or benzo[a]pyrene served as positive controls, negative controls received 50 μL acetone. Two weeks after initiation, the animals were promoted with twice-weekly applications of 50 μL of phorbol myristate acetate (PMA) (also known as 12-O-tetradecanoylphorbol-13-acetate or TPA) for 6 months. Tumors were identified visually and were not characterized further by histopathology. The time of tumor appearance, the number of mice with tumors, and the number of tumors per mouse were recorded as measures of response. The following coal distillates were used as initiators: heavy distillate (HD) boiling point range 550–850 EF; 300–700 EF boiling point range fraction, and an 800–850 EF boiling point range fraction. In addition the following chemical fractions were prepared from HD: basic (BF), basic tar (BTF), neutral tar (NTF), and polynuclear aromatic (PNA) fractions. The promoting activity of middle distillate (MD), boiling point range 380–550 EF, was tested by initiating with 50 μg DMBA, followed 2 weeks later, by twice weekly applications of a 50% solution (w/v) of MD in acetone. Animals that received no DMBA, but were treated twice weekly with MD, were used as controls. DMBA was a more potent initiator than benzo[a]pyrene. Initiation with HD resulted in about the same incidence of tumors as benzo[a]pyrene. NTF was almost as active an initiator as HD, while BTF was only slightly less active. BF and PNA were considerably less active initiators. The 800–850 EF fraction showed a low degree of initiating activity, while the response of the 300–700 EF group was the same as the acetone controls. MD showed a low level of promotion in animals initiated with DMBA. No uninitiated mice showed tumors after 12 months, 17% of initiated mice had tumors at 6 months, and incidence increased to 52% by 12 months.

The carcinogenic activity of two high-temperature-derived coal tar creosote oils ("light" and "blended") was studied by Poel and Kammer (1957). The principal components of light oil are benzene, toluene, xylene, and solvent naphtha. Blended oil is a mixture of creosote oil, anthracene oil and the oil drained from the naphthalene recovery operation. Its principal components are methylated naphthalenes, acenaphthene, fluorene, phenanthrene, anthracene, and carbazole. The blended or light oils were applied by drops to the skin of mice at concentrations of 20 or 80% (blended oil) or 50% (light oil) 3 times/week for life. Both oils induced skin tumors in every exposure group by 26 weeks of application. Seven of the eight mice exposed to each concentration of blended oil had tumors that progressed to malignancy. One tumor regressed before the death of a mouse in the 80% group and one mouse in the 20% group had a papilloma that had not become malignant by the end of the experimental period. There was no evidence of tumor regression in the tests with light oil. Several mice exhibited metastases to the lungs or regional lymph nodes. The fractions tested did not contain benzo[a]pyrene (limit of detection=0.03% benzo[a]pyrene), so the authors concluded that the carcinogenic activity of the coal tar creosote oil used in the experiment was not due to benzo[a]pyrene.

Crude coal tar (10, 25, and 100%) in petrolatum was applied to the ear of male Australian albino rabbits (3 per group) 3 times/week for 15 weeks (Kligman and Kligman 1994). Crude coal tar was both comedogenic and carcinogenic at all doses tested (10, 25, or 100%). Tumors developed as early as 1–2 weeks after 3 weeks of treatment with 10% coal tar. The tumors were classified as papillomas, squamous cell carcinomas, keratoacanthomas, and cutaneous horns, and became extremely numerous with longer treatment.

Standard Reference Material (SRM) 1597 obtained from the National Institute of Standards and Technology, was tested in an assay of tumor initiation in female SENCAR mice (Marston et al. 2001). SRM 1597 is a mixture derived from a medium crude coke oven coal tar dissolved in toluene. Certified values have been published for selected PAH components of this mixture including B[a]P. Dibenzo[a,l]pyrene (DB[a,l]P) is not a component of SRM 1597. SRM 1597 (1 mg per 125 μL, which contains 10.4 μg B[a]P) was painted onto the shaved skin of 6–7-week-old mice over a period of 2 weeks (the number of applications was not reported) and in some cases, treatment with SRM 1597 was followed 5 minutes later with B[a]P or DB[a,l]P). The treatment groups were as follows: 10 mice with 200 μL toluene as a control; 30 mice with 1 mg SRM 1597; 35 mice with 200 nm (50.4 μg) B[a]P in 100 μL toluene; 35 mice with 1 mg SRM 1597 plus 200 nm (50.4 μg) B[a]P in 100 μL toluene; 35 mice with 2 nmol (0.6 μg) DB[a,l]P; and 35 mice with 1 mg SRM 1597 plus 2 nmol DB[a,l]P. Two weeks after initiation, twice-weekly promotion was begun with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) at

1 μg/200μL acetone per mouse for 25 weeks. Mice were examined weekly for papillomas and at 25 weeks, tumors were confirmed histologically at necropsy. In the test of SRM 1597 and B[a]P, no papillomas were found in the control group, SRM 1597 initiated 5.3 tumors per tumor-bearing animal, B[a]P initiated 8.9 tumors per tumor-bearing animal and B[a]P plus SRM 1597 produced 8.8 tumors per tumor-bearing animal. Results of statistical analysis of mice treated with SRM 1597 compared with controls were not reported. Compared with B[a]P, cotreatment with SRM 1597 did not significantly change tumor incidence, either over time, or specifically at 25 weeks. In contrast, in the test of SRM 1597 and DB[a,l]P, 1 papilloma was found on one mouse in the control group, SRM 1597 initiated 4.1 tumors per tumor-bearing animal, DB[a,l]P initiated 8.1 tumors per tumor-bearing animal, and DB[a,l]P plus SRM 1597 produced 5.2 tumors per tumor-bearing animal. There were significant differences in the number of tumors per tumor-bearing animal for all three treated groups and, compared with DB[a,l]P alone, cotreatment with SRM 1597 significantly reduced the number of tumors per tumor-bearing animal. This reduction may be due to decreased metabolism of DB[a,l]P with consequent reduction in DB[a,l]P metabolite-DNA adduct formation in the presence of SRM 1597 (see Section 3.3).

In conclusion, the results of these studies indicate that coal tar creosote and several of its fractions can be carcinogenic when applied to the skin of mice or rabbits. Dermally applied coal tar creosote can also act as a tumor-initiating agent. Thus, it is likely that individuals whose skin comes into contact chronically with coal tar creosote would be at higher risk for skin cancer, particularly when exposure to other carcinogenic substances also occurs, as is a possible scenario in areas surrounding hazardous waste sites.

3.3 Genotoxicity

Creosote Bush. No studies were located regarding genotoxic effects of the creosote bush in humans or animals.

Wood Creosote. Zeiger et al. (1992) tested beechwood creosote in the Ames assay using *Salmonella typhimurium* strains TA 97, TA98, TA100, TA102, TA104, TA1535, TA1537, and TA 1538, with and without metabolic activation, and found it to be nonmutagenic.

Coal Tar Products. Studies of workers exposed to coal tar, bitumen fumes, coal tar pitch, or coal tar pitch volatiles have shown an association between exposure to these mixtures and significant increases in genotoxic effects; however, it must be noted that a recurrent limitation of these studies is the lack of precise exposure data. Significant increases in the frequency of chromosomal abnormalities and sister

chromatid exchanges (SCE) were observed in the peripheral blood lymphocytes (PBL) of 49 workers exposed to coal tar for 6–10 years compared with 50 age-matched, non-exposed individuals (Yadav and Seth 1998). There were similar findings in a study of 30 steelworkers occupationally exposed to coal tar pitch volatiles (Bender et al. 1988). Burgaz et al. (1998) reported an elevated incidence of SCE and micronuclei (MN) in PBL of 28 workers exposed to bitumen fumes during paving operations. A study of 24 workers exposed to coal tar pitch for 7–32 years showed a significant increase in SCE and serum P21 (the protein product of the *ras* oncogene) compared to 10 non-exposed individuals (Wu et al. 1998). Urine samples taken from 19 individuals occupationally exposed to coke oven emissions in a steel mill and 31 controls (De Meo et al. 1987) and urine samples from 30 coke oven workers and 26 controls (Mielzynska and Snit 1992) showed an association between exposure and increased mutagenic activity in the Ames *Salmonella typhimurium* test. However, an examination of the mutagenic activity of urine from only three workers exposed to coal tar creosote vapors at a wood preserving factory (Bos and Jongeneelen 1988; Bos et al. 1984a, 1984c) reported no mutagenic activity in 10-day urine samples. The absence of mutagens in these urine samples was ascribed by the study authors to a relatively low level of exposure, improper timing for urine sample collection, and the insensitivity of the assay.

Some studies have also documented increases in the number of DNA adducts in the blood of patients undergoing dermal coal tar therapy. For instance, Santella et al. (1995) reported increases in benzo[a]pyrene (B[a]P) DNA adducts in blood of psoriasis patients treated with 20–100 g tar per day. However, Pavanello and Levis (1994) found that there were no differences between the number of PAH-DNA adducts formed *in vivo*, determined by the ^{32}P-postlabeling method, in the PBL of psoriatic patients treated with 50% coal tar paste for up to 8 days and adduct levels in healthy individuals not treated with coal tar. Moreover, the levels of PAH-DNA adducts detected in patients before, during, and 16 days after coal tar therapy were statistically unchanged. In a previous study, Pavanello and Levis (1992) had examined the effect of coal tar treatment on DNA adduct formation *in vitro* in human lymphocytes taken from four male psoriatic patients 25–70 years old treated for 4–10 days with a paste containing 50% coal tar and nine healthy individuals who did not take any medication. No significant difference was detected in the total amount of B[a]P-DNA adducts in blood lymphocytes from patients or controls or between patients before and after treatment. In contrast, patients treated with a 50% coal tar paste, a 2% coal tar ointment, or a combination of pure coal tar and 2% ointment for 3–17 days had *in vivo* B[a]P-DNA adduct levels, determined by ELISA technique, that were higher during therapy than 2–5 months after therapy termination (Pavanello and Levis 1994). A study by Sarto et al. (1989) showed an association between the frequency of chromosomal aberrations and SCE in blood lymphocytes and the level of

exposure to coal tar of patients undergoing therapy for psoriasis with topical applications of pure coal tar or 4% coal tar-containing ointment.

Increases in the number of DNA adducts in skin biopsy samples have been observed in patients undergoing coal tar therapy with ointments containing 3–5% coal tar for at least 7 days (Zhang et al. 1990) and in patients treated for an average of 21 days with an ointment containing as much as 10% coal tar (Godschalk et al. 2001). Schoket et al. (1990) observed elevated levels of adducts in skin biopsy samples taken from psoriasis patients receiving coal tar and juniper tar (cade oil) therapy. Sarto et al. (1989) examined the mutagenicity of urine samples taken from patients treated for psoriasis with topical applications of pure coal tar or 4% coal tar-containing ointment. The results suggest that urinary mutagen levels were related to the levels of exposure to coal tar. Similar findings of mutagenicity of urine collected from psoriatic patients treated with coal tar were reported in other studies (Clonfero et al. 1990; Gabbani et al. 1999; Granella and Clonfero 1992).

There is some indication that genetic polymorphisms may play a role in the manifestation of genotoxic effects in individuals exposed to coal tar products. A study of 15 patients treated with a 2% coal tar ointment for at least 3 days showed that urinary mutagenicity, determined by *S. typhimurium* strains TA98 and YG1024 in the presence of microsomal enzyme, was associated with glutathione S-transferase M1 (GSTM1) genotype (Gabbani et al. 1999). The mean value of urinary mutagenicity of subjects with genotype GSTM1-null was double that of GSTM1-positive subjects and the difference was significant. In a study of 10 patients being treated for atopic eczema with an ointment containing up to 10% coal tar for an average of 21 days, Godschalk et al. (2001) showed that aromatic DNA adduct levels in skin biopsies of coal tar-treated patients were 2-fold higher in GSTM1(-/-) individuals compared to GSTM1(+) individuals, but the difference was not statistically significant. Significantly (10-fold) higher levels of p53 were found in the basal layer of GSTM1(-/-) individuals compared with GSTM1(+) patients. Analyses of skin biopsies of atopic dermatitis patients treated with 3–10% coal tar for 1 week revealed that the presence of a mutant myeloperoxidase genotype was associated with a reduction in the formation of B[a]P-adducts (Rojas et al. 2001). Adduct levels in patients without the mutant gene were 14.2 and 18.4 adducts per 10^8 nucleotides, while in patients with the mutant gene adduct, levels were 2.2 and 5.0 adducts per 10^8 nucleotides.

Several *in vivo* studies have shown increased DNA adduct formation in animals following oral administration of coal tar or coal tar waste. Dose-related increases in DNA adduct levels were observed in $B6C3F_1$ mice fed up to 1,750 mg coal tar/kg/day for 28 days (Culp and Beland 1994; Culp et al. 1996a). DNA adducts were detected in liver, lung, and forestomach. Weyand et al. (1991) reported dose-

related increases in DNA adduct formation in the lung of $B6C3F_1$ mice fed up to 1% coal tar waste for 15 days but these increases were not correlated with the total PAH content of the coal tar. $B6C3F_1$ mice fed 0.05, 0.25, or 0.50% coal tar waste for 94 or 185 days showed dose-related increases in DNA adduct formation in both lung and forestomach tissue (Weyand et al. 1994). Numerous other studies have also documented the formation of DNA adducts in animals fed coal tar waste from manufactured gas plants (Bordelon et al. 2000; Goldstein et al. 1998; Koganti et al. 2000). Some studies suggest that lungs are more sensitive than forestomach tissue to DNA adduct formation in mice (Weyand and Wu 1995; Weyand et al. 1994). The results of additional *in vivo* studies are summarized in Table 3-6.

The role of PAHs other than B[a]P in the mutagenicity of coal tar is still not clearly understood. Oral administration of 636 mg/kg/day MGP residue to mice for 14 days produced a range of lung and forestomach DNA adducts with three major components. Two of the adducts were identified as produced by B[a]P (10% of the lung adducts and 47% of forestomach adducts) or benzo[b]fluoranthene (13% of the lung adducts). The identity of the third adduct (41% of lung adducts, 32% of forestomach adducts) was unknown (Weyand and Wu 1995). Culp et al. (2000) and Culp and Beland (1994) reported that DNA adduct formation was higher in mice fed coal tar than in those fed B[a]P and Koganti et al. (2000) proposed that *7H*-benzo[c]fluorene, not B[a]P, was responsible for the formation of DNA adducts in lungs of mice fed coal tar. Genotoxic effects have been observed in several tissues after dermal application of coal tar products. For instance, DNA adducts were detected in mouse skin after dermal application of coal tar fractions (Marston et al. 2001; Springer et al. 1989) and in skin, lungs, and lymphocytes of rats after dermal application of bitumen fume condensates (Genevois et al. 1996). Dermal application of 250 mg/kg creosote in olive oil to rats for 24 hours resulted in the excretion of mutagens in urine (Bos et al. 1984c).

Various *in vitro* studies using the Ames *S. typhimurium* test (Bos et al. 1984a, 1984c) or the mouse lymphoma assay (Mitchell and Tajiri 1978) have demonstrated the genotoxicity of several coal tar products, including samples from creosote-treated wood. Using a modified Ames assay with *S. typhimurium*, Machado et al. (1993) found that coal tar pitch was more strongly mutagenic than asphalt fume condensates. The temperature at which the fumes were collected was positively correlated with mutagenicity. Bos et al. (1987) showed that creosote contains mutagens that are volatile at 37 EC. Simmon and Shepherd (1978) demonstrated that the genetic mode of action of creosote is induction of a frame-shift mutation. The results of additional *in vitro* studies are summarized in Table 3-7.

Table 3-6. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vivo*

Species (test system)	End point	Results	Reference
	CREOSOTE		
Mammalian systems:			
Rat/liver	DNA adducts	+	Chadwick et al. 1995
Mouse/lung, forestomach, spleen	DNA adducts	+	Weyand et al. 1991
	COAL TAR		
Non-mammalian systems: Perch/liver	DNA adducts	+	Ericson et al. 1998, 1999
Mammalian systems:			
Human/lymphocytes	Chromosomal aberrations/sister chromatid exchange	+	Sarto et al. 1989
Human/lymphocytes	Sister chromatid exchange	+	Wu et al. 1998
Human/lymphocytes	Chromosomal aberrations/sister chromatid exchange	+	Yadav and Seth 1998
Human/skin	DNA adducts	–	Schoket et al. 1990
Human/skin	DNA adducts	+	Zhang et al. 1990
Human/skin	DNA adducts	+	Rojas et al. 2001
Human/skin, blood cells	DNA adducts	+	Godschalk et al. 1998
Human/lymphocytes	DNA adducts	–	Pavanello and Levis 1992
Human/lymphocytes	DNA adducts	+	Pavanello and Levis 1994
Human/blood	DNA adducts	+	Santella et al. 1995
Rat/liver, lung, forestomach	DNA adducts	+	Culp and Beland 1994
Rat/lymphocytes, lung, skin	DNA adducts	+	Genevois et al. 1996
Rat/lung, liver, forestomach	DNA adducts	+	Goldstein et al. 1998
Rat/lung, liver	DNA adducts	+	Bordelon et al. 2000
Mouse/forestomach, small intestine	DNA adducts	+	Goldstein et al. 1998

Table 3-6. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vivo* (*continued*)

Species (test system)	End point	Results	Reference
	COAL TAR (cont'd)		
Mammalian systems (*cont'd*): Mouse/forestomach, small intestine	DNA adducts	+	Culp et al. 1996a
Mouse/lung, forestomach	DNA adducts	+	Weyand and Wu 1995
Mouse/lung, forestomach	DNA adducts	+	Weyand et al. 1994
Mouse/skin, lung, liver, kidney heart	DNA adducts	+	Randerath et al. 1996
Mouse/forestomach, lung, liver, intestine	DNA adducts	+	Culp et al. 2000
Mouse/lung	DNA adducts	+	Koganti et al. 2000
Mouse/lung	DNA adducts	+	Koganti et al. 2001
Mouse/skin	DNA adducts	+	Hughes et al. 1993
Mouse/skin	DNA adducts	+	Phillips and Alldrick 1994
Mouse/skin	DNA synthesis	+	Walter et al. 1978
Mouse/skin	Gene mutation	+	Vogel et al. 2001
	COAL TAR PITCH AND BITUMEN VOLATILES		
Mammalian systems:			
Human blood cells	Chromosomal aberrations	+	Bender et al. 1988
Human/white blood cells	DNA adducts	+	Lewtas et al. 1997
Human/lymphocytes	sister chromatid exchange (SCE)/high frequency SCE	(+/–)	Burgaz et al. 1998
Human/lymphocytes	Micronuclei	+	Burgaz et al. 1998
Rat/lung	DNA adducts	+	Lewtas et al. 1997

+ = positive results; – = negative results; (+/–) = mixed results; DNA = deoxyribonucleic acid; SCE = sister chromatid exchange

Table 3-7. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vitro*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Calf thymus DNA	DNA adducts	+	No data	Akkineni et al. 2001
Calf thymus DNA	DNA adducts	+	No data	Koganti et al. 2000
Calf thymus DNA	DNA adducts	+	No data	Reddy et al. 1997
Salmon testes DNA	DNA adducts	+	–	Genevois et al. 1998
Prokaryotic organisms:				
Salmonella typhimurium (histidine auxotrophs)	Gene mutation	+	–	Simmon and Shepherd 1978[a]
S. typhimurium	Gene mutation	+	+	Agurell and Stensman 1992
S. typhimurium	Gene mutation	+	No data	Reeves et al. 2001
S. typhimurium	Gene mutation	+	–	Baranski et al. 1992
S. typhimurium	Gene mutation	+	–	Bos et al. 1983, 1984b, 1984c, 1985, 1987
S. typhimurium	Gene mutation	+	–	Donnelly et al. 1993, 1996
S. typhimurium	Gene mutation	+	+	Kesik and Janik-Spiechowicz 1997
S. typhimurium	Gene mutation	+	–	Mayura et al. 1999
S. typhimurium	Gene mutation			Machado et al. 1993
S. typhimurium (taped-plate assay; vapor exposure)	Gene mutation	+	–	Bos et al. 1985, 1987
Escherichia coli WP2 (TK=/–), (tryptophan auxotroph)	Gene mutation	–	–	Simmon and Shepherd 1978[a]
Mammalian cells:				
Human mammary epithelial cells	DNA adducts	No data	+	Leadon et al. 1995
Mouse lymphoma cells	Gene mutation	+	–	Mitchell and Tajiri 1978
V79	Gene mutation	–	–	U.S. Department of Energy 1994
V79	Sister chromatid exchange	+	+	U.S. Department of Energy 1994

Table 3-7. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vitro (continued)*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Mammalian cells *(cont'd)*:				
V79	Micronucleus	+	+	U.S. Department of Energy 1994
Mammalian body fluids:				
S. typhimurium (human urine sample; occupational exposure)	Gene mutation	–	No data	Bos et al. 1984a
S. typhimurium (human urine sample; coal tar treatment)	Gene mutation	+	No data	Clonfero et al. 1990
S. typhimurium (human urine sample; occupational exposure)	Gene mutation	+	No data	De Meo et al. 1987
S. typhimurium (human urine sample; occupational exposure)	Gene mutation	+	No data	Gabbani et al. 1999
S. typhimurium (human urine sample; coal tar treatment)	Gene mutation	+	No data	Granella and Clonfero 1992
S. typhimurium (human urine sample; occupational exposure)	Gene mutation	+	No data	Mielzynska and Snit 1992
S. typhimurium (human urine sample; coal tar treatment)	Gene mutation	+	No data	Sarto et al. 1989
S. typhimurium (rat urine sample)	Gene mutation	+	No data	Bos et al. 1984a
S. typhimurium (rat urine sample)	Gene mutation	+	No data	Chadwick et al. 1995

[a]*S. typhimurium* strains TA1537, TA98, and TA100 showed increases in frameshift mutation; strain TA1535 and *E. coli* straub WP2 showed no increase in base-pair substitutions.

+ = positive results; – = negative results; DNA=deoxyribonucleic acid

3.4 TOXICOKINETICS

Specific information regarding the toxicokinetics of creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles is limited. Several compounds have been detected in coal tar creosote, yet there are no definitive data on which of these compounds people are exposed to in wood-treatment plants or at hazardous waste sites. Analyses have revealed that PAHs are the major components of the coal tar creosote mixture (TOMA 1981). Hence, pharmacokinetic studies on PAHs can be used as surrogates for coal tar creosote. However, this information is only speculative given the possible toxicokinetic interactions that occur among the PAHs and other components in the coal tar creosote mixture, and will be used only when data on coal tar creosote are not available. For more information on the toxicokinetics of PAHs, please refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995). Phenols and cresols are also components of coal tar products. For more information on the toxicokinetics of these chemicals, please refer to the ATSDR *Toxicological Profile for Phenol* (Agency for Toxic Substances and Disease Registry 1998) and the ATSDR *Toxicological Profile for Cresols* (Agency for Toxic Substances and Disease Registry 1992).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located in humans or animals regarding the direct analysis of the extent or rate of absorption of wood creosote following inhalation exposure.

Coal Tar Products. No studies were located in humans or animals regarding the direct analysis of the extent or rate of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatile absorption following inhalation exposure. However, there is evidence to suggest that inhalation absorption of coal tar products may occur. Employees of a coal tar creosote wood-impregnating plant, employees in a coal tar plant, and coke oven workers excreted 1-hydroxypyrene, a metabolite of pyrene, a creosote component, in their urine (Bos and Jongeneelen 1988; Jongeneelen et al. 1985, 1988). Similarly, workers asphalting roads with coal tar excreted 1-hydroxypyrene in their urine (Bos and Jongeneelen 1988; Jongeneelen et al. 1988). Increased levels of 1-hydroxypyrene were observed over the course of the workday for all groups of workers, indicating an accumulation of pyrene during the exposure period (Bos and Jongeneelen 1988). The presence of this metabolite in the urine suggested that coal tar creosote components were absorbed and metabolized following inhalation exposure. However, it is possible that some dermal exposure may have occurred as well.

Measurements were carried out in a creosote impregnation plant where six men volunteered to participate in the study (Elovaara et al. 1995). Personal breathing zone air samples were taken on 5 consecutive days followed by a work-free period of 64 hours. All workers wore leather protective gloves and cotton overalls. Two employees worked overtime (until 6:30 a.m.) on Monday, which was an exception to the regular 8-hour schedule. Particulate PAHs were collected during the whole shift and analyzed within 7 weeks. Workers were asked to collect all urine passed within the 24 hour period into divided samples for the designated periods. Results showed that the geometric mean (range) air concentrations were 4.77 (1.2–13.7) mg/m^3 (n=30) for total particulate PAHs (including pyrene) and 1,254 (370–4,200) mg/m^3 (n=30) for naphthalene. The PAH profile was similar in all samples. 1-Hydroxypyrene was found in the urine samples.

Exposure of assemblers (all smokers) handling creosote-impregnated wood railroad ties and one worker (smoker) chiselling coal tar pitch insulation to coal tar products was assessed by analyzing the breathing zone air for airborne PAHs, and assaying urinary excretion of 1-hydroxypyrene (Heikkilä et al. 1995). The concentration of pyrene and 11 other PAHs in particulate matter had been measured both in the work room and in the breathing zone of the assemblers a year earlier during 2 working days. In the present setting the ties were impregnated with the same type of creosote as a year earlier, which contained 0.2 weight-percent (w%) of pyrene. Urine samples were collected during 3 working days (Monday, Wednesday, and Friday) and over the following weekend. Urine samples from one chiseller were collected in the morning before work, during lunch time, at the end of the shift, in the evening and on the next morning. The total concentrations of PAH and of 4–6 aromatic ring-containing PAHs (when chiselling) were 440 µg/m^3 (50-fold higher than assemblers) and 290 µg/m^3 (200-fold higher than assemblers), respectively. The estimated mean of inhaled pyrene for assemblers measured on Monday, Wednesday, and Friday was found to be 0.009, 0.007, and 0.024 mmol/shift, respectively. The estimated inhaled pyrene measured on the chiseller was 1.2 mmol/shift. Excretion of urinary 1-hydroxypyrene was detected for all participants.

Four rotation crews of about 29 workers and one day crew of 22 workers worked in a 5-day shift, 8 hours/day in the potrooms (Ny et al. 1993). All workers wore disposable respirators that were renewed 4–5 times/day, thick cotton working clothes with long sleeves, safety shoes, safety glasses, gloves, and helmets. Other groups that worked occasionally in the potrooms were also included in this study. Some employees who worked in dusty environments also wore facial protective clothing. Personal breathing zone air samples taken randomly from 38 workers were sampled once. Measurements were done on 3 out of 5 working days for the rotation crews and on 4 days in 2 work weeks for the day crew. The filter holders and the XAD-2 tubes used in sampling were analyzed. Urine samples were collected from 33 of

38 workers before and after the 5-day work week. Control urine samples were taken from 10 guards not exposed to coal tar pitch volatiles. 1-Hydroxypyrene in urine was determined by liquid chromatography (LC). Results showed that field blanks were not contaminated with coal tar pitch volatiles. No benzo[a]pyrene was found on XAD-tubes. Vapor phase measurement showed 48% pyrene and 24% total PAHs. The highest filter sample (particulate) concentration of pyrene was 170 mg/m^3, and the highest sorbent tube (vapor) concentration of pyrene was 94 mg/m^3. The correlation between these two variables was 0.70. Individuals who worked continuously in the potrooms were exposed to variable concentrations of coal tar pitch volatiles, ranging from 10–2,710 mg/m^3. Multiple regression analysis of increased urinary 1-hydroxypyrene was strongly related to the environmental PAH exposure. Increased urinary 1-hydroxypyrene was greater among those using facial protective clothing under their respirators; this was probably caused by poor fitting or by facial coverings becoming contaminated by PAH. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for coal tar pitch volatiles was 4.3 mmol/mol creatinine. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for benzo[a]pyrene, was 4.3 mmol/mol creatinine.

Data from studies of inhabitants of log homes that were built with logs treated with pentachlorophenol indicate inhalation exposure to pentachlorophenol fumes occurs (Hernandex and Stressman-Sundy 1980). Similar exposure may result from coal tar creosote-treated logs (Cammer 1982).

Tumor-susceptible ICR CF-1 and tumor-resistant CAF1-JAX mice were exposed to 10 mg/m^3 coal tar aerosol-BTX mixture continuously, or for 90 days, or intermittently for 18 months (MacEwen et al. 1977). Coal tar used to generate the aerosol was of various samples from multiple coke ovens blended together with a 20% by volume amount of BTX fraction of the coke oven distillate. The coal tar-BTX mixture was comparable to the material inhaled by topside coke oven workers. Mice were serially sacrificed during the exposure period for the determination of coal tar lung burden and the time to tumor induction. Control animals were held in a vivarium. All animals were examined daily during the exposure and postexposure periods. Coal tar fluorescence retained in mouse lung and skin tissues (n=4) were measured. The amount of coal tar found on mouse skin did not change to any great degree after the first week of exposure. Lung tissue accumulated coal tar aerosol at a fairly steady rate during 18 months of intermittent exposure as compared to a high increased rate (from graph) during the 90 days of continuous exposure. The coal tar lung burden in mice was approximately equal for both exposure modes for the 180-day exposure period.

PAHs extracted from coal fly ash were intratracheally administered to pregnant Wistar rats at a dose of 20 mg/kg, once/day, on gestational days 18 and 19 (Srivastava et al. 1986). The presence of the PAHs in

both the maternal and fetal lungs and livers on gestational day 20 indicated that pulmonary absorption occurred following intratracheal administration, but inhalation exposure was not examined.

Pulmonary absorption may be influenced by carrier particles, and by solubility of the matrix or vehicle in which the compounds are found. Due to the variable composition of coal tar creosote, coal tar, and coal tar pitch, the predictive value of inhalation absorption studies conducted with pure PAHs is limited.

3.4.1.2 Oral Exposure

No studies were located regarding the direct analysis of the extent or rate of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatile absorption following oral intake in humans or animals.

Wood Creosote. Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote capsule and 200 mL water after a light breakfast (Ogata et al. 1995). Peripheral venous blood and urine samples were collected at various time intervals. Phenols in serum and urine were analyzed by HPLC. Wood creosote used in this study as determined by gas chromatography (GC) contained 11.3% phenol, 24.3% guaiacol, 13.7% *p*-cresol, and 18.2% cresol (w/w). Concentrations found in peripheral venous blood and urine were 15 mg/L phenol, 32 mg/L guaiacol, 18 mg/L *p*-cresol, and 24 mg/L cresol. HPLC analysis of 30-minute postdose serum detected low concentrations of guaiacol and *p*-cresol.

Coal Tar Products. The presence of coal tar creosote metabolites in the urine of humans and rabbits receiving calcium creosote (a calcium salt of creosote) tablets was evidence that this salt of creosote was absorbed following ingestion (Fellows 1937, 1939b). Furthermore, evidence exists that certain PAHs found in coal tar creosote such as anthracene (Rahman et al. 1986), benzo[a]pyrene (Hecht et al. 1979; Rahman et al. 1986; Rees et al. 1971; Yamazaki et al. 1987), chrysene (Chang 1943; Modica et al. 1983), and phenanthrene (Rahman et al. 1986) are absorbed following oral administration in animals.

Male $B6C3F_1$ mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar/day in feed for 28 days (Culp and Beland 1994). At the end of the feeding period, DNA adduct formation was quantified in the liver, lungs, and forestomach by ^{32}P-post-labeling. The adduct levels were then compared with those obtained by feeding benzo[a]pyrene to mice for 3 weeks at concentrations corresponding to the amount of benzo[a]pyrene in the coal tar doses. DNA adduct formation was found to increase as a function of dose in each tissue with both coal tar and benzo[a]pyrene, indicating absorption after oral exposure. Five groups of $B6C3F_1$ mice (24 males, 24 females) were fed a control gel diet containing 0.05, 0.25, or 0.50% MGP (Weyand et al. 1994). The urinary excretion of 1-hydroxypyrene by male

mice (12 per group) treated with 0.25 and 0.50% MGP was evaluated throughout the 185 days of diet administration. 1-Hydroxypyrene was detected in the urine, indicating absorption of MGP components.

Based on data on PAHs, absorption of PAH components of coal tar products after oral exposure may be positively influenced by the presence of oils and fats in the stomach, and bile in the intestines (Agency for Toxic Substances and Disease Registry 1995). Due to relative water insolubility of PAHs, absorption is enhanced by solubilization in an intermediate phase than can be metabolized during the process of lipid digestion and absorption. Excretion after oral exposure may be detected hours to days after exposure. Due to the variable composition of coal tar creosote, coal tar, and coal tar pitch, the predictive value of oral absorption studies conducted with pure PAHs is limited.

3.4.1.3 Dermal Exposure

No studies were located in humans or animals regarding the direct analysis of the extent or rate of absorption of wood creosote following dermal exposure.

Coal Tar Products. No studies were located in humans or animals regarding the direct analysis of the extent or rate of coal tar creosote, coal tar, or coal tar pitch absorption following dermal exposure. However, reports of workers who developed cancer subsequent to dermal exposure suggested that coal tar creosote was absorbed through the skin (Cookson 1924; Henry 1946, 1947; Lenson 1956). Human exposure studies also demonstrate that coal tar creosote or its components are absorbed dermally in humans, based on excretion of metabolites after dermal exposure (Bickers and Kappas 1978; Bos and Jongeneelen 1988; Cernikova et al. 1983; Clonfero et al. 1989; Hansen et al. 1993; Jongeneelen et al. 1985; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995). Van Rooij et al. (1993a) examined differences in the absorption of PAH between anatomical sites and individuals following dermal exposure of volunteers to 10% coal tar in a vehicle of zinc oxide paste. The surface disappearance of PAH and the excretion of urinary 1-hydroxypyrene after coal tar application were used to assess dermal absorption following controlled exposures. Surface disappearance measurements show low but significant differences in dermal PAH absorption between anatomical sites: shoulder > forehead; forearm, groin > ankle, hand (palmar site). Differences between individuals in PAH absorption are small (7%) in comparison with differences between anatomical sites (69%). Urinary excretion of 1-hydroxypyrene verified that the coal tar creosote and its components were absorbed through the skin, but the site of application had no effect on the excreted amount of 1-hydroxypyrene although the time to excrete half of the total metabolite varied between 8.2 and 18.9 hours.

Another study of dermal absorption was conducted by Van Rooij et al. (1993b) in a wood preserving plant in the Netherlands in October 1991. Volunteers for this study worked near the impregnation cylinders (three subjects) and the assembly hall (seven subjects). Exposure measurements were performed in 2 consecutive weeks on a Monday after a weekend off. On one Monday, the workers wore protective clothing over their clothes and on the other Monday, no protective clothing was used. PAH contamination on the skin and PAH concentration was measured on the two Mondays tested for all workers. Urine samples were collected from Sunday morning up to and including Tuesday morning for the assessment of the internal exposure to PAH. For assessing PAH contamination on the skin, six exposure pads were pasted on the skin of the workers (jaw, shoulder, upper arm, wrist, groin, and ankle) during work hours. Immediately after exposure, the pads were removed, packed in aluminum foil and stored until analysis. Results showed that extra protective clothing reduced the PAH contamination on the pads of the shoulder, upper arm, and groin. At the other skin sites, no significant reduction was found. On the average, the coveralls reduced the pyrene contamination on the worker's skin by 35%. The excreted amount of 1-hydroxypyrene in urine decreased significantly from 6.6 to 3.2 mg (30.2–14.7 nmol), indicating a change in the extent of absorption with the change in protective clothing.

Another indication that coal tar components are absorbed transdermally was reported by Paleologa et al. (1992). In particular, these investigators evaluated the occurrence of B[a]PDE-DNA adducts in white blood cells of 23 psoriatic patients undergoing clinical coal tar therapy. Two to 5 months after therapy, 10 of the patients were reanalyzed. The actual dose levels varied among the treated individuals because the application ranged from pure coal tar to 4% coal tar-based paste or ointment. No relationship appeared to exist between exposure level and concentration of B[a]PDE-DNA adducts. The results show that the mean adduct level during the treatment period was 0.26±0.16 fmole benzo[a]pyrene/g DNA (7.7±4.9 adducts/10^8 nucleotides), while 2–5 months later, the mean adduct level had decreased significantly to 0.11±0.08 fmole benzo[a]pyrene/g DNA (3.3±2.4 adducts/10^8 nucleotides).

A coal tar solution (crude coal tar diluted to 20% with ethanol and polysorbate 80) was applied to clinically unaffected skin of three patients with severe atopic dermatitis and six patients with generalized psoriasis (Bickers and Kappas 1978). Another skin area at least 10 cm away was not treated or was treated with 100 mL of the vehicle alone. Twenty-four hours later, a 6-mm punch biopsy was obtained from coal tar treated and control areas and the effect on AHH activity was determined. Application of coal tar to the skin caused induction of cutaneous AHH activity that varied from 2.4- to 5.4-fold over the enzyme activity in untreated skin areas, suggesting absorption after topical application.

Five female patients (two nonsmokers, three smokers) suffering from eczematous dermatitis on the arms and legs were treated for several days with an ointment containing 10% *pix lithanthracis dermata* (coal tar), representing 16.7 mg/g pyrene and 7.0 mg/g benzo[a]pyrene (Bos and Jongeneelen 1988). During treatment, the ointment was removed daily and a fresh dose of approximately 40 g was rubbed in. Urine samples were collected, one before application and two during the day for the first 3 days of treatment. 1-Hydroxypyrene was detected in the urine of all patients, indicating absorption of a component of the coal tar.

Twenty-eight patients that required coal tar treatment on an area larger than two-thirds of the body surface were studied (Cernikova et al. 1983). Tar paste (10 and 20%) was used for treatment; in one application, approximately 1–6 g of coal tar containing 0.6% acridine was spread on the patient's skin. Urine analysis was performed by TLC to obtain information on polyaromatic and heterocyclic substances excreted in the urine. Further identification of the substance was performed by GC/mass spectrometry (GC/MS). The presence of acridine in urine after the coal tar application was identified by MS. The detection of acridine in urine provided proof of the absorption of a coal tar component through the skin. However, without additional information, no statements can be made regarding the dermal absorption of other coal tar components or whether acridine was preferentially absorbed through the skin.

Sixteen urine samples were collected from 4 male, nonsmoking psoriatic patients, undergoing treatment with the Goeckerman regimen (cutaneous application of coal tar based ointment, followed by exposure to UV irradiation) in the Dermatology Clinic of the University of Padua (Clonfero et al. 1989). Patient A was treated with pure coal tar for 1 day; patients B, C, and D were treated with 4% coal tar based ointment for 2, 8, and 13 days, respectively. Body surface involved by psoriasis was 30, 40, 35, and 60% for patients A, B, C, and D, respectively. Total PAH (and pyrene) content of the two coal tar preparations was 28,800 (3,100) and 470 (104) ppm, respectively. The samples were collected at different times after the beginning of therapy (from 12 hours after the 1st application of coal tar to 72 hours after the last application). 1-Hydroxypyrene and other PAHs were detected in the urine, indicating absorption of components of the coal tar.

Santella et al. (1994) also observed urinary excretion of PAH metabolites after dermal application of coal tar, indicating absorption. Studies confirming that coal tar creosote is capable of inducing phototoxicity of the skin indicate dermal absorption after exposure (Diette et al. 1983).

It can also be concluded that dermal absorption occurred as evidenced by the development of skin tumors (Boutwell and Bosch 1958; Lijinsky et al. 1957; Poel and Kammer 1957; Roe et al. 1958) and lung

tumors (Roe et al. 1958) in mice following the dermal application of coal tar creosote (see Section 3.2.3.7). Other studies in animals support absorption of coal tar products after dermal application. Coal tar solution (0.05 mL of a 20% solution) was applied to the skin of six neonatal rats (4–6 days of age) and 24 hours later AHH activity was measured in the skin and liver (Bickers and Kappas 1978). There was greater than a 10-fold induction of skin AHH activity (298±13 versus 26.3±19 pmol hydroxy-benzo[a]pyrene/mg protein/hour in controls) and marked increased hepatic AHH activity (16,300±899 versus 750±35 pmol hydroxy-benzo[a]pyrene/mg protein/hour in controls) after topical application of the coal tar solution.

Based on data on PAHs, absorption of PAH components of coal tar products after dermal exposure may be limited by binding and/or metabolism in the skin, thus leaving less for systemic absorption (Agency for Toxic Substances and Disease Registry 1995). Excretion of PAHs following dermal application may be detected in hours or days, and is improved by solubilization of the compounds in a fat or oil mixture prior to application. Due to the variable composition of coal tar creosote, coal tar, and coal tar pitch, the predictive value of dermal absorption studies conducted with pure PAHs is limited. A further problem with the use of individual PAHs to estimate absorption of coal tar is that individual PAHs differ in their rates of absorption. The concentrations of nine different PAHs were measured after topical application of coal tar to a blood-perfused pig-ear (VanøRooij et al. 1995). There was a variation of accumulations of the various PAHs in the perfused blood, ranging between 830 pmol cm^{-2} for phenanthrene to <4 pmol cm^{-2} for benzo[b]fluoranthene, benzo[a]pyrene, and indeno[123-cd]pyrene. These data show that different components of coal tar are absorbed at different rates, and that using a single PAH to represent absorption of the mixture is likely to over- or under-estimate the absorption of other components.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located in humans regarding the distribution of wood creosote following inhalation exposure.

Coal Tar Products. No studies were located in humans regarding the distribution of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation exposure. Because coal tar products are composed of hydrocarbons, they are likely to distribute to lipid-rich tissues (Agency for Toxic Substances and Disease Registry 1995). PAHs and their metabolites are known to cross the placenta (Agency for Toxic Substances and Disease Registry 1995). PAHs have also been detected in human breast milk (Madhavan and Naiduka 1995). Individuals concerned with the potential exposure of breast-feeding infants to PAHs should consult their doctor. Coal tar creosote is also likely to distribute to the liver as evidenced by the presence of metabolites in the urine, indicating microsomal enzyme induction.

Tumor-susceptible ICR CF-1 and tumor-resistant CAF1-JAX mice were exposed to 10 mg/m^3 coal tar aerosol-BTX mixture continuously, or for 90 days, or intermittently for 18 months (MacEwen et al. 1977). The coal tar-BTX mixture was comparable to the material inhaled by topside coke oven workers. Mice were serially sacrificed during the exposure period for the determination of coal tar lung burden and the time to tumor induction. Control animals were held in a vivarium. All animals were examined daily during the exposure and postexposure periods. Coal tar fluorescence retained in mouse lung and skin tissues were measured. The amount of coal tar found on mouse skin did not change to any great degree after the first week of exposure. Lung tissue accumulated coal tar aerosol at a fairly steady rate during 18 months of intermittent exposure as compared to a high increased rate (from graph) during the 90 days of continuous exposure. The coal tar lung burden in mice was approximately equal for both exposure modes around the 180-day exposure period.

When [^{3}H]-benzo[a]pyrene was administered intratracheally to rats at a dose of 0.001 mg/kg, radioactivity was distributed to all tissues (Weyand and Bevan 1987). During the 6 hours following administration, >20% of the dose was detected in the carcass. The activity steadily increased in the intestine and the intestinal contents over the 6 hours. Levels of activity in the liver and lung were moderate and declined over time. Trace amounts of activity were detected in other tissues (Weyand and Bevan 1987).

Intratracheal administration of [^{3}H]-benzo[a]pyrene, along with the benzene extract of coal fly ash, to pregnant rats (20 mg/kg/day) on days 18 and 19 of gestation resulted in their distribution to the maternal lung and liver (Srivastava et al. 1986). The amount of radioactivity found in the maternal liver was

approximately 68% of the amount of radioactivity found in the maternal lung. The amounts of radioactivity found in the placenta, fetal lung, and fetal liver were approximately 4, 1.9, and 1.4%, respectively, of the amount of radioactivity found in the maternal lung. Much of the radioactivity was attributable to metabolites. These results in rats suggest that components of coal tar creosote and their metabolites can pass through the placenta and distribute to fetal tissue.

3.4.2.2 Oral Exposure

No studies were located in humans or animals regarding the distribution of, coal tar creosote, or coal tar pitch volatiles following ingestion. Based on chemical structure, it is likely that PAHs would have a strong affinity for adipose tissue. For example, benz[a]anthracene, chrysene, and triphenylene distributed to all tissues following oral administration (22.8 mg/kg) to female rats, but its greatest distribution was to adipose tissue. In this study, benz[a]anthracene concentrations were 10 times higher in adipose than in other tissues (Bartosek et al. 1984).

The distribution of nonmetabolized PAHs is dependent on their water-solubility. The more water-soluble PAHs, such as triphenylene, are generally more available to tissues other than fat (Bartosek et al. 1984). In humans, distribution of coal tar creosote following ingestion is likely to be qualitatively similar to that seen in the animal studies. The lipophilicity of PAHs allows the chemicals to be readily absorbed and preferentially accumulated in fatty tissues. Furthermore, PAHs are likely to be present in adipose and highly perfused organs such as the lungs and liver.

Wood Creosote. Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote by capsule with 200 mL water after a light breakfast (Ogata et al. 1995). Peripheral venous blood and urine samples were collected at various time intervals. Phenols in serum and urine were analyzed by HPLC. Wood creosote used in this study as determined by GC contained 11.3% phenol, 24.3% guaiacol, 13.7% *p*-cresol, and 18.2% cresol (w/w). Concentrations found in peripheral venous blood and urine were 15 mg phenol, 32 mg guaiacol, 18 mg *p*-cresol, and 24 mg cresol. HPLC analysis of 30-minute postdose serum detected low concentrations of guaiacol and *p*-cresol.

Coal Tar Products. Culp and Beland (1994) fed male $B6C3F_1$ mice 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar/day in feed for 28 days. A second group of mice was fed benzo[a]pyrene for 21 days at levels corresponding to those found in the coal tar-containing feed mixtures. At the end of the feeding period, DNA adduct formation was quantified in the liver, lungs, and forestomach by ^{32}P-post-labeling. The adduct levels were then compared with those obtained from the mice fed benzo[a]pyrene.

DNA adduct formation was found to increase as a function of dose in each tissue with both coal tar and benzo[a]pyrene. DNA adduct levels were in the order forestomach > liver > lung at lower dose groups, while the order changed to liver > forestomach > lung at the highest dose group. Total DNA binding was greater in the coal tar fed mice than in the benzo[a]pyrene fed animals (. 10- to 30-fold greater in the liver and forestomach, and over 90-fold greater in the lungs at the lower doses).

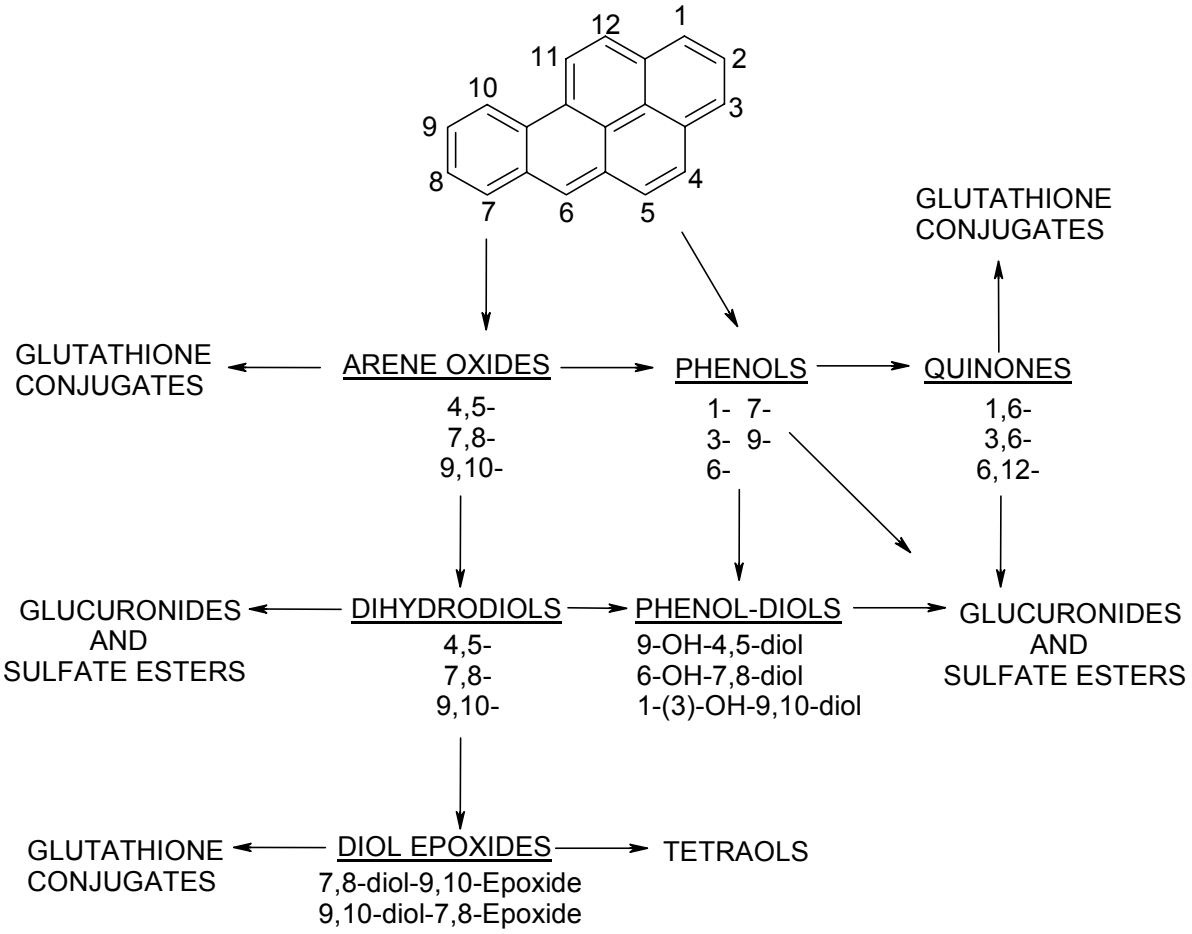
3.4.2.3 Dermal Exposure

No studies were located in humans or animals regarding the distribution of wood creosote, coal tar creosote, coal tar, or coal tar pitch following dermal exposure. Distribution of creosotes or coal tar products in humans following dermal exposure is expected to be qualitatively similar to that seen in animals or in humans following any route of exposure.

3.4.3 Metabolism

Generally, the PAH components of wood creosote, coal tar creosote, coal tar, and coal tar pitch are metabolized by oxidative enzymes in the liver and lungs to generate active metabolites that can bind to macromolecules. The metabolic profiles vary among species and compounds, but the components follow the same major reaction pathways. Hence, the metabolites are structurally very similar. The proposed metabolic scheme for a representative PAH, benzo[a]pyrene, is presented in Figure 3-4. The principal

Figure 3-4. Proposed Metabolic Scheme for Benzo[a]pyrene



products include phenols, dihydrodiols, quinones, anhydrides, and conjugates of these products (Autrup and Seremet 1986; Dahl et al. 1985; Fellows 1939b; Geddie et al. 1987; Hopkins et al. 1962; Jongeneelen et al. 1985, 1986, 1988; Ogata et al. 1995; Petridou-Fischer et al. 1988; Povey et al. 1987; Rice et al. 1986; Santella et al. 1994; Weyand and Bevan 1987).

Metabolic studies of wood or coal tar creosote have generally been confined to measurements of metabolites in the blood or urine (Bieniek 1997; Bowman et al. 1997; Chadwick et al. 1995; Fellows 1939b; Grimmer et al. 1997; Heikkila et al. 1997; Jongeneelen et al. 1985, 1986, 1988; Malkin et al. 1996; Ogata et al. 1995; Santella et al. 1994; Weston et al. 1994). However, a number of studies have examined the role of individual enzymes in the metabolism of coal tar products. Experiments by Bickers and Kappas (1978), Li et al. (1995), Luukanen et al. (1997), Genevois et al. (1998), and Fielden et al. (2000) assessed metabolic induction and activity of AHH, glucuronosyltransferase, and cytochrome P450 in response to coal tar.

Application of coal tar for 24 hours to the healthy skin of psoriasis and dermatitis patients caused a 2–5-fold induction of AHH activity compared to untreated skin from the same individuals (Bickers and Kappas 1978). Incubation of human skin with coal tar solution *in vitro* also caused induction of AHH, which reached a maximum after 24 hours. Application of coal tar to the skin of rats produced significant induction of AHH both in skin (10-fold) and in liver (>20-fold).

Dermal treatment of healthy volunteers with 10% coal tar for 4 days produced an 18-fold induction of CYP1A1 mRNA levels in coal-tar-treated skin (Li et al. 1995). *In vitro* incubation of DNA with coal tar fume concentrates in the presence of mouse and yeast microsomes expressing various cytochrome P450 isoforms or the aryl hydrocarbon hydroxylase receptor (AHR) demonstrated that coal tar fume condensates require metabolic activation to produce DNA adducts (Genevois et al. 1998). Both the AHR and CYP1A were involved in the metabolism of coal tar fume condensate. It was also shown that the reactive metabolites formed by CYP1A are substrates for microsomal epoxide hydrolase.

Microsome preparations from the livers of rats gavaged with coal tar creosote were used to assay the activities of two glucuronosyltransferases, 1-hydroxypyrene UGT and *p*-nitrophenol UGT, and to estimate the kinetic parameters of the two enzymes (Luukanen et al. 1997). Pretreatment with creosote increased the ratio of V_{max}/K_m by 18-fold for 1-hydroxypyrene UGT and by 2–3-fold for *p*-nitrophenol, suggesting that a highly efficient form of glucuronosyltransferase was selectively induced by creosote.

3.4.3.1 Inhalation Exposure

Coal Tar Products. Workers in a coal tar creosote wood-impregnating plant were exposed to coal tar creosote by inhalation during the course of their jobs (Jongeneelen et al. 1985, 1988). The creosote that these employees inhaled contained 19.8 mg pyrene/g creosote (approximately 2%). A metabolite of pyrene, 1-hydroxypyrene, was detected in their urine at levels that were above the mean values of controls (Jongeneelen et al. 1985, 1988). Similarly, workers asphalting roads with coal tar excreted 1-hydroxypyrene in their urine (Jongeneelen et al. 1988).

A study of workers occupationally exposed to coal tar creosote compared the concentration of 1-naphthol (a urinary metabolite of napthalene) in six workers from a creosote impregnation plant and five male smokers not occupationally exposed to creosote (Heikkila et al. 1997). Exposed workers wore gloves and cotton overalls to reduce dermal exposure to creosote, but did not wear respirators. The average concentrations of naphthalene in the workers air varied from 0.4 to 4.2 mg/m^3. There was a poor correlation between the amount of naphthalene in the air and the concentration of PAHs. However, the concentration of 1-naphthol was consistently greater in exposed workers than in unexposed controls and was highest for exposed workers at the end of the work shift. There was a correlation of $r=0.745$ between the concentration of naphthalene in breathing zone air and urinary 1-naphthol concentrations at the end of the shift.

A similar study was carried out in a coke plant in Zabrze, Poland (Bieniek 1997). The concentrations of 1-naphthol and 2-naphthol in the urine of 102 workers from the coke plant were compared with those of 36 controls not occupationally exposed to coal tar volatiles. Significant differences were found between the concentrations of 1- and 2-naphthols in the urine of exposed and unexposed workers ($P<0.05$). The correlation between the concentrations of naphthols in urine and napthalene in air were statistically significant ($P<0.001$).

Another study of metabolites of coal tar volatiles was carried out by Grimmer et al. (1997). Urine samples were collected from workers at a coke plant over a period of four days. Two workers were exposed to high levels of PAH and two were exposed to lower levels. The concentration of metabolites of phenanthrene, fluoranthene, pyrene, chrysene, and benzo[a]pyrene (in total, about 25 compounds) in urine were measured by GC/MS. The urinary metabolite profile for each individual remained similar over the four days analyzed. However, there was a significant difference between individuals for the absolute amounts of metabolites excreted and also for the ratio of metabolites produced (e.g., only one worker formed the 3,4-dihydrodiol of phenanthrene, the other two did not).

Similar results were obtained for measurements of the concentrations of metabolites of phenanthrene, fluoranthene, pyrene, chrysene and benzo[a]pyrene in urine of female Wistar rats exposed to coal tar pitch aerosols (dose and duration not stated) (Grimmer et al. 1997). The urinary metabolite profile for each individual rat did not show significant variation during the course of the experiment, but there was a significant difference between individuals for both the absolute amounts of metabolites excreted and also for the ratio of metabolites produced.

3.4.3.2 Oral Exposure

Wood Creosote. Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote by capsule with 200 mL water after a light breakfast (Ogata et al. 1995). Peripheral venous blood and urine samples were collected at various time intervals. The metabolites in the serum started to rise 15 minutes after the oral dose, reaching the maximum 30 minutes after dosing. The maximum serum concentrations (Cmax) of glucuronides were 0.18±0.07, 0.91±0.38, 0.33±0.18, and 0.47±0.23 mg/L, and of sulfates were 0.16±0.06, 0.22±0.09, 0.17±0.07, and <0.04 mg/L for phenol, guaiacol, *p*-cresol, and cresol, respectively. The Cmax for unconjugated phenols were 0.06±0.01, 0.05±0.01, 0.12±0.05, and <0.04 mg/L for phenol, guaiacol, *p*-cresol and cresol, respectively. Rats receiving a single dose of either 0.0002, 0.002, 0.02, 0.2, or 2.0 mg pyrene/kg by gavage in olive oil excreted 1-hydroxypyrene in the urine in a dose-dependent manner (Jongeneelen et al. 1986). This metabolite could be detected up to 96 hours after administration. No unchanged pyrene was excreted.

Coal Tar Products. Calcium creosotate was orally administered to humans at daily doses of 7–30 mg/kg for 3 days (Fellows 1939b). Calcium creosotate phenols were excreted in the urine. In addition, large unspecified doses of calcium creosotate were orally administered to rabbits. Analysis of the rabbit urine revealed that free and conjugated phenols were excreted (Fellows 1939b).

Induction of glucuronosyltransferase activity in liver microsomes from male Wister rats treated with coal tar creosote (200 mg/4 mL olive oil/kg) by gavage 72 and 24 hours before death was compared with activity in microsomes from untreated control animals (Luukanen et al. 1997). Microsome preparations from the livers of these rats were used to assay the activities of 1-hydroxypyrene UGT and *p*-nitrophenol UGT and estimate the kinetic parameters of the two enzymes. Pretreatment with creosote lowered the apparent K_m value for 1-hydroxypyrene UGT and significantly increased the estimated maximum velocity V_{max} over 4-fold. The apparent K_m values of *p*-nitrophenol UGT were higher and the V_{max} values lower than the ones for 1-hydroxypyrene UGT, but again, treatment with creosote lowered the apparent K_m value and increased the estimated maximum velocity V_{max}. Pretreatment with creosote increased the ratio

of V_{max}/K_m for 1-hydroxypyrene UGT by 18-fold and for *p*-nitrophenol 2–3-fold. These results suggest that a highly efficient form of glucuronosyltransferase was selectively induced by creosote.

Male Fischer 344 rats received 50 mg/kg coal tar creosote in peanut oil daily by gavage for 1 or 3–5 weeks (Chadwick et al. 1995). Controls were dosed with the vehicle. After treatment with creosote, six control and six treated rats were administered 75 mg/kg 2,6-DNT in DMSO by gavage and 24-hour urine was collected. Urine was also collected from two control and two treated rats dosed with DMSO. Urinary excretion of mutagenic metabolites from rats pretreated with creosote and dosed with DNT at 1, 3, and 5 weeks peaked after 3 weeks and then declined by 33% after 5 weeks of treatment. Low levels of mutagenic metabolites were also found in the urine of animals treated with creosote alone.

Induction of CYP1A1 and CYP2B10 in liver microsomes from ovariectomized mature and immature DBA/2 mice and ICR mice gavaged with 10, 50, or 100 mg/kg creosote in sesame oil once a day for 4 days was compared with that in microsomes derived from control animals that received only sesame oil (Fielden et al. 2000). CYP1A1 and CYP2B10 activities were assessed based on EROD (ethoxyresorufin-O-deethylase) and PROD (pentoxyresorufin-O-depentylase) activities, respectively. Creosote treatment significantly increased the activity of CYP1A1 and CYP2B10 in both immature and mature mice, but the CYP1A1 increase was age-dependant, with immature mice showing a 5.9-fold increase in EROD activity after treatment with 100 mg/kg/day creosote while mature mice treated similarly had an 11.4-fold increase in liver EROD activity. No age-dependent difference was seen in induction of CYP2B10 since PROD activity was increased by creosote treatment 1.6–2.2-fold in both mature and immature mice.

It is evident in both human and animal studies that hydroxylation is a principal oxidative pathway of PAH metabolism, and consequently, coal tar creosote metabolism. In these studies, there were no discussions to suggest that the researchers attempted to identify other metabolites.

3.4.3.3 Dermal Exposure

Coal Tar Products. A number of studies have shown that PAH components of coal tar appear to be metabolized following dermal exposure in humans. Two patients suffering from eczema on the arms and legs were treated for several days with an ointment containing 10% *pix lithanthracis dermata* (coal tar) (Jongeneelen et al. 1985). The daily dermal dose was approximately 1 mg/kg. Analysis of the urine samples collected from these patients prior to treatment and in the morning and evening of the first 3 days of treatment showed that 1-hydroxypyrene was excreted at levels 200 times that which was detected before the treatment started (Jongeneelen et al. 1985).

Urine samples collected from 43 patients being treated in the hospital for psoriasis with a coal tar ointment and from 37 controls who had never been treated with coal tar were analyzed for the presence of 1-hydroxypyrene-glucuronide and r-7,t-8,t-9,c-10-tetrahydroxy-7,8,9,10-tetrahydro-benzo[a]pyrene (Bowman et al. 1997). The metabolite, r-7,t-8,t-9,c-10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene, was detected in urine of 20 (47%) of the patients, but only 4 (10%) of the controls. The other metabolite studied, 1-hydroxypyrene-glucuronide, was detected in all samples, but the mean level for patients was 40.96±72.62 pmol μmol^{-1} creatinine and that for controls was 0.38±0.32 pmol μmol^{-1}; this difference was significant ($P<0.0001$). The ratio of urinary levels of the two metabolites was examined in the coal tar-treated patients and found to vary by approximately 6,000-fold, suggesting wide variation between individuals in the ability to metabolize benzo[a]pyrene and pyrene.

Similar results were obtained in another study of psoriasis patients (43 patients and 39 untreated controls) being treated with a coal tar ointment (Weston et al. 1994). The benzo[a]pyrene metabolite, r7,t8,t9,c10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene, was detected in urine of 18 psoriasis patients (42%) and 4 untreated subjects (10%). There was a significant difference in the levels of r7,t8,t9,c10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene in patients and untreated individuals with levels varying from undetectable to 330 fmol/mL for patients and from undetectable to 40 fmol/mL for untreated individuals. A second metabolite 1-hydroxypyrene-glucuronidide was found in all urine samples, but levels were significantly higher in psoriasis patients than in untreated controls, ranging from 180 to 50,000 fmol/mL in patients and 36–650 fmol/mL in untreated individuals.

Patients with psoriasis (57) and healthy volunteers (53) with no reported exposures to coal tar shampoos or ointments, self-applied either an ointment or a gel-based coal tar product, or both, to the entire body surface at least once a day, followed by UV-B treatment (Santella et al. 1994). The estimated exposure was 20–100 g of tar/day. Twenty-four hour urine samples were collected from all subjects. Urinary 1-hydroxypyrene was analyzed by HPLC. Urinary PAH metabolites measured by PAH-ELISA were

elevated in patients (mean 730±1,370 mmol) as compared to untreated volunteers (110±90 mmol equivalents of B[a]P/mol creatinine). Urinary levels of 1-hydroxypyrene were also elevated in patients (mean 547±928 mmol/mol creatinine) as compared with untreated volunteers (mean 0.14±0.17 mmol).

Metabolism of pyrene was reported for 18 workers from a coke oven included in a NIOSH environmental survey (Malkin et al. 1996). Personal breathing zone air was checked for the presence of PAHs and coal tar pitch volatiles (identity not specified). The levels of naphthalene, benzene and pyrene were specifically recorded. Sludge samples were also analyzed for the presence of PAHs. Preshift and postshift urine samples were collected from the workers and analyzed for the presence of 1-hydroxypyrene, a metabolite of pyrene. Pyrene was found in analysis of the sludge samples at levels between 6.3 and 36 mg/g, but was detected in only one breathing zone air sample. Preshift 1-hydroxypyrene levels were significantly increased at the end of the work shift. Preshift levels varied from 0.16 to 3.0 μmol/mol creatinine (mean 1.0) and postshift levels ranged from 0.24 to 4.85 μmol/mol creatinine (mean 1.7). Smoking was not found to be significantly related to 1-hydroxypyrene levels in exposed workers, although preshift levels were slightly increased in smokers relative to nonsmokers.

Experiments by Bickers and Kappas (1978), Li et al. (1995) and Genevois et al. (1998) have examined the role of AHH and cytochrome P450 in the metabolism of coal tar products. A coal tar solution (crude coal tar diluted to 20% with ethanol and polysorbate 80) was applied to clinically unaffected skin of three patients with severe atopic dermatitis and six patients with generalized psoriasis (Bickers and Kappas 1978). Another skin area at least 10 cm away was not treated or was treated with 100 mL of the vehicle alone. Twenty-four hours later, a 6-mm punch biopsy was obtained from coal tar treated and control areas and the effect on AHH activity was determined. Application of coal tar to the skin caused induction of cutaneous AHH activity that varied from 2.4–5.4-fold over the enzyme activity in untreated skin areas. There were no sex differences in inducibility between patients with psoriasis and patients with atopic dermatitis. Relative inducibility of human skin AHH by coal tar did not appear to be a function of the basal level of the enzyme.

Coal tar solution (0.05 mL of a 20% solution) was applied to the skin of six neonatal rats (4–6 days of age), and 24 hours later, AHH activity was measured in the skin and liver (Bickers and Kappas 1978). There was greater than a 10-fold induction of skin AHH activity (298±13 versus 26.3±19 pmol hydroxy benzopyrene/mg protein/hour in controls) and marked increased hepatic AHH activity (16,300±899 versus 750±35 pmol hydroxy benzopyrene/mg protein/hour in controls) after topical application of the coal tar solution.

Cytochrome P4501A1 (CYP1A1) expression was increased in healthy volunteers treated dermally with 10% coal tar for 4 days producing an 18-fold induction of CYP1A1 mRNA levels in coal-tar-treated skin (Li et al. 1995). *In vitro* incubation of DNA with coal tar fume concentrates in the presence of mouse and yeast microsomes expressing various cytochrome P450 isoforms or the AHR demonstrated that coal tar fume condensates require metabolic activation to produce DNA adducts (Genevois et al. 1998). Both the AHR and CYP1A were involved in the metabolism of coal tar fume condensate, but neither was absolutely required. The role of microsomal epoxide hydrolase was also tested, and it was shown that the reactive metabolites formed by CYP1A are substrates for epoxide hydrolase. Addition of epoxide hydrolase to the microsome preparations caused an 80% reduction in the relative level of DNA adducts produced from coal tar fume condensates by CYP1A1.

3.4.4 Elimination and Excretion

Coal Tar Products. Excretion of the PAH compounds of coal tar creosote is controlled by their rate of metabolism. Excretion of these metabolites or any remaining parent compound is primarily in the urine, bile, and feces. Weyand and Bevan (1987) demonstrated this by cannulating the bile ducts of rats that received [^{3}H]-benzo[a]pyrene intratracheally. Those rats with the biliary cannulas had significantly lower levels of activity in their intestines, intestinal contents, and stomach than rats without biliary cannulas. Sanders et al. (1986) showed that PAHs were primarily removed in the feces after dermal administration of [^{14}C]-benzo[a]pyrene and [^{14}C]-7,12-dimethylbenz[a]-anthracene, suggesting hepatobiliary excretion. Urinary excretion of PAH metabolites also occurs, but to a lesser extent than by the other routes. Excretion of the major portion of experimental doses of PAHs suggests half-lives in hours to days, with inhalation exposure yielding the fastest elimination, followed by oral exposure and dermal exposure (Agency for Toxic Substances and Disease Registry 1995). It is known that PAHs and their metabolites cross the placenta (Agency for Toxic Substances and Disease Registry 1995) and have been detected in human breast milk (Madhavan and Naiduka 1995). Individuals concerned with the potential exposure of breast-feeding infants to PAHs should consult their doctor.

Studies of excretion of coal tar products have used urinary levels of PAHs and their metabolites as an estimate of excretion of the parent mixture. These studies give information as to the rates of elimination of individual PAHs, but not their extent, since a significant proportion of these chemicals is eliminated in the bile and feces. The conclusions that can be drawn from these studies are also limited by evidence that the rates at which individual PAHs are absorbed can vary by several orders of magnitude (VanøRooij et al. 1995) so that no individual PAH can be taken as representative of the entire coal tar mixture.

3.4.4.1 Inhalation Exposure

No studies were located regarding the excretion of wood creosote following inhalation exposure in humans or animals. Some studies were located that estimate excretion of individual PAHs or their metabolites in urine. Excretion of PAHs and their metabolites after inhalation exposure may be detected hours to days after exposure (Agency for Toxic Substances and Disease Registry 1995).

Coal Tar Products. Measurements were carried out in a creosote impregnation plant where 6 men volunteered to participate in the study (Elovaara et al. 1995). Personal breathing zone air samples were taken on 5 consecutive days followed by a work free period of 64 hours. All workers wore leather protective gloves and cotton overalls. Two employees worked overtime (until 6:30 a.m.) on Monday, which was an exception to the regular 8-hour schedule. Particulate PAHs were collected during the whole shift and analyzed within 7 weeks. Workers were asked to collect all urine passed within the 24-hour period into divided samples for the designated periods. Results showed that the geometric mean (range) air concentration of total particulate PAHs (including pyrene) was 4.77 (1.2–13.7) mg/m^3 and that of naphthalene was 1,254 (370–4,200) mg/m^3. The PAH profile was similar in all samples. The lowest concentrations of 1-hydroxypyrene in creosote workers were found in the Monday morning urine samples after 64 hours off work. The highest concentrations were consistently found in the evening samples (6–9 hours after work) but lower at the end of the shift. The urinary 1-hydroxypyrene levels on Monday morning before work ranged from 4 to 22 mmol/mol creatinine; levels on Tuesday morning to Saturday morning ranged from 16 to 120 mmol/mol creatinine; and levels at end of shift ranged from 19 to 85 mmol/mol creatinine. The evening after work (taken on Monday, Wednesday, and Friday) urinary levels of 1-hydroxypyrene ranged from 27 to 122 mmol/mol creatinine.

Exposure of assemblers (all smokers) handling creosote-impregnated wood and one worker (smoker) chiselling coal tar pitch insulation to coal tar products was assessed by analyzing the breathing zone air for airborne PAHs, and assaying urinary excretion of 1-hydroxypyrene (Heikkilä et al. 1995). The concentration of pyrene and 11 other PAHs in particulate matter had been measured both in the work room and in the breathing zone of the assemblers a year earlier during 2 working days. In the present setting the ties were impregnated with the same type of creosote as a year earlier, which contained 0.2 w% of pyrene. Urine samples were collected during 3 working days (Monday, Wednesday, and Friday) and over the following weekend. Urine samples from one chiseller were collected in the morning before work, during lunch time, at the end of the shift, in the evening, and the next morning. The total concentrations of PAHs and of 4–6 aromatic ring-containing PAH (when chiselling) were 440 (50-fold higher than assemblers) and 290 (200-fold higher than assemblers) mg/m^3, respectively. The estimated

means of inhaled pyrene for assemblers measured on Monday, Wednesday, and Friday were found to be 0.009, 0.007, and 0.024 mmol/shift, respectively. The estimated inhaled pyrene measured on the chiseller was 1.2 mmol/shift. Excretion of urinary 1-hydroxypyrene for assemblers measured on Monday, Wednesday, and Friday for assemblers showed mean pyrene doses (pyrene doses=breathing volume [25 L/minute] x work period x pyrene concentration x 50% retention) of 0.010, 0.13, and 0.19 mmol/24 hours, respectively. Excretion of urinary 1-hydroxypyrene measured on the chiseller showed a pyrene dose of 0.492 mmol/24 hours.

Four rotation crews of about 29 workers and one day crew of 22 workers worked a 5-day shift of 8 hours/day in the potrooms (Ny et al. 1993). All workers wore disposable respirators that were renewed 4–5 times/day, thick cotton working clothes with long sleeves, safety shoes, safety glasses, gloves, and helmets. Other groups that worked occasionally in the potrooms were also included in this study. Some employees who worked in dusty environments also wore facial protective clothing. Personal breathing zone air samples were taken randomly one time from 38 workers. Measurements were done on 3 of 5 working days for the rotation crews and on 4 days in 2 work weeks for the day crew. The filter holders and the XAD-2 tubes used in sampling were analyzed. Urine samples were collected from 33 of 38 workers before and after the 5-day work week. Control urine samples were taken from 10 guards not exposed to coal tar pitch volatiles. 1-Hydroxypyrene in urine was determined by liquid chromatography. Results showed that field blanks were not contaminated with coal tar pitch volatiles. No benzo[a]pyrene was found on XAD-tubes. Vapor phase measurement showed 48% pyrene and 24% total PAHs. The highest filter sample (particulate) concentration of pyrene was 170 mg/m^3 and the highest sorbent tube (vapor) concentration of pyrene was 94 mg/m^3. The correlation between these 2 variables was 0.70. Individuals who worked continuously in the potrooms were exposed to variable concentrations of coal tar pitch volatiles, ranging from 10–2,710 mg/m^3. Multiple regression analysis of increased urinary 1-hydroxypyrene was strongly related to the environmental PAH exposure. Increased urinary 1-hydroxypyrene was greater among those using facial protective clothing under their respirators; this was probably caused by poor fitting or by facial coverings becoming contaminated by PAH. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for coal tar pitch volatiles was 4.3 mmol/mol creatinine. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for benzo[a]pyrene was 4.3 mmol/mol creatinine.

Urine samples collected from two reference groups of nonoccupationally exposed individuals and four groups of workers were measured for urinary excretion of 1-hydroxypyrene (Viau et al. 1995). The study groups are described as follows: reference group 1 (12 males, 9 females) was workers with no occupational exposure to PAH (single spot urine sample collected during the day); reference group 2

(7 males) was administrative workers in a silicon carbide plant (urine samples obtained Monday morning upon arrival at work); the silicon carbide group (83 males) worked in a silicon carbide plant involved in various occupations (urine samples collected at the beginning and end of work shift on a Monday and Friday); the creosote group (19 males) was workers exposed to creosote in a wood treatment plant (one urine sample collected towards the end of the work week and another sample obtained after at least 64 hours of exposure); the decontamination group (29 males) was workers in various occupations related to the removal of soil contaminated with PAH from the pyrolysis of used tires after a major fire at a dump (single urine sample collected at beginning of shift); and the brushwood cutting group (10 males) was workers responsible for the clearing of brushwood under electricity power lines (single urine sample collected at end of shift). Urine samples from reference group 1, creosote, decontamination, and brushwood cutting groups were analyzed by high performance chromatography; samples from reference group 2 and silicon carbide group were analyzed by GC/MS. Results showed that the creosote group was largely exposed to pyrene. Even after >64 hours without exposure, the mean (geometric) excretion of 1-hydroxypyrene was higher for the creosote group (0.53 mmol/mol creatinine) than for the reference groups 1 (0.08 mmol/mol creatinine) and 2 (0.10 mmol/mol creatinine). The mean (geometric) excretion in creosote workers during their working week was 1.63 (0.18–10.47) mmol/mol creatinine. The brushwood cutting workers excreted more 1-hydroxypyrene than the referents. These results were pooled with those of the nonoccupationally exposed reference groups yielding a total of 140 individuals having a mean (geometric) excretion of 0.08 mmol/mol creatinine and the 5th, 50th, and 95th percentiles of 0.02, 0.09, and 0.32 mmol/mol creatinine, respectively. The mean (geometric) excretion in the 95 nonsmokers and 45 smokers of this pool were 0.07 and 0.12 mmol/mol creatinine, respectively.

3.4.4.2 Oral Exposure

Wood Creosote. Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote by capsule with 200 mL water after a light breakfast (Ogata et al. 1995). Urine samples were collected at various time intervals. Phenols in urine were analyzed by HPLC. Wood creosote used in this study as determined by GC contained 11.3% phenol, 24.3% guaiacol, 13.7% *p*-cresol, and 18.2% cresol (w/w). The urinary recoveries of the sum of the conjugated and unconjugated forms of each phenolic compound were 75±35, 45±36, 103±51, and 74±36% for phenol, guaiacol, *p*-cresol, and cresol, respectively.

Coal Tar Products. No studies were located regarding the excretion of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following oral exposure in humans.

Weyand et al. (1991) fed male mice 0.25% MGP residue, a form of coal tar, in feed for 15 days. The coal tar mixtures were of five different compositions. Analysis of urine collected on the first and last day of exposure indicated that 1-hydroxypyrene was the major metabolite excreted by all groups. Urinary levels of 1-hydroxypyrene were greater on day 15 of ingestion compared to day 1 of ingestion. 1-Naphthol, 1-hydroxyphenanthrene, and 2-hydroxyphenanthrene were also detected in the urine. Animals fed coal tar with a high content of pyrene excreted more 1-hydroxypyrene than animals fed coal tar with low pyrene content. In another study by Weyand et al. (1994), five groups of $B6C3F_1$ mice (24 males, 24 females) were fed a control gel diet containing 0.05, 0.25, or 0.50% MGP residue, a type of coal tar formed as a by-product of coal gasification. The urinary excretion of 1-hydroxypyrene by male mice (12 per group) treated with 0.25 and 0.50% MGP was evaluated throughout the 185 days of diet administration. Urine was collected overnight on days 1, 34, 64, 88, 116, and 182 of diet administration and analyzed by HPLC. Urine collected overnight on days 1, 34, 64, 88, 116, and 182 resulted in increased urinary excretion of 1-hydroxypyrene 19 (day 1) to 203 (day 182) mg/mL per mouse. This increase in concentration paralleled a notable decrease in the total volume of urine excreted by animals. Thus, the total amount of 1-hydroxypyrene excreted reached a maximum of 5–6 mg within 34 days of diet administration.

Male Fischer 344 rats received 50 mg/kg creosote in peanut oil daily by gavage for 1 week, or 3–5 weeks (Chadwick et al. 1995). Controls were dosed with the vehicle. After treatment with creosote, six control and six treated rats were administered 75 mg/kg 2,6-DNT in DMSO by gavage and 24-hour urine collected. Urine was also collected from two control and two treated rats dosed with DMSO. Urinary excretion of mutagenic metabolites from rats pretreated with creosote and dosed with DNT at 1, 3, and

5 weeks peaked after 3 weeks and then declined by 33% after 5 weeks of treatment. Low levels of mutagenic metabolites were also found in the urine of animals treated with creosote alone.

3.4.4.3 Dermal Exposure

No studies were located regarding the excretion of wood creosote following dermal exposure in humans or animals.

Coal Tar Products. Human exposure studies demonstrate that coal tar creosote or its components are absorbed dermally in humans, based on excretion of metabolites after dermal exposure (Bickers and Kappas 1978; Bos and Jongeneelen 1988; Cernikova et al. 1983; Clonfero et al. 1989; Diette et al. 1983; Hansen et al. 1993; Jongeneelen et al. 1985; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995). Van Rooij et al. (1993a) examined differences in absorption of PAH between anatomical sites and individuals following dermal exposure of volunteers to 10% coal tar in a vehicle of zinc oxide paste. Differences between individuals in PAH absorption are small (7%) in comparison with differences between anatomical sites (69%). Urinary excretion of 1-hydroxypyrene verified that the coal tar creosote and its components were absorbed through the skin, but the site of application had no effect on the excreted amount of 1-hydroxypyrene although the time to excrete half of the total metabolite varied between 8.2 and 18.9 hours. Another study of excretion after dermal absorption was conducted by Van Rooij et al. (1993b) in a wood preserving plant in the Netherlands in October 1991. Volunteers for this study were workers who worked near the impregnation cylinders (three subjects) and the assembly hall (seven subjects). Exposure measurements were performed in 2 consecutive weeks on a Monday after a weekend off. On one Monday, the workers wore protective clothing over their clothes and on the other Monday, no protective clothing was used. PAH contamination on the skin and PAH concentration was measured on the two Mondays on all workers. Urine samples were collected from Sunday morning through Tuesday morning for the assessment of the internal exposure to PAH. The excreted amount of 1-hydroxypyrene in urine decreased significantly from 6.6 to 3.2 mg (30.2–14.7 nmol).

Sarto et al. (1989) examined the excretion of coal tar metabolites in male psoriatic patients treated dermally with an ointment containing 2 or 4%, or pure coal tar on 35–60% of the surface skin for 1–13 days. Coal tar content was reported to be 0.49 mg/g for the 4% coal tar ointment, and about 29 mg/g for the pure coal tar. PAHs appeared in the urine within a day after treatment, with peak concentrations 7–10 days after treatment.

Five female patients (two nonsmokers, three smokers) suffering from eczematous dermatitis on the arms and legs were treated for several days with an ointment containing 10% *pix lithanthracis dermata* (coal tar), representing 16.7 mg/g pyrene and 7.0 mg/g benzo[a]pyrene (Bos and Jongeneelen 1988). During treatment, the ointment was removed daily and a fresh dose of approximately 40 g was rubbed in. Urine samples were collected, one before application and two during the day for the first 3 days of treatment. High concentrations of toxic compounds in the urine samples were found and mutagenicity tests were not successful. One out of two nonsmoking patients excreted a large amount of thioether products during the beginning of the treatment: 19.6 mmol thioether (SH)/mol creatinine was measured in the evening urine sample of the first day of treatment and 24.5 mmol SH/mol creatinine in the morning urine sample of the second day of treatment. The concentrations were within the normal range in urine samples measured on the evening of the second day (5.4 mmol SH/mol creatinine) and on the morning of the third day (3.3 mmol SH/mol creatinine). No similar increase in thioether excretion during coal tar treatment was found for other patients, whose values were within or slightly above the normal range. The concentration of 1-hydroxypyrene rose rapidly to 100 times the control value after the beginning of the treatment of these patients reaching 50–500 μmol/mol creatinine. Pretreatment urine samples of the smoker patients contained somewhat higher levels of 1-hydroxypyrene than those for a separate group of control smokers.

Twenty-eight patients who required coal tar treatment on an area larger than two-thirds of the body surface were selected for this study (Cernikova et al. 1983). Tar paste (10 and 20%) was used for treatment; in one application approximately 1–6 g of coal tar containing 0.6% acridine was spread on the patient's skin. Urine analysis was performed by TLC to obtain information on polyaromatic and heterocyclic substances excreted in the urine. Further identification of the substance was performed by GC/MS. The presence of acridine in urine after the coal tar application was identified by MS. Acridine was not quantified.

Sixteen urine samples were collected from four male, nonsmoking psoriatic patients undergoing treatment with the Goeckerman regimen (cutaneous application of coal tar based ointment, followed by exposure to UV irradiation) in the Dermatology Clinic of the University of Padua (Clonfero et al. 1989). Patient A was treated with pure coal tar for 1 day; patients B, C, and D were treated with 4% coal tar based ointment for 2, 8, and 13 days, respectively. Body surface involved by psoriasis was 30, 40, 35, and 60% for patients A, B, C, and D, respectively. Total PAH (and pyrene) content of the two coal tar preparations was 28,800 (3,100) and 470 (104) ppm, respectively. The samples were collected at different times after the beginning of therapy (from 12 hours after the first application of coal tar to 72 hours after the last application). Levels of 1-hydroxypyrene ranged from 25.4 mg/g creatinine to 1,565 mg/g creatinine. Total PAH content in urine ranged from 6.4 mg/g creatinine to 64.2 mg/g creatinine. Baseline levels of

total PAH and mutagenic activity were determined in evening urinary samples of 5 healthy, nonsmoking subjects, not exposed to PAHs. The control group for the determination of 1-hydroxypyrene levels consisted of 52 nonsmokers who exhibited values of 1.3 mg/g creatinine. Results showed levels of 1-hydroxypyrene are 20 and 1,000 times higher in the exposed group than in controls; total PAHs were 3.5–20 times higher in the exposed group than in controls. In 5 of 15 cases, the urinary mutagenicity of the exposed group was not significantly higher than that of the controls, while in one case it was not evaluated due to toxic effects. The mutagenic activity of the urinary extracts of the exposed subjects was at most 8 times greater than the average mutagenicity of the controls.

Patients with psoriasis (57) and healthy volunteers (53) with no reported exposures to coal tar shampoos or ointments, self-applied either an ointment or a gel-based coal tar product, or both, to the entire body surface at least once a day, followed by UV-B treatment (Santella et al. 1994). The estimated exposure was 20–100 g/tar/day. Twenty-four-hour urine samples were collected from all subjects. Urinary 1-hydroxypyrene was analyzed by HPLC. Urinary PAH metabolites measured by the PAH-ELISA were elevated in patients (mean 730±1,370 mmol) as compared to untreated volunteers (110±90 mmol equivalents of B[a]P/mol creatinine). Urinary levels of 1-hydroxypyrene were also elevated in patients (mean 547±928 mmol/mol creatinine) compared with untreated volunteers (mean 0.14±0.17 mmol).

No studies were located regarding the excretion of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following dermal exposure in animals.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al.

1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

The pharmacokinetics of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles have not been defined because of their chemical complexity. Creosotes vary tremendously in composition and hence, mechanisms of action most likely differ among individual samples of creosotes.

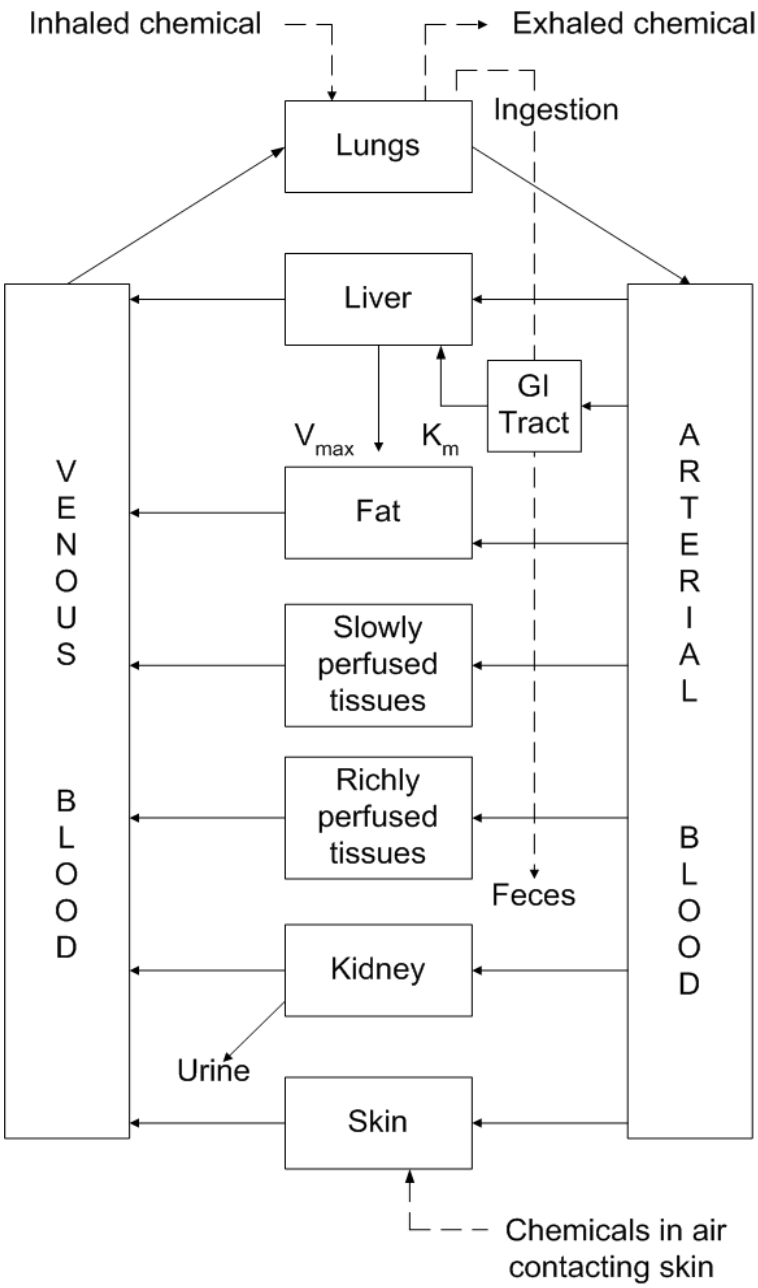
Information on individual components is not adequate to define the properties of the whole mixture and for this reason no PBPK models have been proposed for creosote.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. No studies were located in humans or animals regarding the direct analysis of absorption of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles via the inhalation, oral, or dermal routes. Studies of humans exposed to coal tar creosote have measured increased levels of urinary metabolites of various components of coal tar creosote suggesting that at least some components of coal tar creosote are absorbed by all routes. However, these studies do not provide any information as to the mechanism of absorption. PAHs are lipophilic compounds that are probably absorbed by passive diffusion, but no information was located for mechanism of absorption of other components of creosote. From data on individual PAHs (Agency for Toxic Substances and Disease Registry 1995), gastro-intestinal absorption of the PAH components of coal tar creosote may be increased by the presence of oils and fats in the stomach and bile in the intestines, while dermal absorption is affected by the anatomical site to which it is applied. Dermal absorption of PAHs may also be increased when they are solubilized in a fat or oil mixture prior to application or conversely may be reduced by binding and/or metabolism in the skin. However, due to the variable composition of coal tar creosote, coal tar pitch, and coal tar, the predictive value of studies carried out on single PAHs is limited. For further information on PAHs please refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995).

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Distribution. No studies were located in humans or animals regarding the distribution of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation, oral, or dermal exposure. Coal tar is composed of hydrocarbons, which are lipophilic substances and distribute to lipid-rich tissues including breast milk and the placenta. The frequent presence of metabolites of coal tar in the urine also suggests that it is likely to distribute to the liver. The distribution of nonmetabolized PAHs is dependent on their water-solubility. The most lipophilic PAHs may be preferentially distributed to fatty tissues where they may accumulate while more water-soluble PAHs may be more easily excreted. PAHs are distributed to tissues by transport through the blood, therefore, highly perfused tissues such as the lung and liver are likely to contain PAHs. This may also be the case with phenol and cresol as analysis of blood from volunteers who ingested wood creosote (Ogata et al. 1995) demonstrated the presence of phenol, guiacol, and cresols in the blood. A study of the distribution of intratracheally administered radioactive benzo[a]pyrene mixed with a benzene extract of coal fly ash in pregnant rats found that most radioactivity was distributed to the maternal lung, while 68% of the amount in lung was found in the maternal liver (Srivastava et al. 1986). A small amount of radioactivity was also distributed to the fetal lung and liver and to the placenta, respectively 1.9, 1.4, and 4% of the amount in maternal lung. The route of administration of creosote may affect distribution in that entry via the lungs may initially bypass metabolism in the liver so that parent compounds reach peripheral tissues in higher concentrations than would be seen after oral administration.

Metabolism. No studies were located in humans or animals that specifically addressed the metabolism of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation, oral, or dermal exposure. The PAH components of creosote are metabolized by oxidative enzymes in the liver and lungs to generate active metabolites that can bind to macromolecules. The metabolic profiles of these substances vary among species and compounds, but the components follow the same reaction pathways and so the metabolites are structurally similar. The major products include phenols, dihydrodiols, quinones, anhydrides, and conjugates of these products. Enzymes involved in the metabolism of PAHs vary depending on tissue and the particular PAH, but can include various isoforms of cytochrome P450 (predominantly CYP1A1, but also CYP1A2, CYP1B1, or CYP2C) (Genevois et al. 1998), epoxide hydrolase, glutathione-S-transferases, glucuronidases, and AHH (Agency for Toxic Substances and Disease Registry 1995). For more information on the metabolism of PAHs the reader is referred to the ATSDR *Toxicological Profile on Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995). Phenol is metabolized via three pathways in mammals; P450 catalyzed hydroxylation, sulphate conjugation, or glucuronide conjugation. The two conjugation pathways can be considered competitive pathways in most species of mammal. Thus, the relative amounts of each product formed depend on dose level as well as the relative abundance and kinetic

parameters of the two enzyme systems. For further information on the metabolism of phenol the reader is referred to the ATSDR *Toxicological Profile on Phenol* (Agency for Toxic Substances and Disease Registry 1998).

Excretion. No studies were located in humans or animals regarding the excretion of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation, oral, or dermal exposure. Phenol is a normal constituent of human urine and phenol administered via all routes of absorption is rapidly eliminated in the urine and the bile (Agency for Toxic Substances and Disease Registry 1998). PAHs are lipophilic compounds that could remain indefinitely within fatty tissues, but metabolism of PAHs renders them more water soluble and more excretable. Excretion of the metabolites of PAHs is primarily in the urine, bile, and feces. Experimental data suggests half-lives of hours to days with elimination being fastest after inhalation exposure followed by oral and dermal exposure (Agency for Toxic Substances and Disease Registry 1995). PAHs have been detected in human breast milk (Madhavan and Naiduka 1995).

3.5.2 Mechanisms of Toxicity

Defining a general mechanism of toxicity for creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles is essentially impossible because of their diversity and variability in biological effect and composition. The creosotes vary tremendously in respect to their sources (wood or coal), components, and preparation conditions. Similarly, coal tar, coal tar pitch, and coal tar pitch volatiles will differ in composition depending on the source of the coal. Hence, mechanisms of action most likely differ among individual creosotes, coal tars, coal tar pitch, and coal tar pitch volatiles.

In addition, although a great deal is known about the mechanisms of action for many of the individual components of creosote, the use of individual components to define the properties of the whole mixture may or may not supply adequate information upon which risk from exposure to the whole can be appropriately assessed. An excellent example of this is presented by Warshawsky et al. (1993), who reported that the carcinogenicity for mice of specific coal tar creosote components mixed in different formulations differed in incidence and latency of appearance from their individual carcinogenicities. For instance, coal tar in toluene, which was determined to contain 0.0006% B[a]P, produced tumors in 51% of mice with a latent period of 73 weeks. In contrast, the same concentration of B[a]P administered in toluene without coal tar did not produce tumors. The addition of another solvent, n-dodecane, resulted in increased tumor incidence and reduced latency period. Solutions of methylbenz[a]anthracenes in toluene did not produce tumors, but did result in tumors when administered in n-dodecane. The findings of this

study indicated that (1) low doses of noncarcinogenic PAHs could have an impact on the carcinogenic potential of B[a]P in mixtures, (2) the carcinogenic activity of coal tar cannot be accounted for by the level of B[a]P present, and (3) certain noncarcinogenic components of coal tar can have their carcinogenic potential altered by the presence of other aliphatic compounds.

Individual components of creosote are also metabolized by several different enzyme systems including cytochrome P450, epoxide hydrolase, glutathione-S-transferases, glucuronidases, AHH, phenol sulfotransferase, and glucuronyltransferase. Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. The relative activity of metabolic enzymes may also vary with the age of the individual, which will again affect the relative toxicity of particular components of creosote for old or young individuals (for further discussion of age-related effects, the reader is referred to Section 3.7). Therefore, for creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles, it is not presently possible to define mechanisms of transport, distribution, or the precise chemical or physiological events that lead to toxic damage or carcinogenicity in the biological system.

3.5.3 Animal-to-Human Extrapolations

Animal-to-human extrapolations of the toxicity of creosote are complicated by the inherent chemical variety of these substances. Creosotes are complex mixtures of variable composition and the individual components are likely to show interspecies variation in toxicity. Only one study was located that treated more than one species of animal with the same sample of creosote (Miyazato et al. 1981), and although this study suggested that mice were more susceptible to the acute effects of beechwood creosote than rats, the differential susceptibility observed with this particular sample cannot be applied to creosotes of different composition. In general, the adverse effects observed in animals are similar to those reported for humans with cancer being the most serious, but it is not possible at present to assess whether the doses required to produce adverse effects in animal systems are similar to those required to produce similar effects in humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans after exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles.

Wood Creosote. Effects of wood creosote on the endocrine organs are confined to changes in testis and adrenal gland weights without any accompanying histological alterations. Miyazato et al. (1981) reported that oral exposure of rats to beechwood creosote in the diet for 3 months increased relative weight of the testis. However, there were no accompanying histological changes in the testis and no changes in ovary

weights. No change in testis or ovary weight was observed for mice exposed to beechwood creosote for up to 96 weeks (Miyazato et al. 1981, 1984a, 1984b). Oral exposure of male rats to 313 mg/kg/day beechwood creosote for 96 weeks produced a significant increase in the relative weight of the adrenal glands of male rats (Miyazato et al. 1984b). However, another study of beechwood creosote found no effect on the adrenal glands (Miyazato et al. 1981).

Coal Tar Products. An excess of breast cancer cases in St. Louis Park, Minnesota, was tentatively associated with coal tar contamination of the water supply (Dean et al. 1988). However, in a subsequent analysis of these data, the Minnesota Department of Health (1985) concluded that this study did not provide adequate evidence to associate breast-cancer with coal tar creosote-contaminated water (for a detailed discussion of these data, see Section 3.2.2.7 Cancer). No adverse effects on sperm characteristics were reported in male workers exposed to coal tar pitch volatiles in an industrial setting (Ward 1988). In addition, no adverse reproductive outcomes were detected in a survey of inhabitants of a housing development built on an abandoned creosote factory site, which was known to be contaminated with creosote (Agency for Toxic Substances and Disease Registry 1994). A retrospective study of dermal exposure to coal tar found no increased risk of spontaneous abortion associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

Coal tar creosote was tested for estrogenic activity using both *in vivo* and *in vitro* assays with inconclusive results (Fielden et al. 2000). Results from the *in vitro* tests showed that creosote binds both the estrogen receptor (ER) and the human sex hormone-binding globulin (SHBG), and can induce ER-mediated gene expression. However, *in vivo* assays using ovariectomized DBA/2 mice and ICR mice gavaged with 0, 10, 50, or 100 mg/kg creosote in sesame oil or 0.1 mg/kg 17α-ethynylestradiol (positive control) once a day for 4 days were negative. Treatment with 17α-ethynylestradiol produced a significant increase in uterine weight and vaginal cell cornification compared with animals receiving only sesame oil, but no significant increase in uterine weight or vaginal cell cornification was observed in animals treated with creosote. The study authors also tested the ability of creosote to induce gene expression via the AhR in Hepa 1c1c7 cells, to induce CYP1A1 and CYP2B10 in liver microsomes, and to interact with the estrogen-inducible/dioxin-suppressible pS2-Luc reporter gene. Creosote induced gene expression via the AhR and increased the activity of CYP1A1 and CYP2B10, but although treatment of cells expressing the pS2-Luc reporter gene with increasing concentrations of creosote produced a dose-dependent increase in activity, no consistent inhibition of E2-induced activity in these cells was noted. The AhR in DBA/2 mice is known to be much less responsive to PAHs than that of ICR mice; however, estrogenic effects of creosote were not observed in either strain and the authors concluded that although creosote has the

potential to interact with the endocrine system, it does not appear to be sufficiently potent to produce an effect in this assay.

There is evidence from some animal studies that exposure to coal tar has adverse effects on reproductive success, but these effects are likely to be due to fetotoxicity or maternal toxicity rather than maternal endocrine disruption, and other studies have found no adverse effects. A significant decrease in number of live fetuses/litter and the number of resorptions was observed in female rats gavaged with 370 mg/kg/day coal tar on gestational days 12–16, but no significant difference in the number of live births was observed in female rats gavaged with 740 mg/kg/day coal tar on gestational days 12–14 (Hackett et al. 1984; Springer et al. 1986a). Dermal exposure of rats and mice to 500 or 1,500 mg/kg coal tar on gestational days 11–15 resulted in significant increases in prenatal mortality in all exposed rat fetuses and high dose mice fetuses compared to controls (Zangar et al. 1989). Early resorptions (occurred before dosing) were similar in all groups, but middle resorptions (which corresponded to the dosing period) were significantly increased in exposed rats and high dose mice. Late resorptions were also significantly increased in exposed rats. No adverse effects on reproductive indices were reported by Iyer et al. (1993) after oral exposure of mice to coal tar creosote in DMSO on gestation days 5–9. A similar lack of effect on reproductive organs was observed by Weyand et al. (1994) after oral exposure of mice to MGP residue, a form of coal tar, for 185 days.

There have been some reports of adverse effects of creosote on the reproductive organs of animals, but these are largely confined to changes in organ weight and several other studies have found no effect. Relative ovary weights were significantly decreased in rats and mice exposed to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Testis weight in rats exposed to 140 and 690 mg/m^3 coal tar was significantly increased relative to controls, while testis weight in male mice exposed to 690 mg/m^3 coal tar was decreased relative to controls, but the difference was not significant. Examination of ovarian sections showed a decrease in the amount of luteal tissue in animals exposed to 690 mg/m^3 coal tar. Dermal exposure of rats and mice to 500 or 1,500 mg/kg coal tar on gestational days 11–15 resulted in significant decreases in uterine weight (Zangar et al. 1989).

Adverse effects in other endocrine organs are limited to a few reports of weight changes in the adrenal glands. An increase in adrenal weight was observed in rats gavaged on gestational days 12–16 with 90 mg/kg/day coal tar (Hackett et al. 1984). However, other studies of coal tar creosote have shown no effect on the adrenal glands (Iyer et al. 1993; Springer et al. 1986b, 1987; Zangar et al. 1989).

There is some evidence that certain PAHs, (e.g., benzo[a]pyrene) may act as endocrine disruptors (Agency for Toxic Substances and Disease Registry 1995); however, without data regarding possible synergistic or antagonistic effects, it is not known whether these individual compounds have similar effects when incorporated into a complex mixture such as coal tar creosote. For more information on the health effects of these compounds, the reader can refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995).

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth

and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

The effects of creosote have not been thoroughly studied in children, but they would likely experience the same health effects seen in adults exposed to creosote. The pharmacokinetics of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles have not been defined because of their chemical complexity. Creosotes vary tremendously in composition and hence, mechanisms of action most likely differ among individual samples of creosotes. Information on individual components is not adequate to define the properties of the whole mixture and for this reason no PBPK models have been developed for creosote. Individual components of creosote are metabolized by several different enzyme systems including phase I (cytochrome P450 isozymes, AHH, epoxide hydrolase) and phase II (glutathione-S-transferases, glucuronidases, phenol sulfotransferase, and glucuronyltransferase). Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. The relative activity of metabolic enzymes may also vary with the age of the individual, which will again affect the relative toxicity of particular components of creosote for old or young individuals. For instance, several cytochrome P450 isozymes are known to be absent or expressed at very low levels in the developing human fetus while glucuronyl transferases and sulphotransferases do not reach adult levels until 1–3 years of age (Leeder and Kearns 1997).

Creosote Bush. No information was located pertaining to adverse health effects in children or young animals from the creosote bush. There are very few data on human exposure to the creosote bush. Case

reports of people who drank chaparral tea indicate kidney damage as a likely outcome (Gordon et al. 1995), while dermal exposure to the creosote bush may cause skin irritation (Leonforte 1986; Smith 1937).

Wood Creosote. No information was located pertaining to adverse health effects in children or young animals from wood creosote. There are very few data on human exposure to wood creosote. Ingestion of beechwood creosote exacerbates chronic nephrosis in rats (Miyazato et al. 1984b), and dermal exposure to beechwood creosote may cause skin irritation (Attalla 1968). These studies suggest that dermal contact with creosote from toxic waste sites could cause skin irritation.

No reports of adverse developmental effects on humans or animals after exposure to wood creosote were found in the literature.

Coal Tar Products. Only one study was located that examined effects of exposure to coal tar creosote in children (Agency for Toxic Substances and Disease Registry 1994). This was a survey of inhabitants of a housing development that had been built on part of an abandoned creosote wood treatment plant. In this study, increased incidence of skin rashes compared to unexposed controls was the only health effect reported in children (less than 11 years of age) exposed to coal tar creosote. The incidence of rashes in different age groups varied, but did not show any definite trend.

Data from studies of adult humans occupationally exposed to coal tar creosote indicate that cancer is likely to be the most severe adverse effect of coal tar exposure, although there is also evidence of skin and eye irritation (see Chapter 2 and Section 3.2 for more details). Studies of animals after inhalation, oral, or dermal exposure to coal tar creosote confirm cancer as a likely outcome of coal tar exposure and suggest that there may also be adverse effects to the lungs, liver, spleen, thymus, skin, and eyes (see Chapter 2 and Section 3.2 for more details). However, the concentrations of coal tar used in animal studies are higher than could be expected from proximity to a hazardous waste site and so it is not clear how relevant some of these systemic effects are to children. Children exposed to creosote will probably have a longer potential latency period and may therefore be at greater risk of developing cancer from these substances than individuals exposed as adults.

No reports of adverse developmental effects on humans after exposure to coal tar were found in the literature. No adverse developmental outcomes were detected in a survey of inhabitants of a housing development built on an abandoned creosote factory site, which was known to be contaminated with creosote (Agency for Toxic Substances and Disease Registry 1994). A retrospective study of dermal

exposure to coal tar found no increased risk of birth defects associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

A series of studies (Hackett et al. 1984; Springer et al.1982, 1986a; Zangar et al. 1989) have demonstrated serious developmental toxicity for rats and mice exposed to coal tar. However, some evidence of maternal toxicity in the form of reduced body weight gain and changes in organ weights was also observed for animals treated with doses of coal tar producing developmental toxicity (Hackett et al. 1984; Iyer et al. 1993; Springer et al. 1986a). Treatment of pregnant rats with coal tar by all routes of exposure produces reduced growth (reduced crown-rump length and delayed ossification) of the offspring, and an increase in the incidence of cleft palates and small lungs (Hackett et al. 1984; Springer et al. 1982, 1986a; Zangar et al. 1989). Dermal exposure of pregnant mice to coal tar produces an increase in the incidence of cleft palates dilated ureters and renal pelvic cavitation (Zangar et al. 1989). Zangar et al. (1989) carried out a comparison of the doses producing significant developmental effects in rats (Hackett et al. 1984; Springer et al. 1982; Zangar et al. 1989) and concluded that inhalation may be the most effective route for induction of developmental toxicity, followed by the oral and dermal routes, in that order. However, the authors noted that inhalation dosimetry is more difficult to calculate accurately due to unknown contributions from the oral and dermal routes.

Adverse perinatal effects of coal tar creosote were reported for a study in pigs (Schipper 1961). Farrowing sows housed in cages treated with coal tar creosote had an increase in the number of stillborn piglets compared to control animals farrowing in untreated cages. The surviving piglets were dehydrated, with rough skins and severe diarrhea. Weight gain of the surviving piglets was reduced until the animals were 5–6 weeks old. One-week-old pigs were reported to have a greater tolerance to creosote than newborn animals, suggesting that more mature animals may be less sensitive to some of the effects of coal tar. However, the results of this study are severely limited by lack of exposure data, unequal duration of exposure between treated and untreated groups, and the lack of statistical analysis of the results.

Adverse developmental effects due to coal tar were also seen in a chick embryotoxicity screening test (CHEST) (Mayura et al. 1999). Injection of coal tar (dissolved in corn oil and 0.5% DMSO) into the yolks of 4-day-old chicken eggs produced a dose-dependant increase in embryo mortality. Doses greater than 0.5 mg/kg coal tar produced 100% mortality, 0.25 mg/kg produced 55% mortality, 0.125 mg/kg produced 20% mortality, and 0.0625 mg/kg produced 5% mortality. The main exposure-related abnormalities noted were liver lesions, discoloration of the liver, and edema.

Coal tar exposure produces developmental toxicity in rats and mice, and may also do so in pigs. However, the developmental risk to humans of exposure to coal tar is less clear. The doses that produced developmental toxicity in animals were relatively high and are unlikely to be attained through environmental exposure in the vicinity of toxic waste sites. However, some evidence for species sensitivity exists and the possibility of developmental toxicity in humans from coal tar exposure cannot be discounted.

Data suggest that the PAHs found in coal tar creosote produce developmental toxicity and that children may be more susceptible to the adverse effects of these compounds, but it is not clear whether PAHs that form part of the complex mixture of coal tar creosote will have the same effects as PAHs studied alone. For more information on the health effects of these compounds, the reader can refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995).

Coal tar is composed of hydrocarbons, which are lipophilic substances and are therefore likely to distribute to lipid-rich tissues (Agency for Toxic Substances and Disease Registry 1995). For instance, PAHs and their metabolites are known to cross the placenta (Agency for Toxic Substances and Disease Registry 1995) and have been detected in human breast milk (Madhavan and Naiduka 1995). A study of the distribution of intratracheally administered radioactive benzo[a]pyrene mixed with a benzene extract of coal fly ash in pregnant rats found that a small proportion of the radioactivity was distributed to the fetal lung and liver and to the placenta (respectively 1.9, 1.4, and 4% of the amount in maternal lung).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to creosote are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by creosote are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Creosote

Wood Creosote. No method is currently available to measure the parent wood creosote mixtures. However, phenols can be measured in the urine after exposure to wood creosote (Ogata et al. 1995). Male volunteers were given 133 mg of wood creosote in a capsule, followed by 200 mL water. Urine samples were collected at various time intervals. Phenol, guaiacol, *p*-cresol, and cresol were detected in the urine.

Coal Tar Products. No method is currently available to measure the parent creosote mixture and other coal tar products in human tissues or fluids. However, individual components of the mixture can be measured. Urinary naphthols have been shown to be accurate biomarkers of naphthalene exposure during tar distillation or impregnation of wood with coal tar creosote (Bieniek 1997; Heikkilä et al. 1997). PAH components of the creosote mixture and their metabolites can also be measured in the urine of exposed individuals (Bickers and Kappas 1978; Bos and Jongeneelen 1988; Bowman et al. 1997; Cernikova et al. 1983; Clonfero et al. 1989; Diette et al. 1983; Elovaara et al. 1995; Grimmer et al. 1997; Hansen et al. 1993; Heikkilä et al. 1995; Jongeneelen et al. 1985, 1988; Malkin et al. 1996; Ny et al. 1993; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995; Viau et al. 1995; Weston et al. 1994). For example, Jongeneelen et al. (1985) found a metabolite of pyrene (which is a constituent of coal tar creosote), 1-hydroxypyrene, in concentrations of 1–40 μg/g creatinine in urine samples taken from workers who handled approximately 2,400 g creosote/day. The amount of 1-hydroxypyrene detected in urine samples taken during the weekend was less than that detected during the weekdays, when the exposure was presumably higher than on the weekends. No correlation was found between occupational exposure levels and urine levels, so it is not known whether urine metabolites could be detected following exposure to low levels of creosote. However, in another study, workers exposed to coal tar while asphalting roads with coal tar excreted 1-hydroxypyrene in their urine (Jongeneelen et al. 1988). In these workers, occupational exposure appeared to be related to the amount of 1-hydroxypyrene in the urine. The identification of 1-hydroxypyrene in the urine could serve as a method of biological monitoring of exposed workers, and possibly individuals living in the vicinity of hazardous waste sites where creosote has been detected following both short-and long-term exposure. However, because PAHs are ubiquitous in the environment, detection of PAH metabolites in the body tissues or fluids is not specific for exposure to creosote. PAH exposure can occur from a variety of sources, and there is no way to determine if creosote was the source.

PAHs form DNA adducts that can be measured in body tissues or blood following exposure to creosote that contains PAHs (Culp and Beland 1994; Pavanello and Levis 1994; Schoket et al. 1990; Zhang et al.

1990). These PAH-DNA adducts are not specific for coal tar creosote, and the adducts measured could have been from exposure to other sources of PAHs.

3.8.2 Biomarkers Used to Characterize Effects Caused by Creosote

Coal Tar Products. The available genotoxicity data derived by *in vitro* techniques indicate that coal tar products such as coal tar creosote and coal tar pitch are indirect mutagens (i.e., requiring the presence of an exogenous mammalian metabolic system) and induce gene mutation in bacteria and mouse lymphoma cells. The mutagenicity of creosote and coal tar pitch observed in the conventional *S. typhimurium* assay is at least partially contributed to by the PAHs such as B[a]P and benzanthracene. However, because these results are exclusively from *in vitro* tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to creosote have been negative, or have been positive in instances where exposure to other mutagens may have occurred, these changes cannot be considered specific biomarkers of effects caused by creosote, nor is it possible to determine whether the genotoxic effects result from either acute or chronic exposure to either low or high levels of coal tar creosote because all of the data were from *in vitro* studies. The same can be said for determination of chromosomal aberrations in peripheral lymphocytes from exposed humans (Bender et al. 1988; Sarto et al. 1989). Furthermore, because the mutagenicity of coal tar creosote is at least partially due to its PAH components, exposure to PAHs from other sources could produce the same results. Coal tar creosote exerts its acute toxic effects primarily via dermal exposure, causing architectural damage to the tissues with which it comes in contact. Therefore, burns and irritation of the skin and eyes are the most frequent manifestations of coal tar creosote toxicity following acute dermal exposure to high levels. However, damage to the skin is not specific to creosote, and can be seen with other corrosive or photosensitizing agents. No other biomarkers (specific or otherwise) have been identified following exposure to coal tar creosote.

For more information on biomarkers for renal and hepatic effects of chemicals, see Agency for Toxic Substances and Disease Registry/Centers for Disease Control and Prevention (1990) and for information on biomarkers for neurological effects, see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Coal Tar Products. The primary interactions known to occur between coal tar creosote and other substances involve the induction of cancer. Coal tar creosote is a complex mixture of organic substances consisting predominantly of liquid and solid aromatic hydrocarbons. Several of these components of coal tar creosote are known animal carcinogens as well as cocarcinogens, initiators, promoters, potentiators, or

inhibitors of carcinogenesis. Pretreatment of male Fischer 344 rats with orally administered coal tar creosote resulted in urinary excretion of mutagenic metabolites of creosote, and increased the bioactivation of orally administered 2,6-DNT to mutagenic metabolites, as measured in the Ames assay. Urinary excretion of mutagenic metabolites from rats pretreated with creosote and dosed with DNT at 1, 3, and 5 weeks peaked after 3 weeks and then declined by 33% after 5 weeks of treatment. The increase in urinary excretion of mutagenic metabolites was significantly greater than in rats that received only DNT at weeks 1 and 3, but not at week 5 (Chadwick et al. 1995).

As discussed in Section 3.2.3.7, coal tar creosote and several of its fractions are carcinogenic when applied to the skin of mice. Dermally applied creosote can also act as a tumor-initiating agent when applied prior to croton oil treatment, and can enhance and accelerate tumor induction by B[a]P. Thus, the risk of cancer following dermal exposure to creosote is likely to be enhanced when concurrent exposure to other potential co-carcinogens, tumor promoters, initiators, and potentiators occurs. Due to the ubiquitous nature of PAHs and other carcinogenic substances in the environment, particularly at hazardous waste sites, the likelihood that these types of synergistic interactions with creosote will occur could be important in assessing potential hazards.

Another effect of coal tar creosote exposure that could be affected by interaction with other chemicals is photosensitivity. Certain pharmaceutical agents (e.g., tetracycline) that, in and of themselves, cause photosensitivity whose action may be synergistic with that of coal tar creosote or coal tar.

Pentachlorophenol and arsenical compounds are also used in wood preserving. For this reason, it is likely that they will be found with creosote at hazardous waste sites. However, there is no information available on the potential interactions of creosote with pentachlorophenol or arsenical compounds.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to creosote than will most persons exposed to the same level of creosote in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of creosote, or compromised function of organs affected by creosote. Populations who are at greater risk due to their unusually high exposure to creosote are discussed in Section 6.7, Populations With Potentially High Exposures.

Coal Tar Products. Data indicate that some populations may be at increased risk of developing skin cancer following prolonged dermal exposure to industrial grade coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles. The results of earlier occupational studies (Henry 1946, 1947), case reports (Cookson 1924; Lenson 1956; O'Donovan 1920), and experimental animal studies (Boutwell and Bosch 1958; Poel and Kammer 1957; Roe et al. 1958) indicate that prolonged dermal exposure to coal tar creosote may increase the risk of developing skin cancer. This risk may be increased for people with skin damaged from excessive sun exposure, disease, or exposure to other substances that potentiate the carcinogenic effect of coal tar creosote (Lenson 1956; Lijinsky et al. 1957; Sall and Shear 1940; TOMA 1979, 1981).

There is limited evidence, based on animal studies and the known health effects of the PAH constituents of coal tar creosote, that additional subsections of the population may be susceptible to the toxic effects of creosote. These include people with pre-existing respiratory, kidney, or liver disease. People with deficient immune systems may also be at high risk of developing adverse health effects due to exposure to carcinogens, such as PAHs (Stjernsward 1966, 1969; Szakal and Hanna 1972). Another potentially susceptible group are those individuals with the genetic trait of inducible AHH, one of the mixed function oxidases. When this enzyme is induced, the rate at which aryl compounds, such as PAHs, are biotransformed into toxic intermediates is increased, rendering these individuals at higher risk. It has been proposed that genetically expressed AHH inducibility is related to the development of bronchogenic carcinoma in persons exposed to PAHs contained in tobacco smoke. Approximately 45% of the general population are considered to be at high risk, and 9% of the 45% are considered to be at very high risk of developing bronchogenic carcinoma following exposure to PAHs (Calabrese 1978). These percentages were estimated from the population frequency of genetically controlled AHH induction (Calabrese 1978). Individual components of creosote are metabolized by several different enzyme systems including phase I (cytochrome P450 isozymes, AHH, epoxide hydrolase) and phase II (glutathione-S-transferases, glucuronidases, phenol sulfotransferase, and glucuronyltransferase) enzymes. Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. These enzymes are also known to have age-dependant expression and susceptibility may therefore vary with the age of the individual. However, no studies were located that addressed differential susceptibility of children to the effects of creosote. A detailed discussion of children's susceptibility can be found in Section 3.7.

Coal tar exposure produces developmental toxicity in rats and mice, and may also do so in pigs. However, the developmental risk to humans of exposure to coal tar is less clear. The doses that produced developmental toxicity in animals were relatively high and are unlikely to be attained through

environmental exposure in the vicinity of toxic waste sites. However, some evidence for species sensitivity exists and the possibility of developmental toxicity in humans due to coal tar exposure cannot be discounted and the human fetus may be another susceptible population.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to creosote. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to creosote. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to creosote:

Ellenhorn MJ, ed. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. New York, NY: Elsevier Publishing.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: WB Saunders.

Viccellio P, Bania T, Brent J, et al., eds. 1998. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to creosotes and coal tar mixtures generally means an exposure to a combination of large molecular toxins (including PAHs) and more immediately chemically reactive phenolic chemicals. The phenolic components act as direct caustic agents to skin, mucosa, and cornea, causing burns and scarring. The tars are photosensitizers and potential DNA-combining agents with different and latent clinical consequences, including cancer. Exposure to these compounds may occur via ingestion and direct liquid application. Although relatively nonvolatile, tar absorption following inhalation exposure to mists can occur through mucocilliary trapping and transport followed by gastrointestinal absorption.

The suggested emergency management of direct cutaneous exposure to creosote is prompt and comprehensive decontamination (Haddad et al. 1998). Treatment commonly includes removal of all contaminated clothing and washing of the skin, hair, and nails with large volumes of soapy water. It is recommended that those administering the treatment wear rubber gloves for their own protection. In order to reduce dermal irritation from creosote-contaminated soil and water, limited exposure, through the

wearing of protective clothing, and immediate washing of exposed skin were the recommendations of the Texas Department of Health to residents of a housing development built on an abandoned creosote factory site (Agency for Toxic Substances and Disease Registry 1994).

The treatment to manage exposure from ingestion also focuses on the acute effects of the phenolic and PAH components. Phenolic compounds cause corrosive esophageal burns and there may also be a risk of causing pneumonitis in the patient by aspiration of PAHs in coal tar derivatives, so emesis is contraindicated as a means of elimination (Agency for Toxic Substances and Disease Registry 1995; Haddad et al. 1998). Activated charcoal has been used as a treatment to reduce absorption of hydrocarbons such as PAHs, however, its efficacy is not documented by clinical studies and it could potentially interfere with endoscopic examination of the gastrointestinal tract (Viccellio et al. 1998). Gastric lavage with olive oil avoids the dangers of additional esophageal damage while eliminating the phenols from continued mucosal contact and may be the preferred method of removing creosote, particularly if a substantial amount has been ingested (Haddad et al. 1998; Viccellio et al. 1998).

The treatment for contaminated eyes commonly includes irrigation with copious amounts of room temperature water, or saline if available, for at least 15 minutes. If irritation, lacrimation, or especially pain, swelling, and photophobia persist after 15 minutes of irrigation, it is recommended that an ophthalmologic examination be performed. Phenol burns are more corrosive than organic acids in damaging corneal tissue and delaying recovery.

Should an inhalation exposure occur, treatment commonly includes moving the exposed individual to fresh air and monitoring for respiratory distress. Injuries to the lungs are more likely when there is severe upper respiratory irritation and persistent cough. Emergency airway support and 100% humidified supplemental oxygen with assisted ventilation may be needed.

3.11.2 Reducing Body Burden

Most of the damage relating to the phenolic components in creosote and coal tar is immediate and requires no specific chronic management. It is recommended that mucosal surfaces be evaluated for possible scarring (especially the esophagus or cornea) if exposure was directly injurious. As with other ingested or inhaled PAHs (e.g., from combustion products like cigarette smoke), there are no documented means to enhance elimination of coal tars.

With regard to the possible absorption of the PAH component of coal tar creosote or other coal tar products, there are no known ways of reducing the body burden of PAHs. Data from acute-duration studies in animals indicate that PAHs are rapidly metabolized and eliminated in the urine and feces within days. No data are available to describe possible bioaccumulation after chronic exposure. Since PAHs are lipid soluble, however, it is possible that some accumulation could occur in the tissue fat.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Coal tars produce photosensitivity and photoreactive dermatitis when applied to the skin (Hathaway et al. 1991) even in areas not usually exposed to direct sunlight (e.g., beneath the chin). It is recommended that patients be cautioned about sun exposure and the need for appropriate clothing several days after exposure, to prevent accelerated sunburning. These agents are physically heavy oils and are known to be both irritating and comedogenic (Amdur et al. 1991), so physical sun barriers are preferred to chemical sun screens or oils.

Phenols can produce a "lightening" effect on cutaneous coloration (TOMES 1994) with depigmentation and vitiligo. This is seen most commonly with repeated cutaneous application, but can also follow cutaneous burns. Sun exposure magnifies the evidence of this process and should be avoided. Most patients with chemical vitiligo recover with normal skin color returning after several months.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of creosote is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of creosote.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Creosote

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to creosote are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of creosote. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989c), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-6. Existing Information on Health Effects of Creosote

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●	●	●	●			●	●	●	●
Oral	●	●	●	●	●	●				●
Dermal	●	●	●	●	●	●	●	●	●	●

Human

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●	●	●	●						●
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●	●	●	●	●			●	●	●

Animal

● Existing Studies

The database for the health effects of both wood creosote and coal tar products in experimental animals is inadequate, and consists primarily of acute lethality studies or early animal studies that would be considered inadequate by current standards. The systemic effects of ingested creosote have only been well described for beechwood creosote, although some studies exist for coal tar products. Little information is available on the effects of coal tar creosote following inhalation exposure. However, dermal exposure of mice to coal tar creosote and other coal tar products has been shown in numerous studies to induce skin tumors and, in two cases, lung tumors, while oral exposure has induced tumors in the lung, liver, and forestomach. Since coal tar creosote is a complex mixture consisting primarily of PAHs, the toxic effects of coal tar creosote may be inferred from available information on these constituents. However, given the fact that many of these constituents are known cocarcinogens, initiators, promoters, and potentiators of carcinogenesis, the possibility for the occurrence of synergistic interactions in creosote cannot be ruled out. Thus, information on the toxicity of the various components of coal tar creosote cannot take the place of sound data on the toxic effects of the creosote mixture itself. This can also be assumed to be true for the other coal tar products. An additional factor to be considered when reviewing the database for creosote is the effect of weathering. When creosote is released into the environment, weathering produces rapid changes in chemical composition (see Section 6.3). Thus, although data on toxic effects of unweathered creosote would be useful for individuals who are occupationally exposed to creosote, it is not clear how useful such data will be for individuals undergoing environmental exposure to weathered creosote.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information is available on the effects of oral and dermal acute-duration exposures to wood creosotes (Miyazato et al. 1981; Ogata et al. 1993, 1999) and coal tar products (Hackett et al. 1984; Iyer et al. 1993; Mahlum 1983; Pfitzer et al. 1965; Springer et al. 1986a, 1989; Wrench and Britten 1975; Zangar et al. 1989) in humans and animals. However, there are few well-conducted animal or human studies describing health effects following inhalation exposure (Emmett 1986; Springer et al. 1982). The type of information available includes primarily LD_{50} values and data on acute toxicity in animals (coal tar products and beechwood creosote), and acute toxicity following accidental or intentional ingestion or dermal exposure in humans (coal tar creosote and other coal tar products). Coal tar creosote exerts its acute toxic effects primarily via dermal exposure, causing architectural damage to the tissues with which it comes in contact, such as the skin and eyes. Acute ingestion of coal tar creosote appears to affect primarily the kidney and liver. Thus, the toxic effects of coal tar creosote on the skin following single-dose dermal exposure in humans are well characterized, but little else is known regarding the systemic effects of this form of creosote in either humans or animals.

The available information is insufficient to derive either an acute oral or inhalation MRL for coal tar creosote or other coal tar products because human reports that identified target organs lacked exposure information, and no short-term animal studies exist that describe effects other than death or developmental defects. Identification of target organs from short-term animal studies following oral and dermal exposure would be useful in assessing the risk associated with the acute ingestion or skin contact with coal tar creosote-contaminated water or soils by humans. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it is impossible to predict effects following exposure by one route based on effects observed following exposure by another route.

Intermediate-Duration Exposure. Information is available on the effects of intermediate-duration dermal exposures to coal tar in humans (Franssen et al. 1999; Jones et al.1985; Menter and Cram 1983; Torinuki and Tagami 1988) and the effects of intermediate-duration exposures to beechwood creosote (oral) (Miyazato et al. 1981) and coal tar creosote (oral and dermal) in animals (Boutwell and Bosch 1958; Chadwick et al. 1995; Culp and Beland 1994; Kligman and Kligman 1994; Wallcave et al. 1971; Weyand et al. 1991, 1994, 1995). However, there are few well-conducted animal studies describing the health effects of inhalation exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles (Heinrich et al. 1994a, 1994b; MacEwen et al. 1977; Sasser et al. 1989; Springer et al. 1986b, 1987). The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from anecdotal case reports rather than controlled epidemiological studies. The animal studies with beechwood creosote describe predominantly hepatic and renal end points, and those conducted with coal tar creosote describe dermal, hepatic, renal, hematological, and respiratory end points. Little or no in depth information on respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in animals is available. The available information is insufficient to derive either an intermediate oral or inhalation MRL for coal tar creosote or other coal tar products because no intermediate-duration human or animal studies exist that describe adverse effects other than on the skin. Given the widespread use of coal tar creosote as a wood preservative, and the fact that beechwood creosote is rarely used today, more information on the systemic effects of intermediate-duration exposures to coal tar creosote and other coal tar products by the oral and dermal routes (by conducting 90-day intermediate toxicity studies) would be useful to identify target organs in animals in order to assess the risk associated with the intermediate-duration ingestion of, or skin contact with, coal tar creosote-contaminated water or soils by humans. Since coal tar products give off volatile components, studies of inhalation exposure to these compounds would also be useful. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different

routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Chronic-Duration Exposure and Cancer. Some information is available on the effects of chronic-duration dermal exposures to coal tar creosote and other coal tar products in humans (Cookson 1924; Goulden and Stallard 1933; Henry 1946, 1947; Lenson 1956; Mackenzie 1898; O'Donovan 1920; Shambaugh 1935; Shimauchi et al. 2000) and the effects of chronic-duration exposures to beechwood creosote (oral) (Miyazato et al. 1984b) and coal tar creosote (dermal) in animals (Niemeier et al. 1988; Poel and Kammer 1957). However, there are few well-conducted animal studies describing the health effects of chronic oral or inhalation exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles (Culp et al. 1996a, 1996b, 1998; Heinrich et al. 1994a, 1994b; MacEwen et al. 1977). The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from anecdotal case reports rather than controlled epidemiological studies. The animal studies with beechwood creosote describe predominantly hepatic and renal end points, and those conducted with coal tar creosote describe dermal, but very rarely other systemic effects. Little or no reliable information on respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in animals is available. The available information is insufficient to derive either a chronic oral or inhalation MRL for coal tar creosote because no chronic-duration human or animal studies exist that describe effects other than on the skin. Given the widespread use of coal tar creosote as a wood preservative, and the fact that beechwood creosote is rarely used today, more information on the systemic effects of chronic-duration exposures to coal tar creosote by the oral and dermal routes would be useful to identify target organs in animals in order to assess the risk associated with the chronic-duration ingestion of, or skin contact with, coal tar creosote-contaminated water or soils by humans. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Various case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote exposure with the development of skin cancer (Cookson 1924; Goulden and Stallard 1933; Henry 1947; Lenson 1956; Mackenzie 1898; O'Donovan 1920; Shambaugh 1935; Shimauchi et al. 2000). More recent cancer epidemiological studies and surveys of the literature help to fill in data gaps, but are retrospective, and often fail to provide exact information concerning exposure (Franssen et al. 1999; Liu et al. 1997; Pittelkow et al. 1981; TOMA 1982). Several skin painting studies

have been conducted in animals using coal tar creosote and its various fractions (Cabot et al. 1940; Deelman 1962; Emmett et al. 1981; Hueper and Payne 1960; Lijinsky et al. 1957; Mahlum 1983; Niemeier et al. 1988; Wallcave et al. 1971; Watson and Mellanby 1930). Although some of these studies would be considered inadequate by current standards, the results nevertheless indicate that coal tar creosote and its constituents can induce skin tumors as well as act as tumor initiators and promoters. Carcinogenicity studies conducted with beechwood creosote by the oral route, found no evidence of cancer in mice (Miyazato et al. 1984a, 1984b). However, oral cancer bioassays with coal tar in mice found a significant incidence of liver, lung, and forestomach tumors (Culp et al. 1996a, 1998; Weyand et al. 1995). More information on the carcinogenic potential of chronically ingested coal tar creosote (e.g., an oral bioassay in rats) would be useful. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., skin tumors following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Genotoxicity. The genotoxic potential of coal tar creosote has been investigated almost exclusively using *in vitro* assays (Agurell and Stensman 1992; Baranski et al. 1992; Bos et al. 1983, 1984b, 1984c, 1985, 1987; Donelly et al. 1993, 1996; Kesik and Janik-Spiechowicz 1997; Machado et al. 1993; Mayura et al. 1999; Reeves et al. 2001; Simmon and Shepherd 1978) and animal tissues (Chadwick et al. 1995; Ericson et al. 1998, 1999; Weyand et al. 1991) although some evaluations of chromosomal aberrations in peripheral lymphocytes and DNA adducts in skin and other tissues have been conducted in humans (Pavanello and Levis 1992, 1994; Yadav and Seth 1998; Zhang et al. 1990). The limited genotoxicity tests that have been conducted on urine obtained from humans exposed to creosote had varied results. The available data indicate that creosote is an indirect mutagen and induces gene mutation in bacteria and mouse lymphoma cells. However, a substantial database exists on the genotoxic effects of the PAHs found in the creosote mixture. More *in vivo* assays using human tissues with coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, or specific components of these mixtures, would be useful to more completely characterize the genotoxic potential of these mixtures.

Reproductive Toxicity. Little information on the reproductive effects of coal tar creosote in humans or animals is available. One epidemiological study in humans indicates no reproductive hazard from exposure through environmental contamination (Agency for Toxic Substances and Disease Registry 1994) and another indicated no increased risk of spontaneous abortion from the use of coal tar as a dermal treatment for psoriasis during pregnancy (Franssen et al. 1999). However, animal studies have shown that exposure to coal tar causes increased resorptions, decreased ovary weights (with a loss of luteal tissue),

and increased testis weights in mice and rats (Hackett et al. 1984; Springer et al. 1982, 1986b, 1987). An increase in relative testis weight was also observed in rats administered beechwood creosote in the diet for 3 months (Miyazato et al. 1981). There were no accompanying gross or histopathological lesions of the testes in these animals, so the toxicological significance of this change is not known. Given the widespread potential for exposure to coal tar creosote, and industrial exposure to other coal tar products, and the indication from animal studies that creosote may be a reproductive toxicant, multi-generation reproductive toxicity studies should be conducted by the oral and dermal routes of exposure. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since coal tar has been shown to produce reproductive toxicity in animals by the oral, dermal, and inhalation routes, it appears that reproductive toxicity may not be route-dependent.

Developmental Toxicity. Information on the developmental effects of creosote in humans was not found. Studies have demonstrated serious developmental toxicity for rats and mice exposed to coal tar by all routes, including reductions in fetal ossification, crown-rump length, fetal weight, fetal lung weight, and placental weights (Springer et al. 1982), a significant increase in the incidence of cleft palate (Hackett et al. 1984), increased early mortality in pups of treated dams (Springer et al. 1986a), and significant increases in prenatal mortality in exposed rat and mouse fetuses (Zangar et al. 1989).
In many of these studies, it is not possible to exclude the potential role of maternal toxicity in the development of adverse fetal effects. It would be useful to carry out studies to explicitly evaluate the role of maternal toxicity in the development of creosote-induced adverse developmental effects. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since coal tar has been shown to produce developmental toxicity in animals by the oral, dermal, and inhalation routes, it appears that developmental toxicity may not be route-dependent.

Immunotoxicity. The only available information on the immunological effects of creosote in humans describes the occurrence of acute allergic dermatitis following exposure to creosote bush resin (Leonforte 1986; Smith 1937) and coal tar (Cusano et al. 1992). Animal studies have provided evidence of weight and morphological changes in lymphoreticular tissues following exposure to coal tar (Hackett et al. 1984; Zangar et al. 1989), but no information regarding associated changes in the immune system have been reported. The relevance of these findings to human exposure to creosotes is not known. However, these data are suggestive of possible immunotoxic effects. Immunotoxicity studies of coal tar creosote, coal tar, and coal tar pitch by inhalation and dermal routes and studies of wood creosote by inhalation, oral, and dermal routes would fill the data needs for these mixtures.

Neurotoxicity. The available information about the possible neurotoxic effects of creosote is very limited, but some signs of neurological involvement in humans and animals following exposure to beechwood creosote and creosote bush (Gordon et al. 1995; Miyazato et al. 1981) and coal tar (Hanlon 1938; NIOSH 1980b) have been described. These effects were generally excitatory in nature (e.g., convulsions). No reliable data are available on the short-term neurotoxic effects of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatile exposure by the inhalation, oral, or dermal routes, or long-term neurotoxic effects of low-level exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles by the inhalation, oral, or dermal routes in humans or animals. Reports of individuals exposed to creosote suggest that neurotoxicity (e.g., dizziness, altered vision, etc.) may be an early sign of toxic exposure to creosote. Short-term and long-term neurotoxicity studies in animals, using sensitive functional and neuropathological tests, and exposure by the inhalation, oral and dermal routes would be useful in determining if coal tar creosote is a neurotoxic agent.

Epidemiological and Human Dosimetry Studies. Few controlled epidemiological studies have been conducted in humans on the effects of exposure to coal tar creosote. In particular, epidemiological studies of workers in creosote treatment plants accompanied by accurate occupational exposure data would be useful to more fully assess the risk of inhalation and dermal exposure to coal tar creosote. Most of the available information on the effects of coal tar creosote in humans comes from occupational studies in the wood-preserving and construction industries (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Kerr et al. 2000; Lloyd 1971; Lloyd et al. 1970; Martin et al. 2000; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg and Andersen 1995; Sakabe et al. 1975; Spinelli et al. 1991; Stern et al. 2000; TOMA 1982; Tremblay et al. 1995). Limitations inherent in these studies include unknown exposure concentrations and durations, as well as concomitant exposure to other potentially toxic substances. The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short follow up periods, and brief exposure periods. Despite their inadequacies, studies in humans suggest that coal tar creosote is a dermal irritant and a carcinogen following dermal exposure. Only one epidemiological study of people living in close proximity to a coal tar creosote-contaminated area was found in the literature (Agency for Toxic Substances and Disease Registry 1994). Additional well-controlled epidemiological studies of people with documented exposure to creosote, living in close proximity to areas where coal tar creosote has been detected in surface and ground water, or near hazardous waste sites, and of people occupationally exposed to creosote could add to and clarify the existing database on creosote-induced human health effects. Particular health effects that should be examined in future studies include cancer,

developmental, reproductive, immunotoxic, and neurotoxic effects as well as adverse noncancer dermal effects.

Biomarkers of Exposure and Effect.

Exposure. No method is currently available to measure the parent creosote mixture in human tissues or fluids. However, 1-hydroxypyrene, the metabolite of pyrene, a component of the creosote mixture, can be measured in the urine of exposed individuals following relatively high-level exposures of acute and chronic duration (Bos and Jongeneelen 1988; Jongeneelen et al. 1985, 1988). The identification of PAH metabolites in urine could potentially serve as a method of biological monitoring of exposed workers and possibly individuals living in the vicinity of hazardous waste sites where creosote has been detected. However, because of the ubiquitous nature of PAHs in the environment, detection of PAH metabolites in the body tissues or fluids cannot always be attributed to creosote exposure. PAHs form DNA adducts that can be measured in body tissues or blood following exposure to creosote containing PAHs. Again, these PAH-DNA adducts are not specific for coal tar creosote, and the adducts measured could have been from exposure to other sources of PAHs. Therefore, a biomarker of exposure specific to creosote would be useful to monitor exposure to this mixture.

Effect. The formation of benzo[a]pyrene-DNA adducts has been demonstrated (Pavanello and Levis 1992; Zhang et al. 1990) and may also serve as a biomarker of PAH-induced carcinogenicity. However, these adducts are not specific for coal tar creosote exposure, as exposure to benzo[a]pyrene from sources other than coal tar creosote can occur. Studies to identify and measure effects more diagnostic of coal tar creosote-specific injury would be useful. Also, increasing the sensitivity of these tests would be valuable in evaluating the health status of individuals who have been exposed to low levels of creosote.

Absorption, Distribution, Metabolism, and Excretion. Studies monitoring the pharmacokinetics of the coal tar creosote mixture are limited. Much of the information regarding the disposition of creosote is based on indirect evidence or the pharmacokinetic information available on a single class of creosote components, the PAHs. For more information on the toxicokinetics of PAHs, please refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995).

Absorption of creosote occurs following all routes of exposure. The presence of creosote components in tissues and the presence of metabolites in urine are evidence of its absorption. However, no studies are available that quantify the extent and rate of creosote absorption. Studies in humans regarding the

distribution of creosote are not available and little information is available for animals. Its distribution is based on assumptions derived from studies that monitored the distribution of PAHs, components of creosote.

The metabolism of creosote has not been extensively studied, but preliminary results indicate that hydroxylation of the major PAH components is a principal degradation pathway in both humans and animals following all routes of exposure. 1-Hydroxypyrene is one metabolite that has been identified, but there were no studies available regarding the identification of other metabolites. Elucidation of additional biotransformation pathways and products is also important in examining potential toxic effects of creosote. Also, no studies were located regarding the rate or extent of creosote metabolism.

Studies regarding the excretion of creosote by humans or animals were not available. It is known that PAHs and their metabolites are primarily excreted in the bile and the feces. However, direct excretion studies with creosote would be more useful. Information is available regarding the disposition of creosote's individual components, but no information is available regarding how these components interact to affect the overall disposition.

In summary, no data are available regarding the toxicokinetics of the creosote mixture and all information must currently be inferred from what is known about the PAH components of creosote. Interactions between the components of the creosote mixture could occur that could alter the rate and extent of absorption, distribution, metabolism, and excretion of creosote from what might be predicted based on what is known about the individual PAH components. Therefore, more information on the toxicokinetics of the creosote mixture itself would be useful to predict possible target organs of toxicity as well as allow for extrapolation of toxic effects across routes of exposure.

Comparative Toxicokinetics. The available information indicates that the absorption, distribution, metabolism, and excretion of creosote is qualitatively similar in humans and rodents. This general conclusion was primarily based on evidence derived from studies on the individual PAH components of creosote. Recent papers have described specific kinetic aspects of individual components of the coal tar products. Little work has been done to address this topic for wood creosote. Detailed pharmacokinetic studies in humans and animals specific to the creosote mixture would provide a better indication of species differences and indicate whether the ability to extrapolate across species may be possible in the future.

Methods for Reducing Toxic Effects. Current methods for reducing toxic effects focus on reducing peak absorption after exposure. Recommendations are primarily based on methods devised for phenolic compounds, and it is not certain how appropriate these are for all forms of creosote, particularly those derived from coal tar. There is currently no method for reducing body burden of creosote once it has been absorbed or of interfering with its toxic effects. Treatment is generally supportive of respiratory and cardiovascular functions. Clinical information as to the efficacy of currently recommended practices such as gastric lavage would be a useful addition to the database for these chemicals.

Children's Susceptibility. Studies addressing the effects of creosote in children are limited to a single survey of health effects among residents of a housing development that had been built on a creosote waste site (Agency for Toxic Substances and Disease Registry 1994). Other human studies are predominantly of occupationally exposed adults. Studies of effects in young animals are also limited, but include several developmental studies that demonstrate fetotoxicity and developmental defects in mice and rats due to coal tar exposure (Hackett et al. 1984; Springer et al. 1982, 1986a; Zangar et al. 1989). Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No data are available to determine whether children vary from adults either in the health effects they are likely to experience from creosote exposure, or in their relative susceptibility to these effects. Epidemiological studies of environmentally exposed populations (if such a population could be located), which include children might help to clarify the types of health effects observed in children after creosote exposure. A small retrospective study of women exposed to coal tar (as a treatment for psoriasis) during pregnancy found no increased incidence of abortion or birth defects (Franssen et al. 1999). Expanding this study to include a larger number of individuals and data as to the stage of pregnancy during which the women were exposed, could provide information as to whether the developmental defects observed in animals are also of concern for humans. Animal studies that compare the effects of creosote exposure on animals of different ages would provide information on the comparative susceptibility of young and adult individuals.

The pharmacokinetics of creosote have not been defined because of the chemical complexity of these mixtures. Information on individual components is not sufficient to define the properties of the mixture and for this reason no PBPK models have been proposed for creosote. Individual components of creosote are metabolized by several different enzyme systems including phase I and phase II enzymes. Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. The relative activity of metabolic enzymes may also vary with the age

of the individual, which will again affect the relative toxicity of particular components of creosote for old or young individuals. However, the interactions taking place when creosote components are metabolized are likely to be extremely complex so that information on age-related activity of any particular enzyme will probably not be very informative as to differential toxicity of the mixture.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Creosote is currently subject to an EPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) registration standard and data call-in, and the Creosote Council II is currently conducting a research program that includes testing in intermediate inhalation, intermediate dermal, developmental, and reproductive toxicity. The Federal Research in Progress database (FEDRIP 2000) listed ongoing studies of CYP1A1 as a biomarker of exposure and susceptibility to creosote, the effect of wood creosote on diarrhea in rats, and modifiers of PAH carcinogenesis.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

The chemical synonyms and identification numbers for wood creosote, coal tar creosote, and coal tar are listed in Tables 4-1 through 4-3. Coal tar pitch is similar in composition to coal tar creosote and is not presented separately. Coal tar pitch volatiles are compounds given off from coal tar pitch when it is heated. The volatile component is not shown separately because it varies with the composition of the pitch. Creosotes and coal tars are complex mixtures of variable composition containing primarily condensed aromatic ring compounds (coal-derived substances) or phenols (wood creosote). Therefore, it is not possible to represent these materials with a single chemical formula and structure. The sources, chemical properties, and composition of coal tar creosote, coal tar pitch, and coal tar justify treating these materials as a whole. Wood creosote is discussed separately because it is different in nature, use, and risk.

Information regarding the chemical identity of wood creosote, coal tar creosote, and coal tar is located in Tables 4-1 through 4-3.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Wood creosote, coal tar creosote, coal tar, and coal tar pitch differ from each other with respect to their composition. Descriptions of each mixture are presented below.

4.2.1 Wood Creosote

Wood creosotes are derived from beechwood (referred to herein as beechwood creosote) and the resin from leaves of the creosote bush (*Larrea*, referred to herein as creosote bush resin). Beechwood creosote consists mainly of phenol, cresols, guaiacols, and xylenols. It is a colorless or pale yellowish liquid, and it has a characteristic smoky odor and burnt taste (Miyazato et al. 1981). It had therapeutic applications in the past as a disinfectant, laxative, and a stimulating expectorant, but it is not a major pharmaceutical ingredient today in the United States. Beechwood creosote is obtained from fractional distillation (200–220 EC at atmospheric pressure) of beechwood or related plants. The mixture has only recently been characterized to any significant extent (Ogata and Baba 1989). Phenol, *p*-cresol, and guaiacols

Table 4-1. Chemical Identity of Wood Creosote

Characteristic	Information	Reference
Chemical name	Wood creosote	Merck 1989
Synonym(s)	Beechwood creosote, creosote, creasote	Merck 1989
Registered trade name(s)	Not applicable	
Chemical formula	Not applicable	
Chemical structure[a]	Not applicable	
Identification numbers:		Windholz 1983
CAS registry	8021-39-4	Merck 1989
NIOSH RTECS	G05870000	HSDB 2000
EPA hazardous waste	U051	HSDB 2000
OHM/TADS	No data	
DOT/UN/NA/IMCO	UN 2810; IMO 6.1	HSDB 2000
HSDB	1979	HSDB 2000

[a]Wood creosote is a mixture composed primarily of phenolic compounds.

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Chemical Identity of Coal Tar Creosote

Characteristic	Information	Reference
Chemical name	Coal tar creosote	American Wood Preserver's Association 1988
Synonym(s)	Creosote, creosote oil, dead oil, brick oil, coal tar oil, creosote P1, heavy oil, liquid pitch oil, wash oil, creosotum, cresylic creosote, naphthalene oil, tar oil, AWPA #1, Preserv-o-sote	HSDB 2000
Registered trade name(s)	Sakresote 100	HSDB 2000
Chemical formula	Not applicable	
Chemical structure[a]	Not applicable	
Identification numbers:		
CAS registry	8001-58-9	Merck 1989; Weiss 1986
NIOSH RTECS	GF9615000	HSDB 2000
EPA hazardous waste	U051	HSDB 2000
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	UN 1136/1137; IMO 3.2/3.3	HSDB 2000
HSDB	6299	HSDB 2000
NCI	No data	

[a]Coal tar creosote is a mixed compound composed primarily of polycyclic aromatic hydrocarbons including phenanthrene, acenaphthene, fluorene, anthracene, and pyridine.

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-3. Chemical Identity of Coal Tar

Characteristic	Information	Reference
Chemical name	Coal tar	Merck 1989
Synonym(s)	Crude coal tar, pixalbol, tar	HSDB 2000
Registered trade name(s)	Psorigel, Clinitar	Merck 1989
Chemical formula	Not applicable	
Chemical structure[a]	Not applicable	
Identification numbers:		
CAS registry	8007-45-2	HSDB 2000
NIOSH RTECS	No data	
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO	UN 1999; IMO 3.2/3.3	HSDB 2000
HSDB	5050	HSDB 2000
NCI	No data	

[a]Coal tar is a mixed compound composed primarily of polycyclic aromatic hydrocarbons including phenanthrene, acenaphthene, fluorene, anthracene, and pyridine.

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

(guaiacol and 4-methylguaiacol) comprise the bulk of beechwood creosote. Xylenols, other methylated guaiacols, and trimethylphenols account for virtually all of the remaining phenolics in the material. Since beechwood creosote is obtained from different sources using nonstandardized procedures, its composition may vary to some degree. For the sample analyzed by Ogata and Baba (1989), more than two-thirds of the more than 20 compounds identified (Table 4-4) were represented by just four components (phenol, p-cresol, guaiacol, and 4-methylguaiacol). Selected chemical and physical properties of wood creosote are shown in Table 4-5.

Creosote bush resin consists of phenolics (e.g., flavonoids and nordihydroguaiaretic acid), neutrals (e.g., waxes), basics (e.g., alkaloids), and acidics (e.g., phenolic acids). The phenolic portion comprises 83–91% of the total resin. Nordihydroguaiaretic acid accounts for 5–10% of the dry weight of the leaves (Leonforte 1986). No other relevant chemical/physical data are available for creosote bush resin; the substance is therefore not addressed further in this profile.

4.2.2 Coal Tar Creosote, Coal Tar, and Coal Tar Pitch

These three substances are very similar mixtures obtained from the distillation of coal tars. The physical and chemical properties of each are similar, although limited data are available for coal tar, and coal tar pitch. Chemical Abstracts Service Numbers (CAS #) are associated with coal tar creosote (8001-58-9), coal tar pitch (67996-93-2), and coal tar (8007-45-2). Literature searches for coal tar pitch produce data identical to that obtained for coal tar creosote. A distinction between these materials is provided in the following discussion.

Coal tars are by-products of the carbonization of coal to produce coke and/or natural gas. Physically, they are usually viscous liquids or semi-solids that are black or dark brown with a naphthalene-like odor. The coal tars are complex combinations of polycyclic aromatic hydrocarbons, phenols, heterocyclic oxygen, sulfur, and nitrogen compounds. By comparison, coal tar creosotes are distillation products of coal tar. They have an oily liquid consistency and range in color from yellowish-dark green to brown. The coal tar creosotes consist of aromatic hydrocarbons, anthracene, naphthalene, and phenanthrene derivatives. At least 75% of the coal tar creosote mixture is polycyclic aromatic hydrocarbons (PAHs). Unlike the coal tars and coal tar creosotes, coal tar pitch is a residue produced during the distillation of coal tar. The pitch is a shiny, dark brown to black residue which contains polycyclic aromatic hydrocarbons and their methyl and polymethyl derivatives, as well as heteronuclear compounds

Table 4-4. Identity of Major Components of Wood Creosote[a]

Compound	Relative peak area, (percent total peak area)
phenol	14.45
methylhydroxycyclopentenone	0.23
o-cresol	3.22
dimethylhydroxycyclopentenone	0.50
p-cresol	13.60
guaiacol	23.76
2,6-xylenol	1.04
3,4-xylenol	0.70
6-methylguaiacol	0.31
3,5-xylenol	2.94
2,4-xylenol	2.80
2,5-xylenol	0.68
unknown	1.31
2,3-xylenol	0.70
3-methylguaiacol	1.85
5-methylguaiacol	1.29
4-methylguaiacol	19.01
2,4,6-trimethylphenol	0.40
2,3,6-trimethylphenol	0.48
4-ethylguaiacol	6.36
4-ethyl-5-methylguaiacol	0.21
4-propylguaiacol	0.45

[a]As identified by gas chromatography/mass spectrometry (Ogata and Baba 1989); composition of wood creosotes may vary from source to source.

Table 4-5. Physical and Chemical Properties of Wood Creosote

Property	Information	Reference
Molecular weight	Not applicable	
Color	Yellowish to colorless	Merck 1989
Physical state	Liquid	Weiss 1986
Melting point	No data	
Boiling point	. 203 EC	Merck 1989
Specific gravity at 25 EC	1.08	Merck 1989
Odor	Characteristic smokey odor	Merck 1989
Taste	Caustic, burning taste	Merck 1989
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water	150–200 parts	Merck 1989
Organic solvent(s)	Miscible with alcohol, ether, fixed, or volatile oils	Merck 1989
Partition coefficients:	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	74 EC (closed cup)	Clayton and Clayton 1981
Flammability limits in air	No data	
Explosive limits	No data	
Other	The major components of wood creosote (phenols) are susceptible to oxidative degradation when exposed to air (oxygen), particularly if the material is basic (high pH).	Not applicable

(American Wood Preserver's Association 1988). Coal tar creosote is defined by the latter organization as:

> A distillate derived from coal tar. As used in the wood preserving industry, creosote denotes a distillate of coal tar produced by the high temperature carbonization of bituminous coal. Coal tar creosote consists principally of liquid and solid aromatic hydrocarbons and contains some tar acids and tar bases; it is heavier than water and has a continuous boiling range beginning at about 200 EC.

Coal tar creosote is now commonly defined by function, and refers to "the fractions or blends of fractions specifically used for timber preservation" (IARC 1987). Coal tar creosote is referred to as “creosote” by the U.S. EPA. The substance is a complex mixture typically composed of approximately 85% PAHs and 2–17% phenolics (Bedient et al. 1984). The composition of the mixture may also vary across lots and across manufacturers. Properties of coal tar creosote are shown in Table 4-6.

Coal tar pitch is the tar distillation residue produced during coking operations (NIOSH 1977). The grade of pitch thus produced is dependent on distillation conditions, including time and temperature. The fraction consists primarily of condensed ring aromatics, including 2–6 ring systems, with minor amounts of phenolic compounds and aromatic nitrogen bases. The number of constituents in coal tar pitch is estimated to be in the thousands (HSDB 2000). A list of the components comprising the PAH fraction of coal tar pitch is shown in Table 4-7. Properties for this substance are similar or identical to those shown in Table 4-6 for coal tar creosote.

Coal tar itself is produced by the carbonization, or coking of coal. Coal tar is defined by Hawley (1977) as:

> A black, viscous liquid (or semi-solid), naphthalene-like odor, sharp burning taste; obtained by the destructive distillation of bituminous coal, as in coke ovens; 1 ton of coal yields 8.8 gallons of coal tar. Combustible. Specific gravity 1.18–1.23 (66/60 EF). Soluble in ether, benzene, carbon disulfide, chloroform; partially soluble in alcohol, acetone, methanol, and benzene; only slightly soluble in water.

The composition of the creosote mixture is dependent on the sources and preparation parameters of the coal tar, and as a result the creosote components are rarely consistent in their type and concentration. An example of the composition variability among creosote samples was recently presented by Weyand et al. (1991). In that study, the concentrations of several PAHs were analyzed in four coal tars. All of the PAHs identified exhibited 2-fold to nearly 20-fold differences in concentration among the four samples.

Table 4-6. Physical and Chemical Properties of Coal Tar Creosote

Property	Information	Reference
Molecular weight	Not applicable	
Color	Translucent brown to black; oily liquid; yellowish to dark green-brown	Merck 1989
Physical state	Liquid	Weiss 1986
Melting point	No data	
Boiling point	194–400 EC	Clayton and Clayton 1981
Specific gravity	1.07–1.08	Clayton and Clayton 1981
Odor	Aromatic smokey smell Characteristic sharp odor	DOT 1985 Merck 1989
Odor threshold:		
Water	No data	
Air	No data	
Taste	Burning, caustic taste	Clayton and Clayton 1981
Solubility:		
Water	Slightly soluble	Clayton and Clayton 1981
Organic solvent(s)	Miscible with alcohol, ether, fixed or volatile oils	Clayton and Clayton 1981
Partition coefficients:	1.0 (log K_{ow})	HSDB 2000
Vapor pressure	No data	
Autoignition temperature	335 EC	Merck 1996
Flashpoint	74 EC	Merck 1989
Flammability limits in air	No data	
Explosive limits	No data	

Table 4-7. Identity of PAH Components of Coal Tar Pitch[a]

Peak No.	Compound[b]	Peak No.	Compound[b]
1	naphthalene	31	acridine
2	benzo(b)thiophene	32	phenanthridine
3	quinoline	33	carbazole
4	2-methylnaphthalene	34	methylphenanthrene, -anthracene
5	1-methylnaphthalene	35	methylphenanthrene, -anthracene
6	biphenyl	36	methylphenanthrene, -anthracene
7	2-ethylnaphthalene	37	4H-cyclopenta(def)phenanthrene
8	dimethylnaphthalene	38	methylphenanthrene, -anthracene
9	dimethylnaphthalene	39	methylphenanthrene, -anthracene
10	dimethylnaphthalene	40	methylcarbazole
11	methylbiphenyl	41	methylcarbazole
12	acenaphthene	42	2-phenylnaphthalene
13	naphthonitrile or azaacenaphthylene	43	dihydropyrene or isomer
14	dibenzofuran	44	fluoranthene
15	fluorene	45	azafluoranthene, -pyrene
16	methylacenaphthene	46	phenanthro(4,5-bcd)thiophene
17	methylacenaphthene	47	azafluoranthene, -pyrene
18	methylacenaphthene	48	pyrene
19	methyldibenzofuran	49	benzonaphthofuran
20	methyldibenzofuran	50	benzacenaphthene or isomer
21	9,10-dihydroanthracene	51	benzacenaphthene or isomer
22	9,10-dihydrophenanthrene	52	benzonaphthofuran
23	methylfluorene	53	benzonaphthofuran
24	methylfluorene	54	benzo(lmn)phenanthridine
25	methylfluorene	55	benzo(kl)xanthene
26	methylfluorene	56	methylfluoranthene, -pyrene
27	1,2,3,4-tetrahydroanthracene	57	4H-benzo(def)carbazole
28	dibenzo(bd)thiophene	58	azafluoranthene, -pyrene
29	phenanthrene	59	benzo(a)fluorene
30	anthracene	60	methylfluoranthene, -pyrene

Table 4-7. Identity of PAH Components of Coal Tar Pitch[a] *(continued)*

Peak No.	Compound[b]	Peak No.	Compound[b]
61	benzo(a)fluorene	91	7H-benzo(c)carbazole
62	benzo(c)fluorene or isomer	92	methylbenz(a)anthracene or isomer
63	methylbenzacenaphthene or isomer	93	tetramethylfluoranthene or isomer
64	methylbenzonaphthofuran or isomer	94	5H-benzo(b)carbazole
65	methylpyrene or isomer	95	methylbenzophenanthridine or isomer
66	methylpyrene or isomer	96	dimethylbenzo(cdf)carbazole
67	methylbenzonaphthofuran or isomer	97	methylchrysene or isomer
68	methylbenzonaphthofuran or isomer	98	methylchrysene or isomer
69	methylazapyrene or isomer	99	methylbenz(a)anthracene or isomer
70	methylbenzonaphthofuran or isomer	100	dimethylbenz(a)anthracene or isomer
71	methylbenzofluorene	101	methylbenz(a)anthracene or isomer
72	dihydrochrysene or isomer	102	dimethylbenz(a)anthracene or isomer
73	dimethylfluoranthene, -pyrene	103	11H-benz(bc)aceanthrylene or isomer
74	trimethylfluoranthene, -pyrene	104	methylbenz(a)anthracene or isomer
75	dimethylfluoranthene, -pyrene	105	4H-cyclopenta(def)chrysene or isomer
76	benzo(b)naphtho(2,1-d)thiophene	106	methylbenz(a)anthracene or isomer
77	benzo(c)phenanthrene	107	binaphthalene or isomer
78	benzo(ghi)fluoranthene	108	4H-cyclopenta(def)triphenylene or isomer
79	dimethylbenzonaphthofuran	109	dimethylbenz(a)anthracene or isomer
80	benzo(b)naphtho(1,2-d)thiophene	110	methylbenz(a)anthracene or isomer
81	dibenzoquinoline or isomer	111	binaphthalene or isomer
82	tetrahydrochrysene or isomer	112	dimethylbenz(a)anthracene or isomer
83	benzo(a)naphtho(2,3-d)thiophene	113	methylbenz(a)anthracene or isomer
84	benz(a)anthracene	114	binaphthalene or isomer
85	chrysene	115	phenylphenanthrene or isomer
86	11H-benzo(a)carbazole	116	dihydrobenzofluoranthene or isomer
87	naphthacene	117	dimethylchrysene or isomer
88	methylbenzonaphthothiophene	118	dibenzophenanthridine or isomer
89	methylbenz(a)anthracene or isomer	119	biquinoline
90	tetramethylfluoranthene or isomer	120	biquinoline

Table 4-7. Identity of PAH Components of Coal Tar Pitch[a] *(continued)*

Peak No.	Compound[b]	Peak No.	Compound[b]
121	benzo(j)fluoranthene	151	methylbenzopyrene or isomer
122	dihydrobenzofluoranthene or isomer	152	methylbenzopyrene or isomer
123	benzo(b)fluoranthene	153	11H-cyclopenta(ghi)perylene or isomer
124	dihydrobenzofluoranthene or isomer	154	methylbenzopyrene or isomer
125	benzo(k)fluoranthene	155	dimethylbenzopyrene or isomer
126	dibenzonaphthofuran or isomer	156	methylbenzopyrene or isomer
127	dihydrobenzofluoranthene or isomer	157	methylbenzopyrene or isomer
128	dimethylchrysene or isomer	158	dimethylbenzopyrene or isomer
129	azabenzopyrene or isomer	159	11H-indeno(2,1,7-cde)pyrene or isomer
130	dibenzonaphthofuran or isomer	160	dimethylbenzopyrene or isomer
131	benzophenanthrothiophene	161	dinaphthothiophene
132	azabenzopyrene or isomer	162	dimethylbenzopyrene or isomer
133	benzo(e)pyrene	163	dibenzophenanthridine or isomer
134	dibenzonaphthofuran or isomer	164	dibenzonaphthothiophene
135	benzo(a)pyrene	165	dimethylbenzopyrene or isomer
136	dibenzonaphthofuran or isomer	166	dibenzocarbazole
137	perylene	167	dimethylbenzopyrene or isomer
138	dibenzonaphthofuran or isomer	168	dibenzo(bg)phenanthrene or isomer
139	methylbenzofluoranthene or isomer	169	benzo(g)chrysene or isomer
140	methylbenzofluoranthene or isomer	170	dinaphthothiophene
141	azabenzopyrene or isomer	171	dimethylbenzofluoranthene or isomer
142	4H-naphtho(1,2,3,4-def)carbazole or isomer	172	dibenzoacridine or isomer
143	methylbenzofluoranthene or isomer	173	dinaphthothiophene
144	dibenzofluorene or isomer	174	dinaphthothiophene
145	dihydroindenopyrene or isomer	175	benzo(c)chrysene or isomer
146	dibenzofluorene or isomer	176	dibenzocarbazole
147	dibenzofluorene or isomer	177	dimethylbenzofluoranthene or isomer
148	methylbenzopyrene or isomer	178	dibenz(aj)anthracene
149	dibenzo(cg)phenanthrene or isomer	179	indenopyrene or isomer
150	dimethyldibenzonaphthofuran or isomer	180	dimethyldibenzonaphthofuran

Table 4-7. Identity of PAH Components of Coal Tar Pitch[a] *(continued)*

Peak No.	Compound[b]	Peak No.	Compound[b]
181	methyldibenzophenanthrene, -anthracene	191	dimethyldibenzonaphthofuran
182	indenopyrene or isomer	192	picene
183	methylbenzophenanthrothiophene	193	dimethylbenzopyrene or isomer
184	dibenz(ac)anthracene	194	dimethyldibenzonaphthofuran
185	methyldibenzophenanthrene, -anthracene	195	benzo(ghi)perylene
186	dimethylbenzofluoranthene or isomer	196	benzo(a)naphthacene or pentacene
187	dibenz(ah)anthracene	197	dimethyldibenzonaphthofuran
188	trimethylbenzofluoranthene or isomer	198	anthanthrene
189	dimethyldibenzophenanthrene, -anthracene	199	methyl indenopyrene or isomer
190	benzo(b)chrysene		

[a]As reported by Guillén et al. 1992; compounds presented in elution order
[b]Tentative identification by gas chromatography/mass spectrometry

Benzo[a]pyrene, a component whose individual toxicity has been examined extensively, ranged from nondetectable levels (detection limit 0.3 g/kg) to 1.7, 6.4, and 3.9 g/kg of coal tar.

Limited chemical/physical data exist for coal tar. Table 4-8 summarizes the current information. Because of the variability in feedstock and manufacturing processes, presentation of exact values for various properties presented in Tables 4-6 and 4-8 is not possible.

Table 4-8. Physical and Chemical Properties of Coal Tar

Property	Information	Reference
Molecular weight	Not applicable	
Color	Almost black, thick liquid, or semisolid	Merck 1989
Physical state	Semisolid	Weiss 1986
Melting point	No data	
Boiling point	No data	
Specific gravity	1.18–1.23	Hawley 1981
Odor	Naphthalene-like	Osol 1980
Odor threshold:		
Water	No data	
Air	No data	
Taste	Sharp, burning taste	Osol 1980
Solubility:		
Water	Slightly soluble	Merck 1989
Organic solvent(s)	Mostly dissolves in benzene; partially dissolves in alcohol, ether, chloroform, acetone, and petroleum ether	Merck 1989
Partition coefficients	No data	
Vapor pressure	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Explosive limits	No data	

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Wood creosote, coal tar creosote, coal tar, and coal tar pitch differ from each other in composition. Wood creosotes (CAS Registry number 8021-39-4) are derived from beechwood (referred to herein as beechwood creosote) and the resin from leaves of the creosote bush (*Larrea*, referred to herein as creosote bush resin). Beechwood creosote is not commercially produced in the United States (HSDB 2000).

Coal tars are by-products of the carbonization of coal to produce coke and/or natural gas. By comparison, coal tar creosotes are distillation products of coal tar. Unlike the coal tars and coal tar creosotes, coal tar pitch is a residue produced during the distillation of coal tar. Coal tar pitch volatiles are compounds given off by coal tar pitch when it is heated, and thus vary with the composition of the coal tar pitch (see Table 4-7). The volatile component of coal tar has not been addressed separately from coal tar pitch in this section.

Because coal tar is a by-product of steel manufacturing, domestic production of coal tar products may vary depending on demand for steel (USITC 1987). Coal tar production in the United States was 168.6 million gallons in 1986 (USITC 1987) and 188.5 million gallons in 1987 (USITC 1988). In 1992, 7.03×10^8 kg (1.55×10^9 pounds) of crude coal tar was produced (USITC 1994). Creosote has been produced commercially in the United States since 1917 (IARC 1985). Creosote production falls into two categories: distillate (100% creosote), and creosote in coal tar solution. Distillate production in 1986 was 46.8 million gallons; creosote in coal tar solution was 31.6 million gallons (USITC 1987). Distillate production in 1987 was 47.3 million gallons. Production of creosote in coal tar solution in 1987 was not disclosed, but solution sales in 1987 were 34.3 million gallons (USITC 1988). Distillate production in 1992 was 2.41×10^8 kg (5.32×10^8 pounds); creosote in coal tar solution was 1.10×10^8 kg (2.43×10^9 pounds) (USITC 1994). The U.S. International Trade Commission classifies pitch of tar as hard (melting point $161 EF), medium (melting point 110–160 EF), or soft (melting point 80–109 EF) (USITC 1994). Production of hard pitch in 1987 was 4.93×10^5 tons. Soft pitch production data for 1987 were not disclosed, but 6.52×10^5 tons were sold (USITC 1988). Production of hard pitch was 6.08×10^8 kg (1.34×10^9 pounds) in 1992. Production and sales figures for medium and soft pitch were not disclosed for 1992 (USITC 1994).

Table 5-1 lists the number of facilities in each state that manufacture or process coal tar creosote, the intended use, and the range of maximum amounts of creosote that are stored on site. The data listed in Table 5-1 are derived from the Toxics Release Inventory (TRI) (TRI99 2001). Only certain types of facilities are legally required to report; therefore, this is not an exhaustive list.

5.2 IMPORT/EXPORT

Available figures on imports and exports (NTDB 1994) are based on millions of gallons of all forms of creosote. Figures from the period 1984–1987 show fluctuations in the range of 1–10 million gallons of creosote products in both import and export levels. Recent data pertaining to the import or export of creosote (NTDB 1995) are presented in Table 5-2. The categories used by the National Trade Data Bank do not directly correspond to the four categories described in Section 5.1.

5.3 USE

Coal tar creosote has been used as a wood preservative pesticide in the United States for over 100 years. Wood preservation accounts for over 97% of current coal tar creosote production (Santodonato et al. 1985). Coal tar creosote is applied to wood by commercial pressure treatment or by home and farm dipping or brushing, although this latter use is not significant since creosote now has restricted use as a wood preservative pesticide (EPA 1986b). Coal tar creosote is a wood preservative and water-proofing agent for log homes, railroad ties, telephone poles, marine pilings, and fence posts. In addition, coal tar creosote prevents animal and vegetable growth on concrete marine pilings, and is a component of roofing pitch, fuel oil, and lamp black, and a lubricant for die molds (Cammer 1982; HSDB 2000). Other uses include animal and bird repellent, insecticide, animal dip, fungicide, and a pharmaceutical agent for the treatment of psoriasis (IARC 1985). Coal tar is registered as a pesticide active ingredient with the U.S. EPA and in 1998 was being evaluated for re-registration (HSDB 2000). The leaves of the creosote bush are ground to produce an herbal nutritional supplement for use as an antioxidant or free radical scavenger to retard aging and to treat a variety of skin conditions including acne. The supplement is claimed, in nonscientific publications, to have antiamoebic, antifungal, and antiviral properties. Suggested uses include oral applications for colds, influenza, diarrhea, urinary tract infections, and topical applications for dandruff (Katz and Saibil 1990).

Table 5-1. Facilities that Produce, Process, or Use Coal Tar Creosote

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	7	10,000	9,999,999	1, 4, 9
AR	3	10,000	9,999,999	1, 3, 8, 9, 13
AZ	1	10,000	99,999	9
CA	4	100	999,999	8, 9, 13
CO	2	1,000	9,999,999	2, 4, 9
CT	1	100,000	999,999	9
FL	1	100,000	999,999	9
GA	2	100,000	999,999	2, 4, 8, 9, 12
ID	1	10,000	99,999	13
IL	4	100,000	49,999,999	1, 4, 9
IN	3	100,000	9,999,999	1, 3, 9
KY	4	100,000	9,999,999	8, 9, 13
LA	4	100,000	9,999,999	9
MI	1	1,000,000	9,999,999	8
MO	1	1,000,000	9,999,999	9
MS	7	10,000	49,999,999	2, 3, 9
NC	1	1,000	9,999	13
NE	1	10,000	99,999	13
NJ	2	1,000	999,999	9, 13
NY	1	100,000	999,999	2, 3, 4, 9
OH	3	1,000	49,999,999	1, 4, 13
OK	2	1,000	999,999	9, 13
OR	5	1,000	9,999,999	1, 6, 8, 9, 13
PA	5	100,000	49,999,999	1, 2, 4, 8, 9
SC	2	100,000	9,999,999	9, 13
SD	1	10,000	99,999	9
TN	1	10,000	99,999	9, 10
TX	5	10,000	9,999,999	9, 12, 13

Table 5-1. Facilities that Produce, Process, or Use Coal Tar Creosote (*continued*)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
UT	3	1,000	9,999,999	1, 4, 13
VA	3	100,000	9,999,999	8, 9
WA	1	100,000	999,999	12
WI	3	1,000	999,999	9
WV	5	100	49,999,999	1, 3, 4, 8, 9, 12

Source: TRI99 2001

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses

Table 5-2. Import/Export Volumes for Creosote

Tariff Category	Imports/Exports	1991	1992	1993	1994	1995
Creosote oils	Exports (1,000 kg)	3,978	8,027	9,158	14,900	6,838
	Imports (1,000 L)	NR	17,584	22,674	17,994	9,466
Other oils and products of coal tar distillation	Exports (1,000 kg)	10,842	0	0	0	0
	Imports (1,000 L)	NR	10,690	40,475	219,424	12,643
Pitch from coal and other mineral tars	Exports (1,000 kg)	39,592	76,586	91,659	103,034	43,740
	Imports (1,000 L)	NR	6,226	115,688	77,791	50,315

Source: National Trade Data Bank (NTDB 1995)

NR = not reported

Beechwood creosote and its compounds calcium creosotate, creosote carbonate, and creosote valerate were used in the past as antiseptics and expectorants (Merck 1989). Treatments for leprosy (Samson and Limkako 1923), pneumonia (McKinlay 1933), and tuberculosis (Fellows 1939a) also involved ingestion of beechwood creosote. Beechwood creosote is rarely used in the United States for medicinal purposes today.

The major use of coal tar pitch is as the binder for aluminum smelting electrodes. Pitch is also used in roofing, surface coatings, and for pitch coke production. Pipe-coating enamels made from pitch are used to protect buried oil, gas, and water pipes from corrosion (IARC 1985).

5.4 DISPOSAL

According to the TRI, 616,938 pounds of coal tar creosote were transferred off-site from facilities that use or process coal tar creosote, presumably for treatment and disposal (TRI99 2001). Treatment of creosote sludge generated from coal tar creosote production includes fixing, solidifying, and covering with clay. In the past, settling lagoons were used in treatment. However, they are no longer being used, and those which were used are now being remediated. "Disposal in place" requires groundwater monitoring for a 30-year period (Ball et al. 1985). Four Resource Conservation and Recovery Act (RCRA) hazardous wastes are listed due, in part, to their creosote content (40 CFR 261.31 and 261.32 [EPA 1981a, 1981b]). These are:

- Waste waters, process residuals, preservative dripage, and spent formulations from wood preserving processes generated at plants that use creosote formulations
- Bottom sediment sludge from the treatment of waste waters from wood preserving processes
- Waste water treatment sludges generated in the production of creosote
- Off-specification creosote (does not meet desired chemical composition).

Due to RCRA Land Disposal Restrictions, creosote can no longer be disposed in hazardous waste landfills unless it meets EPA specified treatment standards (EPA 1990c). No technology- or concentration-based standards for the three RCRA hazardous wastes containing creosote specify creosote as a constituent for monitoring treatment performance (40 CFR 268.43 [EPA 1988b]). Industrially used creosote-treated wood can be burned in an industrial incinerator or boiler (EPA 1986b). Treated wood used in the home or farm should be buried or disposed with household garbage; it should not be

incinerated (American Wood Preserver's Association 1988). The potential for many types of hazardous pollutants to be included with creosote wastes seriously diminishes the potential for recycling or re-use.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Creosote has been identified in at least 46 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2002). However, the number of sites evaluated for creosote is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, all 46 are located within the United States and none are located in the Commonwealth of Puerto Rico (not shown).

Coal tar creosote is a complex commercial mixture of some 300 organic constituents. The most common forms are derived from coal tar distillation, yielding coal tar creosote in temperature ranges between 210 and 280 EC. Coal tar and coal tar pitch share many of the polycyclic aromatic hydrocarbons (PAHs) components of coal tar creosote. For the coal tar derivatives, the composition of the mixture varies from batch to batch depending on the coking process used. Creosote consists primarily of PAHs and, therefore, the fate of many of the components of the mixture is similar to that of PAHs.

Coal tar creosote has been widely used as a wood-treatment pesticide since the turn of the century. As a result of this widespread and long-term use, workers in the wood-preserving industry have been exposed to coal tar creosote for many years. Human exposure to coal tar creosote can occur by inhalation or direct dermal contact. Studies have indicated that dermal exposure to creosote used in wood treatment or in coking oven processes contributed more significantly to the total body burden than respiratory exposures (Klingner and McCorkle 1994; Malkin et al. 1996; Van Rooij et al. 1993b). In other industries, such as rubber processing, occupational exposure to coal tar pitch volatiles may lead to excessive respiratory exposure to PAHs, including benzo[a]pyrene (Rogaczewska and Ligocka 1994). Individuals working in wood-preserving facilities are one of the largest exposed groups. Exposure may also occur during handling and installation of treated wood products in structures such as bridges, piers, retaining walls, cross ties, and fencing; as a result of burning treated scrap wood; and through contact with contaminated media at hazardous waste sites. The general public is unlikely to experience any significant exposure to liquid creosote through the direct use of wood preservative products because EPA canceled all nonwood uses of the material and restricted use of coal tar creosote products to certified applicators in January 1986 (EPA 1986b; R.U.P. 1994).

Figure 6-1. Frequency of NPL Sites with Creosote Contamination

Children are exposed to creosote via the same routes that adults are, and small children are more likely than adults to be in close contact with yard dirt or playground dirt, lawns, and indoor (carpet) dust, all of which may be contaminated with creosote residues. Because of a tendency to put their unwashed hands and foreign objects into their mouths, and to chew on objects, children may be exposed to creosote through oral ingestion of the chemical. Dermal exposure may occur through contact with treated wood used for utility poles, bridges, fences, and railroad crossties. Children may be exposed by playing near pools of discarded creosote or by playing at abandoned hazardous waste sites.

Pharmaceutical creosote preparations are derived from the processing of such woody plants as beechwood (von Burg and Stout 1992). Wood creosote (beechwood creosote) is a yellow, transparent liquid with a characteristic smoky odor, obtained by fractional distillation of wood tar. It is composed primarily of phenol, phenols, cresols, guaiacols, xylenols, and small amounts of alkyl-2-hydroxy-2-cyclopenten-1-ones. It has been used as an expectorant, a "gastric sedative," a gastrointestinal antiseptic, and particularly as an antidiarrheal agent (Ogata et al. 1993). Wood creosote and coal tar creosote are chemically distinct, and should not be confused with one another (see Chapter 4).

Coal tar creosote has been identified in at least 46 of the 1,613 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 2002). However, the number of sites evaluated for creosote is not known. The frequency of these sites within the United States can be seen in Figure 6-1. Biotransformation by microbes is the primary process by which creosote constituents are degraded in soils, surface waters, and groundwater. The mixture is relatively stable and persistent in the environment; half-life data are not available. Wood creosote was not identified at any of the current or former NPL hazardous waste sites.

6.2 RELEASES TO THE ENVIRONMENT

There are no known natural sources of the creosote mixture (IARC 1973). However, several of the PAH constituents of the mixture are known to have natural sources; the reader is referred to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995) and the ATSDR *Toxicological Profile for Cresols* (Agency for Toxic Substances and Disease Registry 1992) for additional information on natural sources, releases, and levels of PAHs and cresols associated with creosote production, use, and disposal.

Creosote has been identified in a variety of environmental media (surface water, ground water, soil, and sediment) collected at 46 of the 1,613 EPA NPL hazardous waste sites (HazDat 2002).

According to the U.S. Department of Agriculture (USDA), the major source of creosote released to the environment is waste water effluents from wood treatment facilities (USDA 1980). Companies that preserve wood with coal tar creosote may treat their aqueous wastes in on-site biological treatment plants or release the waste water into a municipal water treatment system (EPA 1975, 1978a). According to the Toxics Release Inventory (TRI), coal tar creosote manufacturing and processing facilities listed for 1999 (TRI99 2001) report that the major portion of creosote released to the environment is released to air and soil. Table 6-1 lists releases to the environment in 1999 from facilities that manufacture or process coal tar creosote. Only certain types of facilities are legally required to report; this is not an exhaustive list.

Coal tar creosote components may also be slowly released from the surface of treated wood products by oil exudation, leaching by rain water, or volatilization. Losses of creosote from impregnated wood are dependent on the kind of coal used to produce the coal tar, the kind of coke oven used to make the coal tar, and the conditions under which the wood is used (Leach and Weinert 1976).

Treatment of waste waters from wood-preserving processes that use creosote and/or pentachlorophenol produces bottom sediment sludge. EPA defines these as K001 sludges (EPA 1980); in the early 1990s, approximately 1,000 metric tons per year of K001 sludges were produced from active wood-preserving facilities (Davis et al. 1993). At that time, 55 wood-preserving facilities had been identified as NPL sites primarily because of contamination with K001 sludge (Davis et al. 1993).

Creosote-containing materials are also encountered at abandoned dump sites or abandoned facilities where creosote was produced or used in significant amounts. In addition to wood-preserving facilities, coal tar creosote was a by-product of the production of so-called town gas, an illuminating gas made from coal (Arvin and Flyvbjerg 1992; EPA 1987b; Flyvbjerg et al. 1993). Around the turn of the century, virtually every large community in the United States had such a manufactured gas facility (EPA 1987b). From 1816 to 1947, more than 11 billion gallons of coal tar were generated at manufactured gas plants in the United States (Lee et al. 1992). The total number of town-gas sites may have approached 11,000. Several hundred of the larger sites have been evaluated for the NPL. Coke-producing facilities also generate coal tar wastes, including cresol emissions to the atmosphere (Grosjean 1991).

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Coal Tar Creosote

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AL	7	234,952	1,914	No data	0	236,866	20,380	257,246
AR	3	31,068	1,209	No data	900	33,177	3,578	36,755
AZ	1	7,505	No data	No data	No data	7,505	No data	7,505
CA	4	4,215	10,564	No data	29,672	44,451	250	44,701
CO	2	8,593	280	No data	2,087	10,960	288,005	298,965
CT	1	500	No data	No data	No data	500	No data	500
FL	1	255	No data	No data	No data	255	No data	255
GA	2	2,300	8	No data	No data	2,308	No data	2,308
ID	1	5	No data	No data	30,000	30,005	No data	30,005
IL	4	26,968	2,901	No data	0	29,869	17,652	47,521
IN	3	7,055	400	No data	16,845	24,300	No data	24,300
KY	4	13,394	66	No data	0	13,460	4,742	18,202
LA	4	94,977	103	No data	0	95,080	No data	95,080
MI	1	10,529	No data	No data	No data	10,529	No data	10,529
MO	1	3,600	300	No data	No data	3,900	No data	3,900
MS	7	31,231	1,770	No data	0	33,001	79,961	112,962
NC	1	13	No data	No data	No data	13	No data	13
NE	1	5	No data	No data	0	5	No data	5
NJ	2	3,037	0	No data	0	3,037	0	3,037
NY	1	78	No data	No data	No data	78	No data	78
OH	3	61,945	1	No data	No data	61,946	1,531	63,477
OK	2	14	No data	No data	129,980	129,994	14,155	144,149
OR	5	17,370	5	No data	270,673	288,048	750	288,798
PA	5	27,416	66	No data	0	27,482	79,168	106,650
SC	2	14,450	53	No data	716,348	730,851	8	730,859

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Coal Tar Creosote *(continued)*

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
SD	1	3,020	110	No data	No data	3,130	10,000	13,130
TN	1	500	No data	No data	No data	500	No data	500
TX	5	51,483	2,186	0	0	53,669	51,197	104,866
UT	3	9,195	No data	No data	12,478	21,673	250	21,923
VA	3	13,244	359	No data	0	13,603	12,782	26,385
WA	1	1,805	10	No data	No data	1,815	6,480	8,295
WI	3	15,336	No data	No data	0	15,336	18	15,354
WV	5	47,019	14	No data	0	47,033	26,031	73,064
Total	90	743,077	22,319	0	1,208,983	1,974,379	616,938	2,591,317

Source: TRI99 2001

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

At older production facilities or places where wastes have been disposed off-site, the creosote materials are often mixed with other chemicals. For instance, pentachlorophenol (PCP) is commonly encountered at NPL sites involved with wood-preserving operations along with such metals as copper, chromium, and arsenic (Davis et al. 1993; Kuehl et al. 1990; Mueller et al. 1989, 1991). At many of these sites, PAHs from combustion sources other than coal tar may have been introduced. The wastes from old town-gas sites may contain benzene, toluene, ethylenebenzene, or xylenes, and sometimes cyanides (Arvin and Flyvbjerg 1992; EPA 1987b; Flyvbjerg et al. 1993).

No major sources of wood creosote releases to the environment have been reported.

6.2.1 Air

Atmospheric releases of creosote from wood-preserving plants are not well defined. Coal tar creosote constituents such as naphthalene, acenaphthalene, acenaphthene, phenanthrene, and fluorene have been detected in emissions at a pressure treatment facility that treated logs for use as utility poles and marine pilings (EPA 1986d). Releases may occur at several points in the treatment process, such as when cylinder doors are opened after a treatment cycle, or when creosote is transferred from the heater to the cylinder at the beginning of the impregnation process. Atmospheric releases vary from plant to plant, depending on the process design, and are considered to be significantly smaller than releases to surface water in aqueous effluents (Henningsson 1983). It should be noted, however, that the more volatile PAHs may be less toxic (and especially less carcinogenic) than the less volatile PAHs.

On a hot, sunny day evaporation of creosote from the surface of treated wood may release coal tar creosote constituents to the atmosphere. Only the volatile creosote components such as acenaphthene and naphthalene will volatilize; the heavier fractions will remain on the wood (USDA 1980). Volatilization may also be greater during warmer months when ambient temperatures are higher. Gevao and Jones (1998) observed greater volatilization of acenaphthene, fluorene, phenanthrene, anthracene, and fluoranthene from creosote-treated wood at 30 EC than at 4 EC.

In a terrestrial microcosm study, release of ^{14}C-labeled creosote components to the atmosphere from treated wood accounted for 1.0% of total acenaphthene and 1.4% of phenanthrene, whereas 93.5 and 95% of these components, respectively, were retained in the wood (Gile et al. 1982).

Other potential sources of atmospheric releases include incineration of scrap wood treated with the mixture and re-entrainment of dust and soils contaminated with components of the mixture in the vicinity of hazardous waste sites. Creosote was not detected in any air samples of the 46 current or former NPL sites where creosote was identified in some environmental medium (HazDat 2002).

According to TRI99 (TRI99 2001), an estimated total of 743,077 pounds of coal tar creosote, amounting to 37.6% of the total environmental release, was discharged to air from manufacturing and processing facilities in the United States in 1999. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

No sources of wood creosote releases to the atmosphere have been reported.

6.2.2 Water

The major source of creosote released into surface waters and ground water is waste water effluents from wood-preserving facilities (USDA 1980). In previous years, waste water generated from wood treatment facilities was often discharged to unlined evaporation/settling lagoons where a sludge was formed. Water-soluble creosote components then percolated through the soil to reach the groundwater table. Waste waters may include process water generated from steam conditioning of the wood; preservative formulation recovery and regeneration water; water used to wash excess preservative from the surface of the wood; condensate from drying kilns used to dry preserved or surface-protected wood; water that accumulates in door and retort sumps; and rain falling on or in the immediate vicinity of the treating cylinder and work tank area. Groundwater contamination from creosote waste waters and sludge stored in unlined surface water impoundments at a wood treatment facility has been reported in Pensacola, Florida (USGS 1988a; Elder and Dresler 1988; Goerlitz et al. 1985). Similar contamination problems have been reported in Conroe, Texas (Borden 1986), and St. Louis Park, Minnesota (Hickock et al. 1982).

Given the very viscous nature of coal tar creosote or creosote-containing wastes, significant migration into groundwater supplies is seldom encountered unless the soils are extremely porous. For instance, a very sandy substrate at the American Creosote Works NPL site at Pensacola, Florida, allowed a significant plume of wood-preserving wastes to enter the ground water (Goerlitz et al. 1985). In most instances, the main concern over creosote materials entering well water is that minute quantities (ng/L) of coal tar components produce extremely objectionable tastes and odors (Arvin and Flyvbjerg 1992).

In addition to discharges or migration into ground water from disposal sites, coal tar creosote has often been introduced to receiving waters as the result of spills while transporting coal tar materials on barges or during loading and unloading accidents around docks or navigation facilities. Well documented examples include a spill near Slidell, Louisiana, on the Bayou Bonfouca (DeLeon et al. 1988). During the years 1986–1991, 1,400 incidents of chemical and petroleum spills into the Newark Bay were documented; among these were spills of 53,000 gallons of liquid asphalt and 75 gallons of creosote (Gunster et al. 1993).

Water-soluble creosote constituents (e.g., phenols) may be released to surface water or ground water by leaching from the surface of creosote-contaminated soils at hazardous waste sites or from treated wood products, such as marine pilings, coming into contact with water. For example, some studies have shown that creosote is lost to a greater extent from marine timber than from timber placed in fresh water as a result of wood cell contraction caused by the high concentration of salts in sea water (Henningsson 1983). Creosote has been detected in groundwater samples collected at 27 of the 46 NPL sites and in surface water samples collected at 8 of the 46 sites where creosote has been identified in some medium (HazDat 2002).

According to TRI99 (2001), an estimated total of 22,319 pounds of coal tar creosote, amounting to 1.1% of the total environmental release, was discharged to water from manufacturing and processing facilities in the United States in 1999. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

No sources of wood creosote releases to water have been reported.

6.2.3 Soil

Coal tar creosote may be released to soils at wood treatment facilities as a result of bleeding of the product from treated timber in stockyard and storage areas. Rain water may also wash the soluble components directly from the surface of treated timber and into the soil (Henningsson 1983). Localized, but severe, contamination of soils is often encountered on the grounds of older (often abandoned) wood-preserving or town-gas facilities (Davis et al. 1993; EPA 1987b).

There is also a potential for release of creosote to soil from hazardous waste sites. Creosote has been detected in soil samples collected at 30 of the 46 NPL sites and in sediment samples collected at 6 of the 46 NPL sites where creosote has been identified in some medium (HazDat 2002).

According to TRI99 (2001), an estimated total of 1,208,983 pounds of creosote, amounting to 61.2% of the total environmental release, was discharged to land from manufacturing and processing facilities in the United States in 1999. The TRI data (Table 6-1) should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

No sources of wood creosote releases to soil have been reported.

6.3 ENVIRONMENTAL FATE

As with other chemical mixtures, the fate and transport processes affecting creosote can be extremely complex. Creosote components may partition to the air, water, soil, or biota depending on their physical and chemical properties. Compounds initially released to the atmosphere may undergo atmospheric deposition and reach surface water directly or through runoff carrying soil-bound compounds (Stangroom et al. 1998). For coal tar creosote materials encountered in old production facilities or waste disposal sites, materials contained in the top several feet of soil will have become "weathered," with virtually all the phenolic and heterocyclic fractions having volatilized, oxidized, or biodegraded (von Burg and Stout 1992). The lighter fractions of the PAH materials will also have degraded. The remaining weathered creosote will show limited ability to move off-site. Johnston et al. (1993) studied the PAH composition of coal-tar-containing samples collected at a number of coal gasworks sites in Australia. Most of these sites were abandoned nearly a century ago. The samples were taken from areas where the coal tar components would have undergone environmental modification to varying degrees since deposition. They concluded that aqueous partitioning and volatilization are probably the main processes that control environmental modification of coal tar at gasworks sites.

Newly produced creosote, or materials from a spill or a more recent disposal site, may pose more serious toxicity concerns. A complicating factor in interpreting the available literature is that creosote alone may not by the only source of toxicity. Especially at NPL or other waste disposal sites, such chemicals as pentachlorophenol (PCP) or heavy metals may be involved. Without an extensive battery of chemical analyses, perhaps combined with bioassay tests, making even semi-quantitative judgements on toxicity issues can be problematic. Much of the remedial work conducted under the Superfund program has

simply aimed to reduce the volume of wastes at NPL sites with creosote contamination. A large percentage reduction by total weight does not always translate into a corresponding reduction in toxicity (Brooks et al. 1998; Hyötyäinen and Oikari 1999b; Mueller et al. 1991).

6.3.1 Transport and Partitioning

Coal tar creosote constituents released to surface waters will differentially partition to the water column or to sediments depending on their water solubility and sorptive properties. For example, PAHs, the major constituents of creosote, generally tend to sorb strongly to soil and sediment particulates, and often have low aqueous solubilities and mobility (Hickock et al. 1982). Many components in the PAH fraction, particularly the higher molecular weight (HMW) PAHs, will remain in a virtually stationary tar-like mass at the place where they were deposited. Nitrogenous bases present in creosote waste water (e.g., aniline, toluidines, and xylidines) are relatively soluble, mobile, and persistent in ground water (Pereira et al. 1983). However, behavior at a given site is also dependent on site-specific characteristics. For example, PAHs, phenol, and heterocyclic components of creosote wood treatment process wastes were found to migrate en masse in ground water through a contaminated sand and gravel aquifer in Pensacola, Florida; sorption of these different classes of organic constituents in the low organic carbon (<0.1%) aquifer materials was not important (USGS 1986). In an investigation of coal-tar contaminated surface sediments, PAHs were observed to have moved 400 meters in ground water from buried subsurface coal tar; persistence of the PAHs, naphthalene in particular, was partially attributed to anoxic conditions (Madsen et al. 1993, 1996). Additionally, sediment-bound creosote components may be released over time. In a laboratory study of creosote-contaminated sediment and natural lake water, Hyötyäinen and Oikari (1999b) found that creosote-derived 4- to 6-ring PAHs released from the sediment during incubation were toxic to water fleas (*Daphnia magna*) and to the photoluminescent bacteria *Vibrio fischeri.*

In an investigation of the partitioning of PAHs from coal tar wastes at manufactured gas plant sites into ground water, partitioning of the various fractions of the complex mixture was observed to be inversely related to solubility, with the more soluble compounds partitioning to water more readily (Lee et al. 1992). Although coal tar is a complex mixture of compounds with varying physical and chemical properties, data analyzed with regard to a partitioning model indicated that ideal behavior was observed for the individual compounds and that the model was useful in estimating concentrations in ground water.

In an investigation of the extent of creosote contamination at four wood-preservative plants with process water surface impoundments, unspecified creosote components were found to have moved 20–60 feet vertically from the impoundments to the water table and up to 500 feet horizontally from the sources (Ball 1987).

In a 50-day microcosm study of the aquifer materials of the Libby, Montana, Superfund site, 59% of radiolabeled phenanthrene was bound to the soil, while only 2.2% was volatilized (Mohammed et al. 1998).

In a terrestrial microcosm study, 2.7% of radiolabeled phenanthrene and 4.3% of radiolabeled acenaphthene were found in soil samples taken in a 10-cm zone around creosote-treated posts, whereas concentrations of the compounds that remained in the posts were 95 and 93.5% of the amounts applied, respectively, after 2.5 months (Gile et al. 1982).

In an investigation of the release of creosote from treated wood into fresh water and sea water, naphthalene, phenanthrene, acenaphthene, dibenzofuran, fluorene, and 2-methylnaphthalene were found to be the major components that migrated into water (Ingram et al. 1982). The rate of migration was found to increase significantly with increasing temperature within the range of 20–40 EC; slower migration occurred from aged than from freshly treated pilings. In a microcosm study of the leaching of PAHs from creosote-impregnated pilings into aquatic environments, the aqueous concentration of PAHs increased with the number of pilings used (Bestari et al. 1998). These authors calculated a rate loss of creosote from the wood pilings into the water of approximately 50 $\mu g/cm^2$/day (273 mg/piling/day). Creosote was observed to be removed from the water rapidly after 7 days, and was close to background concentrations (0.8–6.7 µg/L) by 84 days; losses were attributed to photolysis and microbial degradation, while sorption to sediment was not significant.

In an investigation of the volatilization of PAHs from creosote-treated wood, desorption of acenaphthene, fluorene, phenanthrene, anthracene, and fluoranthene was directly related to concentration and was greater at 30 EC than at 4 EC (Gevao and Jones 1998). The authors reported desorption half-lives of 0.7–31 years at 4 EC and 0.3–1 year at 30 EC for fluoranthene and acenaphthene, respectively. It is also possible to have volatilization from surface soil to the atmosphere. Coal tar constituents have Henry's law constant ranging from 0.11 to 8.65×10^{-8} atm m^3/mole and vapor pressures of 1.2×10^{-8} to 95 mmHg (Swann et al. 1983), indicating that some newly leached compounds may rapidly volatilize from both moist and dry soil before binding to soil can occur.

Limited uptake of some creosote constituents has been detected in plants exposed to creosote-treated wood in nearby soil. Only 0.04% of applied acenaphthene and 0.1% of phenanthrene partitioned to plant tissue in one study (Gile et al. 1982). While systemic uptake may be minimal, such coal tar creosote components as PAHs can adsorb to plant roots or surfaces. This seems a common way that vegetables or other produce for human consumption can pick up trace amounts of creosote materials (Agency for Toxic Substances and Disease Registry 1995).

Animals such as voles, crickets, snails, pill bugs, and worms have exhibited the capacity to assimilate radiolabeled creosote components in terrestrial microcosm studies. Creosote components were found to accumulate to the greatest extent in the vole, with bioconcentration factors (BCFs) of 12–31. The ^{14}C mass balance content of the animals was 1.2% of applied acenaphthene and 0.8% of applied phenanthrene versus 4.3 and 2.7%, respectively, in soils (Gile et al. 1982). In addition, mussels taken from creosote-treated pilings have been found to contain significantly more benzo[a]pyrene, a creosote constituent, than those growing elsewhere (Dunn and Stich 1976). Accumulation of creosote-derived PAHs has been reported in benthic organisms in Pensacola Bay (Elder and Dresler 1988; Rostad and Pereira 1987). Fluoranthene, pyrene, benzo[a]pyrene, anthracene, chrysene, and phenanthrene were detected in higher concentrations in tissues of snails (*Thais haemastoma*) and oysters (*Crassostrea virginica*) taken from offshore sites near an onshore wood-treatment plant compared with those from control sites. Experimental and estimated log K_{ow} values for many of the main constituents of coal tar are 1.22–5.22 (HSDB 2000; Meylan and Howard 1995). Based on these values, BCFs of 5–5,500 have been estimated and are consistent with reported experimental BCFs of 2–9,200 for fish and aquatic organisms, indicating that bioaccumulation may be important in the fate of some components of coal tar (Kobayashi et al. 1979; Linder et al. 1985).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Little information was found in the available literature concerning the transformation of wood or coal tar creosote components in the atmosphere. Some volatile coal tar constituents may undergo oxidation by vapor phase reaction with photochemically produced hydroxyl radicals, with calculated half-lives of 2 hours to 10 days based on experimental and estimated rate constants of $1.12–103 \times 10^{12}$ cm/molecules-second at 25 EC and using an average atmospheric hydroxyl radical concentration of 5×10^5 molecules/cm^3 (Atkinson 1989; Meylan and Howard 1993). Rates may be slowed since some components will exist as

particulate matter in the atmosphere (Eisenreich et al. 1981). Additionally, some components of coal tar may undergo nighttime reactions with nitrate radicals (Atkinson et al. 1987). Based on an experimental rate constant of 3.8×10^{-12} cm/molecules-second for phenol, and an atmospheric nitrate radical concentration of 2×10^{8} molecules/cm^3, a half-life of 15 minutes can be calculated for the compound (Atkinson 1989).

Among the more volatile constituents of creosote are the cresols in its phenolic fraction. These materials comprise only about 1% of the creosote by weight, but it is the cresol components that give creosote its distinctive odor and its resin-like properties. The more generally recognized source categories related to coal tar production or products containing creosote include coal tar distillation facilities or coke ovens, but another source may come from chemical transformation in the air around urban centers (Grosjean 1991).

The air of many urban areas shows appreciable levels of volatile organic compounds (VOCs) such as toluene. A major source is often nonstationary sources such as automobiles since toluene is an octane booster in nonleaded gasolines. Toluene can react with hydroxyl radicals to form the same types of cresols found in the phenols portion of creosote. Although other reaction pathways can lead to the rapid degradation of these cresols, appreciable transient build-ups of cresol vapors are possible. Degradation products include a variety of nitrocresols, aliphatic carbonyls, and ketoacids. These degradation products can become part of other atmospheric reactions in the air of typical urban areas. These transient cresol concentrations could amount to 10–13% of the toluene levels. This cresol source is worth further study in urban areas showing exceptionally high levels of VOCs in the ambient air (Grosjean 1991).

6.3.2.2 Water

Coal tar constituents present in surface waters may be degraded by direct and indirect photolysis. Estimated aqueous photolysis half-lives of 8.4, 71, and 21 hours have been reported for phenanthrene, naphthalene and fluoranthene, respectively (Zepp and Schlotzhauer 1979). Other coal tar constituents which may undergo aqueous photolysis are acenaphthalene, anthracene, benzene, quinoline, phenol, cresol, and carbazide. In a microcosm study, PAHs leached from creosote-impregnated wood pilings were degraded in aquatic environments by photolysis and microbial degradation, while sorption to sediment was not significant (Bestari et al. 1998). Photolysis in water is not expected to be a major route of the environmental fate of creosote constituents, particularly for the less soluble compounds.

Coal tar creosote components are degraded in aquatic environments mainly by microfaunal metabolism (Borthwick and Patrick 1982; Ingram et al. 1982). Microorganisms may act on the creosote-treated wood itself or on creosote components that have leached from the treated wood. Quinoline, the major tar base in creosote, has been reported to be degraded in surface water and ground water by bacteria of the genus *Pseudomonas* (Bennett et al. 1985). Biotransformation of the phenolic components of creosote apparently also occurs under anaerobic conditions in contaminated ground water (Ehrlich et al. 1983; Goerlitz et al. 1985). Adaptation of soil microorganisms to PAH contaminants in ground water originating from creosote treatment plant wastes has also been reported (Wilson et al. 1985).

Work on NPL sites has helped identify numerous bacteria and fungi that can biodegrade creosote materials. In addition to *Pseudomonas*, bacteria in the genus *Alcaligenes* can degrade phenolic compounds under aerobic conditions (Mueller et al. 1989). So long as the ground water is not completely anoxic, numerous soil microorganisms can degrade creosote materials. Work at NPL sites suggests that up to 90% of the creosote degradation is associated with biologically mediated processes. Although this can lead to an appreciable reduction in the quantity of the creosote materials, it is the phenolic and lower molecular weight (LMW) PAHs that are degraded while the HMW PAHs that have been shown to resist biological attack may persist. In a study of biodegradation of creosote-contaminated ground water from the American Creosote Superfund Site, Mueller et al. (1991) observed a toxic and teratogenic response of inland silverside (*Merida beryllina)* embryos to the biotreated water at both 10 and 100% concentrations. They attributed the response to the cumulative effects of carcinogenic HMW PAHs that remained after 14 days of incubation. The higher levels of biodegradation observed for the LMW PAHs was attributed to their greater aqueous solubility and consequent greater bioavailability.

Much less is known about biodegradation processes under more anoxic conditions, which would be typical of ground water and vadose zone waters. Work on town-gas sites in Europe has demonstrated that where nitrate levels are high, or where nitrate is supplied to ground water, various facultative bacteria can degrade coal tar components using the nitrate or nitrite as an electron acceptor (Flyvbjerg et al. 1993). In general, however, biodegradation under anoxic conditions appears to proceed very slowly. Even when supplied with ample quantities of such electron acceptors as nitrates, half-lives in excess of 20 days were observed in laboratory microcosms for the anoxic biodegradation of dimethylphenol components in creosote, and cresol components showed little indication of significant disappearance unless the experiments were continued in excess of 90 days (Arvin and Flyvbjerg 1992).

Creosote components have been detected in surface water samples taken near a wood-treatment facility that ceased operation 30 years earlier (Black 1982). The creosote, which appeared to have permeated the sandy surface soils down to an impervious clay layer, was entering the river via seepages and springs. Weathering processes produced only minor constitutive changes in the creosote with relative losses of the lower molecular weight components. These changes probably reflected the greater volatility and solubilities of the 2–3 carbon ring PAHs.

6.3.2.3 Sediment and Soil

Coal tar creosote components are slowly released from treated wood products by oil exudation, rainwater leaching, and by volatilization of the lighter fractions (Henningsson 1983). USDA (1980) reported that the major components of creosote were not detected in soil samples taken to a depth of 6 inches within 2–24 inches from treated poles, presumably as a result of biotransformation of mobilized components by soil microorganisms. Creosote components released to soils in waste water effluents have been found to be biotransformed by soil microbes under aerobic conditions (Middleton 1984). Bacteria of the genus *Pseudomonas* isolated from a creosote-contaminated waste site have been reported to degrade creosote-derived quinoline (Bennett et al. 1985). Acclimation to creosote phenolic constituents by soil microorganisms has also been demonstrated (Smith et al. 1985).

Where the coal tar creosote is in well-oxygenated conditions, lignin degrading fungi like the white rot fungus *Phanerochaete sordida* can remove much of the PAH fraction (Davis et al. 1993). This fungus can also biodegrade PCP, which has often become mixed with the wastes found at creosote production or disposal sites.

Many of the same bacteria and fungi capable of biodegrading creosote components in aqueous systems can be found in soils. Especially where the creosote is close to the surface and under aerobic conditions, the vast majority of the phenolics can be consumed in less than a year (von Burg and Stout 1992). The majority of the lighter fractions of the PAH components (from 53 to 75% by weight) can be biodegraded within 2 months (there was no significant depletion of heavier fractions with 5-ring or higher PAHs) (Davis et al. 1993).

While biodegradation of PAHs in soil may be enhanced using bioremediation procedures, not all techniques are equally effective at reducing toxicity. In a study of PAH-contaminated soil from the Reilly Tar Superfund Site in St. Louis Park, Minnesota, although total EPA priority pollutant PAH

concentrations were decreased 48–74% following treatment with one of four bioremediation technologies, following two of the four techniques, toxic (mutagenic) compounds were still present (Brooks et al. 1998). None of the four techniques tested was successful at removing the 5- and 6-ring HMW PAHs.

However, persistence of the PAHs, naphthalene in particular, has been observed in seep sediments where groundwater contaminated from buried subsurface coal tar emerged at the base of a hill; persistence of the LMW PAH naphthalene was attributed mainly to anoxic conditions (Madsen et al. 1993, 1996).

For sediments, much of the literature involves biologically oriented tests to identify hotspots with pronounced degrees of toxicity to aquatic and marine species. For instance, bioassays using benthic amphipods and highly creosote-contaminated sediments from Eagle Harbor in Washington's Puget Sound showed several toxic hotspots with acute toxicity to the infaunal marine amphipod *Rhepoxynius abronius* (Swartz et al. 1989). The authors suggest similar causal factors may underlie the common pattern of hepatic lesions and neoplasms observed in English sole from Eagle Harbor. As with bioremediation, natural attenuation of creosote-contaminated sediment may continue to present risks to aquatic organisms as sediment-bound creosote constituents may be released over time. In a laboratory study using contaminated sediment and natural lake water, Hyötyäinen and Oikari (1999b) found that creosote-derived 4- to 6-ring PAHs released from the sediment during incubation were toxic to water fleas (*D. magna*) and to the photoluminescent bacteria *V. fischeri.*

Work at coal tar creosote-contaminated sites on the Elizabeth River in Virginia, indicates a strong positive correlation between exposure to the creosote-contaminated sediments and the incidence of hepatic neoplasms on a resident forage fish, the mummichog (*Fundulus heteroclitus*) (Vogelbein et al. 1990). Similar cancer epizootics in fishes are found at other major harbor sites (e.g., the lower Hudson River, Boston Harbor, and Los Angeles harbor) showing creosote or PAH-laden sediments. Such findings have been proposed (Vogelbein et al. 1990) as indicators of serious toxic concerns in coastal and estuarine environments that may have human health implications if bioaccumulation can be documented.

6.3.2.4 Other Media

Very little information was found in the available literature on the transformation or degradation of coal tar creosote or wood creosote in animals or plants. Eisler (1987) found that many aquatic organisms are able to rapidly metabolize and eliminate PAHs, the major constituents of the commercial mixture.

Transport and transformation of creosote in the environment may affect the coal tar creosote constituents in treated wood. The USDA reported that the relative levels of 18 major creosote residues in treated marine pilings did not change following 9.5 years of service; of the originally applied creosote, 93% was retained on the wood (HSDB 2000). Both creosote and total PAHs decreased during the in-service period.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to creosote depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on creosote levels monitored in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

6.4.1 Air

No information was found in the available literature regarding ambient atmospheric concentrations of wood or coal tar creosote-derived components (i.e., PAHs) in the United States (HSDB 2000). Workplace air concentration data are discussed in Section 6.5. Data on ambient atmospheric concentrations of PAHs derived from other sources can be found in the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995).

6.4.2 Water

No information was found in the available literature regarding ambient water concentrations of wood or coal tar creosote-derived components (i.e., PAHs) in the United States (HSDB 2000). However, in a microcosm study, Bestari et al. (1998) reported that measured background concentrations of 16 monitored creosote-derived PAHs in the microcosm water ranged from nondetectable to 1.5 μg/L which was comparable to background estimates for a variety of natural water sources.

Results from 2 years of groundwater sampling at an abandoned wood treatment facility in Conroe, Texas, where coal tar creosote had been used for about 20 years, showed that monitoring wells were contaminated with levels of up to 3,490 μg/L naphthalene, 1,263 μg/L methylnaphthalene, 425 μg/L dibenzofuran, and 302 μg/L fluorene. The contaminants had apparently migrated through the clay and

sand soils on the site from three waste pits. A plume of groundwater contamination by organics at trace levels was found to extend up to 300 feet from the waste pit locations (Bedient et al. 1984).

At the Koppers Company, Inc. NPL site in Texarkana, Texas, where a creosote wood treatment facility existed for 51 years prior to being converted to a residential area and an industrial site (sand and gravel company), creosote-derived naphthalene, acenaphthene, fluorene, pyrene, and phenanthrene were measured in ground water at levels ranging from nondetectable to 10^5 ppb (Agency for Toxic Substances and Disease Registry 1994). Surface water at the site had no detectable levels of the acid or base/neutral compounds that were monitored.

6.4.3 Sediment and Soil

PAH contamination of soil has been found at the site of a wood-preservation facility that operated in Slidell, Louisiana, from 1892 to 1970, when a fire destroyed the plant facilities. It is believed that environmental releases of creosote occurred throughout the plant's operating history and as the result of the 1970 fire, when creosote was released from storage tanks and flowed over the ground and into adjacent water bodies. Waste creosote and debris have accumulated in eight areas at the site. The deposits are up to 2 feet thick and have contaminated underlying soils (based on visual inspection) to as much as 1 foot below the surface. PAH concentrations show a rapid decrease with increasing depth, ranging from 15,680 mg/kg (ppm) at the surface to 1 mg/kg (ppm) within 9 feet. PAH concentrations as high as 2,488 mg/kg also have been measured in the soils matrix of the shallow aquifer (Acharya and Ives 1994).

Several PAH constituents of creosote were detected in soil samples taken at an abandoned wood treatment facility in Conroe, Texas, at depths of up to 25 feet. Maximum concentrations of the compounds were detected in samples collected at the 0.7–1.8-foot depth. Maximum concentration levels were 3.7 mg/kg for naphthalene, 3.4 mg/kg for methylnaphthalene, 3.8 mg/kg for dibenzofuran, 4.2 mg/kg for fluorene, and 2.2 mg/kg for anthracene. An investigation of vertical variations in contaminant concentrations in the soil zone above the water table revealed that, in general, >90% of the organics were removed within the first 5 feet at the location studied. Organics can be degraded by microbes, adsorbed onto soil, or altered by interactions with soil humus (Bedient et al. 1984).

At the Koppers Company, Inc. NPL site in Texarkana, Texas, where a creosote wood treatment facility existed for 51 years prior to being converted to a residential area and an industrial site (sand and gravel

company), creosote-derived pyrene, fluoranthene, phenanthrene, and anthracene (base/neutral compounds) were measured in surface and subsurface soils at levels ranging from nondetectable to 1,000 ppm (Agency for Toxic Substances and Disease Registry 1994).

In sediment samples from a creek adjacent to the Koppers Company, Inc. NPL site, creosote-derived base/neutral compounds were detected at concentrations up to 100 ppm; one creosote-derived base/neutral compound was detected in downstream sediment at a maximum of 1 ppm (Agency for Toxic Substances and Disease Registry 1994). Creosote-derived base/neutral compounds were also detected in the sediment of the drainage ditch at the site, at levels ranging from 1–100 ppm.

Coal tar creosote-derived phenanthrene, 1,2-benzanthracene, and benzo[a]pyrene have been detected in river sediments at concentrations of up to 231, 62, and 16 mg/kg (wet basis), respectively, directly downstream from the site of a former wood treatment facility. At 4,000 meters from the source, these levels decreased to 0.35, 1.02, and 0.40 mg/kg (wet basis), respectively (Black 1982). Creosote-derived PAHs were also detected in the sediments of Pensacola Bay and a drainage stream in the vicinity of a former wood treatment facility near Pensacola, Florida. PAH concentrations ranged from 200 μg/g for naphthalene to 140 mg/kg for anthracene in stream sediments; concentrations in Pensacola Bay ranged from 75 μg/kg for benzanthracene to 190 μg/kg for fluoranthene (Elder and Dresler 1988).

PAH concentrations have been determined in sediment cores collected from the Arthur Kill, Hackensack River, and Passaic River in northern New Jersey. These rivers are in industrialized areas near former creosote wood-preserving facilities that operated through the 1960s and 1970s. Temporal distributions were determined in each core based on the activities of the radionuclides ^{210}Pb and ^{137}Cs. Sediments at depths corresponding to the years 1978 and 1964 contained total PAHs at concentrations of 1.71 mg/kg (ppm) for 1978, and not detected to 35.7 mg/kg for 1964 (Huntley et al. 1993). In a study of Eagle Harbor, an estuarine bay of the Puget Sound in which sediments were contaminated with creosote from a wood treatment facility, total PAHs were detected at concentrations as high as 6,461 mg/kg (Swartz et al. 1989).

In the vertical profile of sediments in a seep area at the base of a hill where PAHs emerged after being transported approximately 400 meters in ground water from a buried subsurface coal tar source, naphthalene was detected at 2–45 ppm (Madsen et al. 1996).

6.4.4 Other Environmental Media

Since wood and coal tar creosotes are complex mixtures, techniques for relating apparent bioaccumulation or biomagnification in food chains to human health concerns are not well defined. Fish or shellfish directly exposed to coal tar creosote wastes will be tainted by offensive odors and tastes. Extracts of shellfish taken from the wharf of the biological station in St. Andrews and from Passamaquoddy Bay (both in New Brunswick, Canada) indicated contamination with creosote oil (Zitko 1975). Concentrations of creosote oil found were as follows:

Shellfish	Location	Concentration, µg/g lipid
mussel	Biological Station	1,046
periwinkle	Biological Station	3,254
	Passamaquoddy Bay	459
whelk	Biological Station	354
	Passamaquoddy Bay	202
clam	Passamaquoddy Bay	459

The biological station's wharf had been periodically repaired using lumber treated with coal tar creosote; no other sources of coal tar creosote in the vicinity of the Passamaquoddy Bay sampling site were known. The author suggested that the differences in creosote oil concentration in periwinkles and whelks collected in the same localities may indicate that PAHs are not bioaccumulated. However, in an estuarine environment near a Pensacola, Florida, creosote-contaminated wood-preservation facility site, a native mollusc (*T. haemstoma*) and a nonnative mollusc (*C. virginica*) both exhibited bioaccumulation of fluorene, pyrene, and phenanthrene at up to 10 times greater than observed in controls (Elder and Dresler 1988).

Additionally, a study at a creosote spill near Lake Pontchartrain in Louisiana, provided some indications that biomagnification through food chains leading to humans can take place. This study documented the bioaccumulation of creosote-derived PAH fractions in the marsh clam *Rungia cuneata* (DeLeon et al. 1988). With total PAH levels in the ambient water #25 ppb, caged clams introduced to an area near a major creosote spill showed tissue concentrations of benzopyrenes up to 600 ppb after 4 weeks of exposure. This clam is a major food item for crustaceans such as the blue crab that are part of commercial fisheries in the Lake Pontchartrain area.

Creosote-treated wood such as marine pilings may be left in the environment for many years. The USDA reported that residual creosote in marine pilings after 25, 40, and 59 years of service ranged from 280 to 380 kg/m^3 (HSDB 2000).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Potential sources of non-occupational human exposure to creosote include contact with creosote-treated wood products (e.g., railroad ties used for landscaping), incineration of creosote-treated scrap lumber, and contact with contaminated environmental media at hazardous waste sites (e.g., ingestion of contaminated ground water). At the Koppers Company, Inc. NPL site in Texarkana, Texas, where a creosote wood treatment facility existed for 51 years prior to being converted to a residential area and an industrial site (sand and gravel company), a study by the Texas Department of Health found an increased incidence of skin rashes in residents who had dermal contact with soil at the site (Agency for Toxic Substances and Disease Registry 1994).

Risk of exposure to creosote constituents through contact with contaminated ground water will vary with the individual chemicals involved as well as with the mix of chemicals present at any one time and the environmental conditions. Physical and chemical properties of the compounds, including solubility and molecular weight, will affect distance which a contaminant plume may travel from the source, as well as its susceptibility to biodegradation or sorption (King and Barker 1999). The environment in which contamination occurs is also of importance since natural attenuation of chemical compounds may be dependent on whether oxidizing or reducing conditions are present. In an investigation of natural attenuation of contaminant plumes from an emplaced coal tar creosote source, King et al. (1999) observed greater and more rapid decreases in plume mass for some compounds, such as phenol, *m*-xylene, and carbazole, while the dibenzofuran plume mass and extent remained relatively constant, and the plume mass and travel distance from the source for naphthalene and 1-methylnaphthalene increased throughout the 4-year study. Therefore, potential for exposure to creosote constituents present in ground water will differ from location to location and over time.

Direct exposure of homeowners to wood treatment products containing creosote should be limited, since EPA has restricted the sale and use of such products to certified applicators. Industrial sources have noted that there have been no reports or instances of health effects allegations in the last 20 years (ending in 1996), except for rare reports of skin irritation resulting from public contact with creosote-treated wood.

Another potential source of nonoccupational exposure is the therapeutic use of coal tar shampoos for anti-dandruff therapy, coal tar ointments for treatment of eczematous dermatitis, and mineral coal tar for the treatment of psoriasis. Adsorption of PAHs may occur through the skin, lungs, and gastrointestinal tract (Strickland et al. 1996). van Schooten et al. (1994) measured the urinary excretion of a specific PAH metabolite, 1-hydroxypyrene, to assess the internal dose of PAH after acute dermal application of coal tar shampoo. The shampoo selected for the experiment had a PAH concentration of 2,840 mg/kg, including pyrene (285 mg/kg) and benzopyrene (56 mg/kg). In other brands, the concentrations were at least 100 times lower. A single use of the coal tar shampoo resulted in increased 1-hydroxypyrene excretion in all participants. The mean increase of totally excreted 1-hydroxypyrene on day 1 was 10 times the pre-experiment background values. On day 2, the mean increase was 5 times. Interindividual variation was considerable, with a variation in the first day increase of between 3 and 20 times. The 1-hydroxypyrene values observed in coke oven workers are similar to the values obtained on day 1 after a single treatment with coal tar shampoo (0.4–8.3 μmol/mol creatinine) (van Schooten et al. 1994). However, exposure levels determined using the 1-hydroxypyrene biomarker may be affected by the time of measurement following exposure (Viau and Vyskocil 1995). Viau and Vyskocil observed maximum excretions of 1-hydroxypyrene in urine a few hours after exposure to pyrene in a coal tar-based shampoo or following dermal contact with either creosote or pyrene.

Occupational exposure to PAHs and other constituents of creosote may occur in several industries where workers are exposed to coal tar creosote, coal tar, coal tar pitch volatiles, or products containing creosote. Such occupations include jobs in the wood preserving industry, railroad work (installation and removal of crossties), treated lumber installation work involving structures such as fences or bridges, electric utility work involving treated poles, coke oven work, jobs in the rubber industry or tire plants, road paving work, roofing work, chimney cleaning, aluminum smelting work, iron foundry work, steel plant work, and site remediation work involving creosote-contaminated environmental media.

Individuals working in the wood-preserving industry comprise the largest portion of the population potentially exposed to coal tar creosote. Workers employed at creosote pressure-treatment facilities may be exposed by direct dermal contact or by inhalation of volatilized components. Potential exposure to coal tar creosote in these plants is minimized by the use of closed systems for receiving, transferring, mixing, storing, and applying the mixture to wood products. Similarly, dermal exposure from the handling of freshly treated wood is minimized by the use of highly mechanized processes. Exposure via inhalation, however, is more likely to occur. For example, worker exposure may be significant during opening of treatment cylinder doors and cylinder cleaning operations (EPA 1981b). Inhalation and

dermal exposure are also more likely in plants using nonpressure treatment methods such as thermal and dip treatments in open tanks. An estimated 100 workers were involved in commercial thermal and dip treatment operations in the late 1970s. Some of these workers experienced consistently high inhalation exposures (USDA 1980). Other historical nonpressure treatment exposures included an estimated 50,000 individuals (e.g., homeowners, farmers, landscapers) who applied creosote in noncommercial brush, dip, spray, and soak treatments (EPA 1981a). Dermal contact and inhalation may have resulted in exposure to high concentrations of creosote components for these individuals, but the exposures were usually of intermittent frequency (USDA 1980). However, designation of creosote products as restricted use pesticides by EPA in 1986 has probably decreased the number of individuals potentially exposed in these nonpressure wood treatment applications (EPA 1986b).

In 1996, there were 25,000 workers employed in 75–100 domestic wood treatment plants using coal tar creosote. As a result of the use of engineering controls and personal protective equipment (e.g., respiratory protection and impervious gloves) required in the 1986 settlement of the EPA Special Review process,[1] airborne exposures to creosote components in the workplace are generally below the OSHA permissible exposure limit (PEL) of 0.2 mg benzene soluble particulates per m^3 air (Rivers 1990).

However, prior to the consistent use of these controls by industry, workers were potentially exposed to higher airborne concentrations of creosote constituents. For example, the concentrations of creosote (i.e., coal tar pitch volatiles) components in 3- to 8-hour personal air samples, taken over a 2-day period at a railroad tie treatment facility in Somerville, Texas, were found to range from 0.003 to 1.211 mg/m^3 (NIOSH 1980b). Another industrial hygiene survey of worker exposure to creosote at a wood-treatment facility in Tacoma, Washington, showed coal tar pitch volatiles in personal air samples ranging from <0.0004 to 0.112 mg/m^3 (NIOSH 1981b). The higher concentrations were found at the end of the treatment process when the cylinder was opened. NIOSH investigated creosote exposure among dock builders in Brooklyn, New York, in 1980. Employees were reported to have substantial direct skin contact with creosote. Breathing zone concentrations of the cyclohexane extractable fraction of the coal tar pitch volatiles ranged from 0 to 0.059 mg/m^3 of air (NIOSH 1981a). Comprehensive studies of worker

---

A Special Review of a currently registered pesticide may be initiated by EPA when validated data indicate that certain types of toxicity (e.g., carcinogenicity, developmental toxicity, acute effects) exist for humans or for non-target plant or animal species. A formal process exists for notifying registrants and other interested parties, requesting further data regarding the pesticide in question, analyzing and reporting risks and benefits, and requesting public review. The final regulatory decision may be implemented over a period of time or it may be imposed immediately as an emergency action based solely on the EPA's finding of immediate danger to human health or the environment.

exposure to creosote in wood treatment plants have been conducted by Koppers Company, alone and in conjunction with NIOSH (Markel et al. 1977; SRI 1993). Data from these studies indicated that, on the average, employee exposure to particulate polycyclic organic materials (PPOM) was within the permissible level of 0.2 mg/m^3 recommended by NIOSH for coal tar pitch volatiles. The only components that could be reliably measured in the vapor-phase fractions collected were naphthalene, methylnaphthalene, and acenaphthene. The concentrations of these chemicals ranged from 0.54 to 2.0 mg/m^3. Fluorene and phenanthrene-anthracene were detected in trace quantities, but were not quantifiable. Benzene-soluble particulates (PPOM) ranged from 0.02 to 0.10 mg/m^3. The World Health Organization reported that air concentrations of creosote-derived PAHs were 0.05–650 μg/m^3 at a wood treatment plant where railway sleepers were treated with creosote; the main creosote constituents detected were naphthalene, fluorene, and phenanthrene (HSDB 2000). At a second plant, where a coal tar solution was used to treat railway sleepers and telephone poles, PAHs were detected in the air at 0.004–11 mg/m^3 (HSDB 2000).

A gravimetric analytical method has been used in most of these workplace monitoring studies. This method involves the collection of airborne particulates on glass fiber filters and subsequent extraction by solvents, such as benzene or cyclohexane. The extracted fraction of the particulate matter is determined by weighing. As a result of two significant shortcomings of this method, the inability to identify constituents of the airborne particulates and to sample vapor phase components, EPA (1981a) concluded that definitive information was not available on the identity of airborne components of creosote in workplace atmospheres. EPA (1981a) also stated that quantitative estimates of dermal exposures were not available for treatment plant workers. Quantitative inhalation or dermal exposure data for workers applying creosote in nonpressure treatment scenarios and for downstream workers who install, handle, or contact treated wood products were also unavailable. An industrial hygiene survey of wood treatment facilities conducted in Finland revealed that vapor phase components were an important source of worker exposure. Vapors were collected on XAD-2 resin (recovery 82–102%) and analyzed by gas chromatography (GC). PAHs were collected on glass fiber filters and analyzed with high-pressure liquid chromatography (HPLC) using a fluorescence detector. Most of the airborne contaminants in worker breathing zones were in the vapor phase, with naphthalene the main component, averaging 52% of the total concentration; the proportion of particulate PAHs to total concentration of vapors was <0.5–3.7%. The major components in the vapors have acute toxicity potential but are not as tumorigenic or mutagenic as the less volatile PAHs (Heikkilä et al. 1987). A recent study by Becker et al. (1999) demonstrated the feasibility of quantifying thiaarenes (sulfur-containing polycyclic aromatic hydrocarbons). Using GC

with atomic emission detection, these authors measured thiaarene concentrations of 0.4–19.0 μg/m^3 in the personal air space of workers at an aluminum reduction plant who were exposed to coal tar pitch volatiles.

Exposure to coal tar creosote may also occur during installation of treated poles, during inspection and maintenance operations, and through casual contact (USDA 1980). One of the major end point uses of creosote is treatment of railroad cross ties. Since cross ties are installed mechanically by railroad companies, workers generally have minimal dermal exposure in this process. Exposure via inhalation, however, is considered to be moderate and consistent during this type of installation procedure. In other situations, cross ties may be installed manually, in which case, there is consistent moderate to high exposure via skin contact as well as by inhalation. The amount of exposure via skin contact ranges from low to high depending on whether workers wear protective clothing. Skin contact is considered minimal for railroad personnel who inspect ties in use, as well as for the general public who may have casual contact with creosote-treated cross ties. In instances where crossties are used for landscaping purposes, contractors involved in the sale and installation of freshly treated ties experience consistent moderate inhalation exposure and minimal to occasionally high dermal exposure.

Installation of treated lumber and timbers in structures such as bridges, piers, retaining walls, fences, and barns involves a significant amount of manual contact. Likewise, the installation of switch ties, cross planks, crossarms, block flooring, and fence posts is usually done manually. In these situations, human exposure via inhalation is considered moderate while exposure via skin contact may vary from minimal to high depending on the type of protective equipment used (USDA 1980).

Exposure of individuals installing treated fence posts, lumber, and timbers via inhalation of creosote volatiles (e.g., acenaphthene and naphthalene) can also occur when freshly treated materials are handled under calm, hot, sunny conditions (USDA 1980). Exposure may be even greater during warmer months when ambient temperatures are higher. Acenaphthene, fluorene, phenanthrene, anthracene, and fluoranthene were observed to undergo more volatilization from creosote-treated wood at 30 EC than at 4 EC (Gevao and Jones 1998).

The risk of direct dermal contact is particularly high for workers installing treated poles. Activities such as attaching fittings often preclude the use of protective gloves, and as a result of creosote bleeding from the treated poles, the potential for dermal contact of workers performing maintenance operations persists for years after installation (Henningsson 1983).

Individuals employed in industries that manufacture and process creosote or products containing creosote may be exposed to the highest concentrations of this compound. The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated that 241 workers employed at 3 facilities were potentially exposed to creosote in the United States (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

Rubber processing workers at a tire plant in Poland who were occupationally exposed to coal tar pitch volatiles were found to have been exposed to excessive (>0.2 mg/m^3) levels of PAHs, including benzo[a]pyrene (Rogaczewska and Ligocka 1994). Measurements of benzo[a]pyrene were generally in the range of <4–142 ng/m^3, but were as high as 3,470–6,060 ng/m^3 for workers who weighed the raw materials.

In an investigation of the effect of decreased dermal exposure to creosote on the internal dose of PAHs in workers at a creosote wood impregnation plant, the use of Tyvek coveralls worn beneath outer work-clothes decreased the internal dose of pyrene (Van Rooij et al. 1993b). Workers not wearing the overalls had total pyrene skin contamination of 47–1,510 μg/day and had urinary levels of 1-hydroxypyrene of 6.6 μg. For dermally protected workers, dermal pyrene contamination was approximately 35% less than that of the unprotected workers and urinary levels of 1-hydroxypyrene were 3.2 μg. The low level of efficacy was attributed to uncovered skin areas (face, wrists, ankles). Volatile pyrene in the breathing-zone air was measured at 0.3–3.0 μg/m^3. The authors determined that for creosote workers, the level of dermal exposure to PAHs is the main determinant of the internal exposure dose; 15 times more pyrene was absorbed through dermal uptake than through respiratory uptake. Data from earlier studies indicate that the daily skin contamination with pyrene was higher for creosote workers (median of 350 μg) compared with that measured for coke oven workers (70 μg) and road pavers (117 μg); for aluminum workers, a pyrene level of 395 μg was measured (Van Rooij et al. 1993b).

Previously, the only information on biological indicators of exposure to coal tar found in the available literature involved a study of 1-hydroxypyrene in the urine of a creosote wood-treatment plant worker (Jongeneelen et al. 1985). The pyrene metabolite, 1-hydroxypyrene, is now more commonly used as a biological indicator to assess total PAH exposure in several industries as well as for nonoccupational uses of coal-tar based products (Malkin et al. 1996; Strickland et al. 1996). Elovaara et al. (1995) studied inhalation and dermal exposure to naphthalene and 10 large PAHs in creosote impregnation plant workers. Air concentrations of the compounds were measured and compared with measurements of

urinary 1-hydroxypyrene. Urinary concentrations, due to high dermal exposures were high (16–120 μmol/mol creatine) even in the morning, were lower in postshift measurements (19–85 μmol/mol creatine) and then were highest in the evening (27–122 μmol/mol creatine), indicating that time of sampling is important. The authors concluded that the biomarker was useful in determining exposure to 3- to 6-ring PAHs, but not to naphthalene volatiles.

Jongeneelen (1992) related urinary concentrations of 1-hydroxypyrene for coke oven workers exposed to fumes containing PAHs to measured levels of coal tar pitch volatiles in order to equate the biological indicator data with lung cancer relative risk levels determined using epidemiological data obtained from U.S. and European coke plants. A urinary concentration of 2.3 μmol/mol creatine was equated with the threshold limit value (TLV) (ACGIH) of 0.2 mg/m^3 for coal tar pitch volatiles, and consequently with the relative risk for lung cancer of approximately 1.3 for a group of exposed workers. Although an empirical relationship between the biomarker 1-hydroxypyrene and relative cancer risk in an exposed group may be determined, because creosote constituents vary from source to source, and because the carcinogenic PAH fraction and the routes of exposure will also vary, the health risks related to exposure to coal tar creosote versus coal tar pitch volatiles versus coal tar will differ between exposed groups such as creosote and coke oven workers (Viau et al. 1995). Viau et al. (1995) did conclude, however, that PAHs from background environmental contamination and from smoking could be excluded from consideration of urinary excretion of 1-hydroxypyrene within a certain group of workers.

Coal-handling workers at a coke oven who were exposed to coal-tar sludge (67% coal tar) through dermal contact had increased urinary 1-hydroxypyrene concentrations following work shifts (Malkin et al. 1996). Urinary concentrations of the biomarker increased from a preshift mean of 1.00 μmol/mol creatine to a postshift level of 1.7 μmol/mol creatine. The increases were attributed to dermal exposure, as exposure to volatile pyrene was determined to be minimal.

A review paper of studies using the concentration in urine of 1-hydroxypyrene as a biomarker of PAH exposure included levels reported in various studies (Strickland et al. 1996). The respective pre- and postshift urinary excretion levels of 1-hydroxypyrene for coke oven workers were 0.89 and 2.47 μmol/mol creatine; for asphalt pavers, respective levels were 1.35 and 1.76 μmol/mol creatine.

Other biomarkers used to determine exposure to the creosote include urinary concentrations of 1-naphthol, 2-naphthol, and 1-pyrenol. Naphthalene is the main volatile present in creosote vapors. For workers exposed to creosote volatiles during tar distillation, Bieniek (1997) measured volatile

concentrations of 0.77 mg/m^3 for naphthalene, 0.016 mg/m^3 for 1-naphthol, and 0.012 mg/m^3 for 2-naphthol; corresponding urinary concentrations of 693.1 and 264.4 μmol/mol creatine were measured for 1- and 2-naphthol, respectively.

For workers exposed to creosote by chiseling coal tar pitch layer or by handling creosote-impregnated wood, exposure to total PAHs and 4- to 6-ring PAHs was 50 times higher for the worker exposed to the coal tar pitch layer while exposure to volatile naphthalene was >6 times higher for the wood handlers (Heikkilä et al. 1995). Total PAHs and 4- to 6-ring PAHs were measured at 440 and 290 μg/m^3, respectively, in the work area of the chiseler. Urinary concentrations of 1-pyrenol were 2–4 times higher for the chiseler compared with the wood handlers. Volatile naphthalene was measured at 1,000 μg/m^3 in the work area of the wood handlers and 160 μg/m^3 in the work area of the chiseler. Urinary concentrations of 1-naphthol were 15–20 times higher for the wood handlers as compared with the chiseler.

Workers in a creosote railroad tie impregnation plant exposed to 1.5 mg/m^3 naphthalene, 5.9 μg/m^3 particulate PAH, and 1.4 μg/m^3 4- to 6-ring PAHs were measured for the urinary biomarker 1-naphthol (Heikkilä et al. 1997). Postshift urinary concentrations were a mean of 20.5 μmol/L; urinary concentrations in occupationally nonexposed male smokers were below the detection limit of 0.07 μmol/L. The authors concluded that 1-naphthol was a good biomarker for determining exposure to volatile naphthalene from creosote, but was not a good indicator of inhalation or dermal exposure to PAHs from creosote.

Polycyclic aromatic hydrocarbons are capable of forming adducts with DNA in cells. Exposure to PAHs from creosote were measured in the personal work areas of coke oven workers in the Czech Republic (Lewtas et al. 1997). Measured levels of DNA adducts in white blood cells of a nonoccupationally exposed population were well correlated with the low to moderate environmental exposures. The DNA adducts of the coke oven workers who were exposed to carcinogenic PAHs at levels of <5–>200,000 ng/m^3 (<0.005–>200 μg/m^3) did not correlate well with the exposure levels. These authors concluded that various mechanisms were responsible for the lower DNA-binding potency at the higher exposure levels, precluding the use of a linear model for dose-response extrapolation in risk assessment.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are exposed to creosote via the same routes that adults are, including inhalation of contaminated air, ingestion of ground water used as a source of drinking water, and dermal contact with contaminated soil or products treated with coal tar creosote. Additionally, small children are more likely than adults to be in close contact with yard dirt or playground dirt, lawns, and indoor (carpet) dust. Creosote residues bound to soil or dust particles in carpets or on bare floors may present an exposure route for infants and toddlers through dermal contact and oral ingestion. Children are known to participate in frequent hand-to-mouth activity and to have a tendency to put foreign objects into their mouths. As a result of this behavior, children may ingest creosote present in soil and dust or through direct transfer of the chemical from their skin to their mouths. Children are lower to the ground than adults and something which may exist at arm or hand level for an adult may be at mouth level for a child. Because of behavior such as putting their mouths on objects or chewing on objects, children may be exposed to coal tar creosote through oral ingestion of the chemical through chewing on treated wood, such as fences, bridge, or pier railings. Adsorption of PAHs may occur through the skin, lungs, and gastrointestinal tract. However, exposure to certain levels of creosote constituents does not mean that the compounds will be bioavailable at those levels. No U.S. data were found on exposure or body burden measurements made on children.

Coal tar creosote is widely used for the preservation and water-proofing of wood which is used for utility poles, railroad ties, log homes, fence posts, barns, bridges, piers, and marine pilings. Creosote is also used in roofing and road paving; is used and/or produced in coke oven operations, and in the aluminum, iron, and steel industries; and is used therapeutically in coal-tar based shampoos, as a treatment for

psoriasis and eczema, and as a treatment for intestinal ailments. Prior to its designation as a Restricted Use Pesticide in 1986, it was available for home and farm use.

Children are likely to play in or near areas where adults would be less likely to venture, such as areas with no trespassing signs, in creeks, on the ground, in the dirt, in ditches near where utility poles are present, and on or near railroad tracks. Additionally, children are likely to collect and bring home found pieces of wood for use in building clubhouses or treehouses. Because coal tar creosote is used to preserve utility poles and railroad ties, playing near utility (telephone or electrical) poles and near or on railroad tracks may pose a risk of exposure to children. Children are subject to inhalation exposure, which may be of increased risk during warmer months when volatilization of PAHs may be higher. Gevao and Jones (1998) observed greater volatilization of acenaphthene, fluorene, phenanthrene, anthracene, and fluoranthene from creosote-treated wood at 30 EC than at 4 EC. However, if the creosote constituents have leached downward from the treated wood and are present in the soil surrounding the utility poles or railroad tracks, volatilization from the soil surface is not as likely, as the majority of the coal tar creosote would be bound to the soil particles. In that case, and in the case of direct contact with treated poles or railroad ties, children are more likely to be exposed dermally and through oral ingestion which may occur when they put unwashed hands in their mouths. No U.S. data were found documenting significant exposure to children through such means as ingested soil or dust particles.

Children may be exposed to coal tar creosote when playing near abandoned hazardous waste sites or if their parents are occupationally exposed to creosote-contaminated soil through involvement with site remediation or clean-up procedures and bring soil-bound contamination into the home on work clothes or footwear, despite preventative procedures which may be in place at the work site. Creosote constituents have been measured in the surface soil at levels as high as 15,680 ppm (PAHs) at the site of an old wood preservation facility in Slidell, Louisiana, that was destroyed by fire (Acharya and Ives 1994). At an abandoned wood treatment facility in Conroe, Texas, PAH constituents of creosote have been detected in the 0.7- to 1.8-foot soil depth at maximum concentrations of 3.7 ppm for naphthalene, 3.4 ppm for methylnaphthalene, 3.8 ppm for dibenzofuran, 4.2 ppm for fluorene, and 2.2 ppm for anthracene (Bendient et al. 1984). At the Koppers Company, Inc. NPL site in Texarkana, Texas, where a creosote wood treatment facility existed for 51 years prior to being converted to a residential area and an industrial site (sand and gravel company), creosote-derived pyrene, fluoranthene, phenanthrene, and anthracene (base/neutral compounds) were measured in surface and subsurface soils at levels ranging from nondetectable to 1,000 ppm (Agency for Toxic Substances and Disease Registry 1994).

Although biodegradation of creosote in soil, on treated wood, in waste water effluent, and in aquatic environments has been observed, the process may only serve to reduce the total amount of creosote present. While the phenolic and LMW PAHs are degraded, the HMW PAHs that have been shown to resist biological attack may persist. Thus, it is possible that children exposed to the creosote constituents remaining in soil or other media following some biodegradation may be exposed to the more toxic components of creosote. However, the presence of creosote components in soil does not mean that the soil-bound compounds will be bioavailable if ingested. In a study of PAHs and their metabolites in the blood, feces, and urine of rats, the authors observed that rats that were orally exposed to contaminated soils showed significantly higher excretion of unchanged 1-OH-pyrene and benzo[a]pyrene in feces, and significantly lower excretion of 1-OH pyrene in both feces and urine, than did rats that were dosed with the pure compounds, indicating that the ingested soil-bound compounds were less available in the body for metabolism (van Schooten et al. 1997). Similar results were observed in a study of mice that ingested soil-bound coal tar (Koganti et al. 1998). In that study, the bioavailability of PAHs from soil-bound coal tar was estimated to be 9–75% less (based on 1-OH-pyrene excreted in urine) than that observed in mice dosed with an organic extract of the soil; estimates of PAH bioavailability based on chemical-DNA adduct formation ranged from nondetectable to 76%. Other authors have observed differences in bioavailability of soil-bound creosote constituents between types of soil. Goon et al. (1991) observed higher oral bioavailability of soil-bound benzo[a]pyrene with sand soil versus clay soil. The clay fraction of soil is more chemically and physically reactive than the sand fraction, allowing for greater adsorption. In the same study, the authors also observed, however, that the oral bioavailability of the compounds in soil remained at a similar level for the first 30 days following contamination, but decreased by 6 months following the initial contamination.

Children may be exposed to creosote constituents brought into the home by parents or other household members who are occupationally exposed. Creosote residues may be present on clothing items and shoes of workers employed in industries where creosote-derived products are used or produced, and utility company workers who are in contact with treated wood. Exposure to children may occur through dermal contact with contaminated items. Because children are likely to be in close contact with carpet or floors, transfer of contaminated dirt from work shoes to carpeting provides a means of exposure. Respiratory exposure from contact with occupationally exposed workers is not likely to be significant.

A potential source of exposure in infants is the presence of creosote constituents in breast milk. The hydrocarbons found in coal tar creosote are lipophilic substances and, as such, may potentially be found in breast milk, although this has not been assessed. No data were found in the available literature on the

presence of creosote constituents in breast milk. It has been determined that creosote-derived PAHs may cross the placenta (Agency for Toxic Substances and Disease Registry 1993a). For more information on the health effects of PAHs, the reader is referred to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995).

Data were not available in the literature on the weight-adjusted intake of creosote by children. In one documented case, creosote fumes caused methemoglobinemia in an infant, leading to temporary hypoxia and cyanosis (Dean et al. 1992).

Data were not available in the literature on the dietary exposure of creosote to children. Based on the bioaccumulation of creosote constituents in fish and other aquatic organisms, and the potential for uptake or contamination in plant food sources, dietary exposure is theoretically possible, but is unlikely to be significant. An exception to this may be in residential areas such as that built on the old Koppers Company, Inc. site. Homegrown produce grown in contaminated soils may provide a significant source of exposure to children. The drinking of chaparral tea may result in oral exposure to wood creosote. Case reports of people who have drunk chapparal tea indicate kidney damage as a likely outcome (Gordon et al. 1995).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals living in the vicinity of hazardous waste sites and abandoned wood-treatment plants contaminated with coal tar creosote may experience higher levels of exposure than the rest of the general population. These environmental exposures generally are at a lower dose but of longer duration than the occupational exposures.

Individuals who apply coal tar creosote directly to wood, including farmers, carpenters, and homeowners who come in contact with creosote-treated wood products, are believed to be exposed to the highest levels of creosote components via inhalation and dermal contact. It has been estimated that historically about 4,000 workers may have been routinely exposed and up to 50,000 people may have been intermittently exposed to coal tar creosote through its application as a preservative to wood products (USDA 1980). The size of this population may have decreased since EPA restricted the use of creosote to certified applicators.

Other individuals who are potentially exposed to coal tar creosote, coal tar, coal tar pitch volatiles, or products containing creosote include coke oven workers, rubber industry or tire plant workers, road paving workers, roofers, chimney cleaners, aluminum smelting workers, iron foundry workers, steel plant workers, and site remediation workers who are involved with creosote-contaminated soils or water.

Whether from bioaccumulation or from direct exposure, fish and shellfish may accumulate creosote constituents at concentrations high enough to prompt public health officials to issue consumption advisories. As of September 1994, creosote was involved in the two fish consumption advisories listed below (EPA 1995):

State	Waterbody	Geographic Extent
Louisiana	Bayou Bonfouca	7 miles
Oregon	Willamette River	1,000 foot radius from McCormack and Baxter wood treatment site

6.8 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of creosote is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of creosote.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Limited physical property data, such as boiling point and density (see Table 4-2), are available for the coal tar creosote mixture. Additional physical and chemical property data, such as water solubility, vapor pressure, K_{oc}, and Henry's law constant values would be useful in order to predict the partitioning and transformation of coal tar creosote components in air, water, and soil. These values are currently not available because their determination is complicated by the fact that creosote is a mixture of variable composition. However, data on vapor pressure, water solubility, etc., are available for individual components of creosote, and these can be used to estimate the behavior of creosote.

Production, Import/Export, Use, Release, and Disposal. Manufacturing methods are well described in the literature. Production figures are limited because of the confidential nature of this business information. Uses of creosote, both coal tar and beechwood, are well described. Since the use of coal tar creosote as a wood preservative has been restricted, the potential of the population to be exposed is greatly diminished. The major releases of creosote resulting from treatment processes at wood-preserving plants are known, but the levels are not well quantified. Current production, release, and disposal information would assist in identifying the levels of creosote present in the environment and, thus, populations potentially exposed as a result of these processes. Creosote sludge from production processes can be treated and disposed on-site with proper groundwater monitoring. Creosote can no longer be disposed in hazardous waste landfills unless treated to EPA specified standards. Creosote-treated wood used in industrial applications can be burned in an industrial incinerator or boiler; however, treated wood used in domestic or farm applications should be buried rather than incinerated.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 1999, became available in 2001. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The limited information available regarding transport and partitioning of creosote components among environmental compartments indicates mobility of water soluble PAHs, phenol, and heterocyclic constituents of the mixture in water; sorption of PAH components in soils; and bioconcentration of creosote-derived PAHs by terrestrial and aquatic organisms. In an examination of the partitioning of coal tar-derived PAHs into ground water and the usefulness of a computer model to simulate such, Lee et al. (1992) found that theoretically “ideal” behavior was observed for the individual compounds and that the model was useful in estimating concentrations in ground water. This finding indicates that, although coal tar is a complex mixture of compounds with varying physical and chemical properties, the fate of the individual compounds may be modeled as if they were present as single contaminants. Additional studies on the behavior of the transport of the individual components of creosote when present as a mixture may be necessary. Biotransformation appears to be the most important degradation process in soils and aquatic environments. Additional data on the transport of volatile creosote components in the atmosphere and the partitioning of creosote released to surface waters and soils would be useful. Quantitative data on the rates of biotransformation in soils, surface water, and ground water under aerobic and anaerobic conditions would also be useful. Data on the degradation rates or relative persistence of the HMW PAHs would be particularly useful since these components of

creosote are among the more toxic fraction, and are less soluble and less readily degraded than the LMW PAHs. The importance of other transformation processes, such as photolysis, photooxidation, and hydrolysis, in relation to biotransformation and rates of transport between media, should also be defined. These data would be useful to help define potential pathways of human exposure and to estimate ambient concentrations of creosote components in environmental media.

Bioavailability from Environmental Media. Very limited information was found in the available literature regarding the uptake of creosote components by living organisms from contaminated water and soil at hazardous waste sites. Studies have been done with persistent constituents (e.g., PAHs) which show that plant uptake from soils is limited (Agency for Toxic Substances and Disease Registry 1995; Gile et al. 1982), whereas bioconcentration in aquatic organisms from contaminated surface waters has been demonstrated. Data from human and animal studies indicate that creosote components are absorbed following ingestion or inhalation, or after dermal contact with the mixture. Additional data on the bioavailability of creosote components following ingestion or inhalation of creosote-contaminated soils would be helpful. Of particular importance are data on the bioavailability of the HMW PAHs that may persist in soil and are resistant to many bioremediation techniques.

Food Chain Bioaccumulation. Very limited information was found in the available literature regarding the biomagnification of creosote-derived compounds among food chain trophic levels. Many aquatic organisms are able to rapidly metabolize and eliminate PAHs, the major constituents of the commercial mixture (Eisler 1987). However, the marsh clam *Rungia cuneata*, which is a major food item for crustaceans such as the blue crab that are part of commercial fisheries, showed tissue concentrations of benzopyrenes up to 600 ppb after 4 weeks of exposure to creosote after a major spill; total PAH levels in the ambient water were #25 ppb (DeLeon et al. 1988). Additional studies are needed to determine whether this bioaccumulation indeed moves up the trophic chain to pose human exposure concerns. Also, vegetables and other produce grown in or around deposits of creosote wastes may uptake or be contaminated by creosote constituents through adsorption to roots or surfaces. Since these materials will be hard to remove through washing or other food preparation processes, consumption of these may provide a route for exposure. Additional data are needed on the ability of agricultural plants to uptake creosote constituents.

EPA (1993) has issued Fish Sampling and Analysis Guidance that provides an overview of the issues involved in considering fish consumption advisories for PAHs. Since PAHs may be derived from

creosote or other sources such as the combustion of petroleum products, state-issued advisories for PAHs should also be examined to see if creosote-derived sources are at issue.

Exposure Levels in Environmental Media. Limited information is available regarding ambient concentrations of creosote-derived PAHs in soils (Davis et al. 1993; EPA 1987b; HazDat 2002) and no data are available regarding atmospheric concentrations of creosote components. Very limited information is available on concentrations of component compounds in surface waters (DeLeon et al. 1988) and sediments (Madsen et al. 1993, 1996), including those receiving wood treatment plant effluents. Data are still lacking for contaminated media in the vicinity of hazardous waste sites. These data would be useful to estimate the exposure of populations coming into contact with components of the mixture through inhalation of contaminated air, consumption of contaminated surface water or ground water, or direct dermal contact with environmental media.

Reliable monitoring data for the levels of creosote in contaminated media at hazardous waste sites are needed so that the information obtained on levels of creosote in the environment can be used in combination with the known body burden of creosote to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. A population exists that is potentially exposed to creosote through contact with contaminated media at hazardous waste sites and with treated wood products. A second potentially exposed workforce population exists at wood treatment facilities and in other industries in which creosote-derived products are produced or used. Currently, no information exists that demonstrates tissue levels of any components of the mixture in these populations. Although exposure is now estimated in occupationally exposed workers using urinary concentrations of biomarkers, such as 1-hydroxypyrene, actual exposure levels are harder to determine. Estimates of human exposure to creosote constituents, or body burdens of creosote components, are complicated by the lack of information on exposure to creosote constituents and levels of creosote-derived components in the environment. Collecting information on tissue levels of creosote components in humans would be necessary to examine the relationship between levels of creosote-derived compounds in the environment, human tissue levels, and subsequent development of health effects. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Data on the exposure levels and body burden measurements of creosote constituents in children are needed to determine the risks associated with exposure. Because small children are likely to engage in hand-to-mouth activity (with unwashed hands) and to be in close contact with dirt, lawns, and indoor (carpet) dust, and because creosote residues bound to soil or dust particles in carpets or on bare floors, may present an exposure route for infants and toddlers through dermal contact and oral ingestion, bioavailability from soil data are necessary. Bioavailability data are also necessary to determine the amount of contaminant that children may be exposed to through dermal contact with treated wood, such as may occur when children play on railroad tracks. Data on the bioavailability of creosote constituents from treated wood are also necessary because through behaviors such as putting their mouths on objects or chewing on objects, children may be exposed to creosote through oral ingestion of the chemical through chewing on treated wood, such as fences, bridge, or pier railings.

Data are also necessary on whether children are different from adults in their weight-adjusted intake of creosote compounds. Creosote compounds may be present in dietary sources such as fish or food grown in or near contaminated soils. While data on the oral bioavailability of some soil-bound components of creosote are available, it is necessary to determine the exposure contribution of such sources to children and to determine the contribution to body burden in children.

Data are necessary on the number of children (<18 years of age) who may be occupationally exposed to creosote and on the levels of exposure they may experience. It is possible that some workers in industries such as tire plants or those involved in roofing or road paving may be exposed to creosote in their daily tasks. Information on this is may be important in assessing whether occupational exposure in children is similar to the levels observed for all occupationally exposed workers.

Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for creosote were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

A search of federally funded research in progress (FEDRIP 2000) revealed several studies that are discussed in this section. Creosote is currently subject to a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) registration standard and data call-in by EPA. In addition, the Creosote Council II is planning to conduct a research program that includes testing for worker exposure and protection.

Remedial investigation/feasibility studies being conducted at the 46 NPL sites where creosote has been found and at the numerous creosote-contaminated Resource Conservation and Recovery Act (RCRA) corrective action sites should provide data on concentrations of the mixture in contaminated media in the vicinity of hazardous waste sites. For example, creosote constituents have been found in surface water impoundments and soil samples taken near wood treatment facility sites in Colorado, Louisiana, Texas, and Montana.

The Cornell University Superfund Basic Research and Educational Pilot Program was (1992) established with the aim to conduct research on the bioavailability and impact of hazardous substances in health and ecological risk, specifically as related to exposure, neurological, and immunological effects; and the remediation of sites containing polychlorinated biphenyls (PCBs), PAHs, and heavy metals. Relevant areas of study include biodegradation of non-aqueous phase liquids (NAPLs), kinetic controls on environmental fate in soil and aquifers, sequestration in soil and its effects on bioavailability, and microscale parameters modeling macroscale fate in soil. A current study led by Dr. Madsen concerns the determination of factors leading to the persistence of creosote-derived PAHs (naphthalene and phenanthrene) in fresh water sediments at a field site.

The USDA is sponsoring a study by researchers led by Dr. Lee at Purdue University on the interaction of organic chemicals, including coal tar, with soils. Researchers are investigating and modeling the abiotic processes controlling the mobility and bioavailability of organic compounds in soil. They will be determining the adsorption of and release rates of PAHs from a coal tar/soil waste matrix.

The U.S. Geological Survey is investigating the fate and transport of immiscible contaminants, including coal tar and creosote wastes, in subsurface ground water. Models will be developed to simulate and predict the migration of slightly soluble, highly volatile immiscible contaminants in the field. These models will eventually aid in the design of control and abatement techniques.

Researchers at Brown University (Dr. Suuberg principal investigator) are conducting a study funded by OSTI to determine the vapor pressures and heats of vaporization of heavy, primary coal tars. The researchers are attempting to provide needed physical property data by means of direct measurements of the vapor pressures of coal tar fractions. They are also attempting to determine vapor pressures using well-established techniques and modifications of those techniques.

Data from field and laboratory studies of creosote-contaminated ground water are being analyzed by the U.S. Geological Survey to determine the transformation pathways of selected organic compounds, assess the relative importance of physical, chemical, biochemical, and microbial processes in the transformation of these compounds under ambient conditions, and study relevant biotransformation processes occurring in the subsurface ground water.

The National Science Foundation is sponsoring a study led by Dr. Richard Bartha of Rutgers University on the multisubstrate biodegradation kinetics of PAHs from creosote, coal tar, and diesel fuel. The relative biodegradabilities and substrate interactions of PAHs in sole and multi-substrate systems will be determined and related to dissolution kinetics processes governing bioavailability. An integrated mathematical model of the behavior of PAHs in NAPL-contaminated soils will be developed and validated.

The National Science Foundation is sponsoring a study by Princeton University (Dr. Catherine Peters, principal investigator) regarding the chemical, physical, and microbiological processes governing the behavior of mixtures of PAHs in NAPL-contaminated soils.

Dr. Luthy and co-workers at Carnegie-Mellon University, in a study sponsored by Department of Energy, are investigating the physicochemical and biochemical solubilization and mineralization of coal tar-derived PAHs. The study will address the rate-controlling processes for microbial degradation of the PAHs in both the environment and in waste water treatment processes; the kinetics of solute solubilization and rates of mineralization will be determined. The possible synergistic interactions between PAH-degrading bacteria and biosurfactant/emulsifier-producing bacteria will also be investigated. The results of the research should be applicable to both remediation of coal-tar contaminated soils in the environment and treatment systems for coal conversion process effluents.

EPA is sponsoring a study led by Dr. Mahaffey of the Ecova Corporation to develop an *in situ* process that will enhance the rate and efficiency of the biodegradation of hydrophobic organic chemicals at

military installations and Superfund sites. Research activities will focus on the identification of chemical or biological emulsifiers (surfactants) that will enhance the bioavailability of petrogenic waste (including creosote and coal tars), and thus enhance their biodegradation.

Researchers at Tienzyme, Inc. (B.W. Bogan, principal investigator) in State College, Pennsylvania, are investigating the use of surfactant- or surfactant/lipid-based formulations to enhance the removal of HMW PAHs from creosote- and tar-contaminated soils by bioremediation involving white-rot fungi.

The USDA is sponsoring several studies on creosote. Dr. Chow, Dr. Retner, and co-workers at the University of Illinois are investigating the effects of accelerated aging on the rate of biodegradation of creosote-treated red oak ties by common oak decay fungi. The effects of natural weathering on the rate of biodegradation of creosote-treated ties selected from tracks located in the Midwest will be examined. Computer models will compare the rates of biodegradation results of naturally weathered ties and ties exposed to accelerated aging processes.

Researchers at Mississippi State University (Dr. Borazjini, principal investigator) are investigating the *in situ* bioremediation of creosote and PCP contaminated water in an attempt to develop a rapid biological technique for the cleanup of ground water using oxygen, surfactants, cofactors, and micronutrients. Surfactants will be evaluated for their abilities to enhance the bioremediation of wood-preserving process waste water containing high concentrations of PCP, PAHs, oil, and grease.

Dr. Choong and other researchers at Louisiana State University are investigating the recycling of utility poles for use in engineered wood products. Creosote in the poles will be removed using organic extractants and steam, and the poles will be evaluated to determine their residual decay resistance and to determine the effect of residual creosote on the physical, mechanical, and gluing properties of the used utility poles. The study will include the reduction of the poles into smaller sized, defect-free wood materials for the production of engineered woods, as well as the determination of the effect of joint designs on the strength properties of the wood laminated composites made from the pieces of the poles.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring creosote, its metabolites, and other biomarkers of exposure and effect to creosote. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

The analytical methods used to quantify creosote and related mixtures in biological and environmental samples are summarized below. As noted in Chapter 4, coal-derived mixtures (creosote, pitch, tar) are chemically very similar; the methods used for their analysis are directed to the primary components of these mixtures. In most cases uncovered through a search of the recent literature, the methods used for coal-derived mixtures are based on analysis of high-pressure liquid chromatography (HPLC) with ultraviolet (UV) absorbance detection to nondestructively separate these compounds for collection and characterization.

The high resolving power of capillary gas chromatography (GC) is required for the successful analysis of coal-derived materials, since these mixtures can contain hundreds of components with very similar chemical properties. Guillen et al. (1992) and Blanco et al. (1992) have demonstrated the full power of capillary GC using both mass spectrometry (MS) and flame ionization detection (FID) for analyzing coal tar. Specific applications for biological and environmental analyses are described below.

7.1 BIOLOGICAL MATERIALS

The levels of creosote in biological materials can be estimated by measuring the PAH content in biological samples. Methods include GC/FID, GC/MS, and HPLC. Synchronous luminescence spectroscopy (SLS), ^{32}P-postlabeling, and immunoassay techniques, i.e., enzyme linked immunosorbent assays (ELISA) and ultrasensitive enzyme radio immunoassay (USERIA), are methods currently being developed to detect and quantify ultratrace levels of PAH adducts bound covalently to macromolecules

(e.g., DNA). Table 7-1 lists the available analytical methods for determining creosote/coal tar-derived PAH components in biological samples. GC/MS and HPLC have been employed to detect creosote-derived PAH complexes at ppt (pg/g) levels in human tissues, including adipose tissue, blood, and urine (Liao et al. 1988; Obana et al. 1981). The detection and quantification of trace levels of PAHs in biological tissues involves extensive and rigorous clean-up procedures including Florisil, silica, and alumina column chromatography (Liao et al. 1988; Obana et al. 1981).

There is considerable evidence, both *in vitro* and *in vivo*, that PAHs are enzymatically converted to highly reactive metabolites that bind covalently to macromolecules such as DNA, thereby causing carcinogenesis and mutagenesis in mammalian systems. Thus, benzo[a]pyrene (a procarcinogenic PAH and the most thoroughly studied one) is converted by specific cellular enzymes to the syn- and anti-isomers of 7β, 8δ-dihydroxy-(9δ, 10δ)-epoxy-7,8,9,10-tetrahydro-benzo[a]pyrene (B[a]PDE) and binds covalently to DNA, resulting in formation of the putative B[a]PDE-DNA adduct (Autrup and Seremet 1986; Harris et al. 1985; Haugen et al. 1986; Santella et al. 1995).

In an analysis of B[a]P and coal tar pitch volatiles in workplace air conducted by Ny et al. (1993), urine samples were analyzed for the pyrene metabolite 1-hydroxypyrene, and a high correlation between levels of this biomarker and PAH air levels was observed. Analyses were also conducted by HPLC with fluorescence detection. Tolos et al. (1990) reported results of 1-hydroxypyrene urinalysis for aluminum reduction plant workers, and showed a strong positive correlation between the compound and 17 environmental PAHs. This work verified the choice by earlier researchers (Jongeneelen et al. 1988) of the pyrene metabolite as a useful marker of exposure to PAHs. Elovaara et al. (1995) also demonstrated the usefulness of 1-hydroxypyrene as a biomarker for exposure to naphthalene and 10 other PAHs for creosote impregnation plant workers. Particulate PAHs were Soxhlet extracted with cyclohexane and analyzed by HPLC with fluorescence detection.

The ELISA technique has been employed for detecting antibodies in serum bound to B[a]PDE-DNA adducts. The USERIA method involves measuring the immunological response of B[a]PDE-DNA in the presence of rabbit anti-serum, alkaline phosphatase enzyme, and radiolabeled para nitrophenyl phosphate (PNPP). The radioactivity of the hydrolyzed tritiated PNPP is measured by a scintillation counter. Both ELISA and USERIA methods have been employed to detect PAH-DNA adducts at 10^{-15} mol levels in the blood and tissues of humans occupationally exposed to PAH (Amin et al. 1982; Harris et al. 1985;

Table 7-1. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Biological Samples

Form	Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Coal tar creosote, Coal tar	Adipose tissues	Benzene/hexane extraction of adipose tissue; addition of Na_2SO_4; cleanup with Florisil column; elution of PAHs with 8% benzene in hexane, sample concentration.	GC/MS	5–50 ng/g	52–95% recovery	Liao et al. 1988
Coal tar creosote	Liver homo-gentate	Extraction of homogenate with ethyl acetate; water removal (Na_2SO_4), concentration.	HPLC	No data	No data	Amin et al. 1982
		Saponification of minced tissue, extraction with hexane; clean up by solvent partition, concentration; purification by silica/alumina chromatography; concentration of eluent.	HPLC	0.006–0.46 ng/g	No data	Obana et al. 1981
Coal tar creosote	Blood	Separation of white cells; isolation of DNA by standard Rnase and phenol treatment.	ELISA	$1x10^{-15}$ mol BPDE per μg DNA	No data	Perera et al. 1988

Table 7-1. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Biological Samples *(continued)*

Form	Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Coal tar creosote, Coal tar		Isolation of PAH-DNA adduct from white cells; digestion of adduct with radiolabeled (^{32}P)ATP; radiolabeled adduct resolution by TLC.	^{32}P-post-labeling	0.3x10^{-15} mol BPDE per µg DNA	No data	Phillips et al. 1988
Coal tar creosote		Separation of lymphocyte cells and isolation of BPDE-DNA adduct by standard treatments.	ELISA or USERIA and SLS	0.006–0.23x 10^{-15} mol BPDE per µg DNA	No data	Harris et al. 1985
Coal tar creosote	Urine	Animal dosing with radiolabeled B[a]P; collection of urine, addition of MeOH; c-18 Sep-Pak column cleanup; elution with aqueous MeOH.	HPLC	5x10^{-12} mol 7-BPDE-Gua per µg of labeled B[a]P	No data	Autrup and Seremet 1986
Coal tar creosote, Coal tar pitch Coal tar		Hydrolysis of conjugates enzymatically; isolation of 1-pyrenol using SPE column.	HPLC/Fl	0.45 nmol/L	No data	Tolos et al. 1990
Coal tar creosote, Coal tar pitch		Hydrolysis of conjugates enzymatically; isolation of 1-pyrenol using SPE column	HPLC/Fl	10 nmol/L	84–88%	Ny et al. 1993

BPDE benzo[a]pyrene diol epoxide; B[a]P = benzo[a]pyrene; DMSO = dimethyl sulfoxide; ELISA = enzyme linked immunosorbent assay; Fl = fluorescence; Gua = guanine; GC/MS = gas chromatography/mass spectrometry; HPLC = high-performance liquid chromatography; NADP$^+$ = oxidized nicotinamide adenosine dinucleotide; SLS = synchronous luminescence spectroscopy; SPE = solid phase extraction; USERIA = ultra-sensitive enzyme radioimmunoassay

Haugen et al. 1986; Newman et al. 1988; Perera et al. 1988). The ^{32}P-postlabeling method involves a 5'-labeling of DNA adducts that have been digested with nuclease P_1 enzyme system to 3'-mononucleotides. Adducts present in the digest that were resistant to nuclease P_1 were thus labeled with ^{32}P, while unmodified nucleotides were not. The digested DNA adducts are separated by thin-layer chromatography (TLC) and quantified by scintillation counting. A detection limit of 0.3×10^{-15} mol of PAH adduct per μg of DNA (less than one adduct in 10^7 nucleotides) has been achieved (Philips et al. 1988).

7.2 ENVIRONMENTAL SAMPLES

As with biological samples, the PAH component fraction is most often used as an indicator of creosote contamination of environmental media. For example, screening for total PAHs is often used at hazardous waste sites when creosote contamination is suspected. The PAH fraction (neutral) is used in these analyses because it is more persistent than the acidic or basic fractions, which tend to be more mobile and biodegradable. The methods used to measure total PAHs can also be used to detect the nitrogen, oxygen, and sulfur heterocyclic components of the mixture. Table 7-2 lists the available analytical methods for determining creosote/coal tar-derived PAH components in environmental samples.

The efficacy of supercritical fluid extraction was demonstrated to be a promising technique for coal tar pitch (Camel et al. 1993). Extraction procedures for coal tar pitch volatiles on air sampling filters have been compared by Hekmat et al. (1994). Methylene chloride was shown to be superior as an extracting solvent to cyclohexane. For coal tar pitch volatiles collected on poly(tetrafluoroethylene) filters or glass fiber filters and extracted with benzene, cyclohexane, or dichloromethane, Hekmat et al. (1994) found that the highest recoveries were achieved with collection on poly(tetrafluoroethylene) filters, desorption with dichloromethane, and analysis using spectrophotometry (UV quantification). Cyclohexane was not found to be a suitable substitute for benzene. These authors also concluded that spectrophotometric methods were superior to gravimetric methods of measurement of coal tar pitch volatiles.

Hale and Aneiro (1997) reviewed recent progress made in improving analytical techniques for determining components of creosote in environmental media. The multiple extraction and purification steps required prior to chromatographic analysis is problematic in that compounds may be lost through volatilization or transformed through photodegradation. More efficient extraction procedures include supercritical fluid extraction, accelerated solvent, and microwave, and solid-phase extraction. Newer

Table 7-2. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Wooden sleepers (railroad crossties) in playground	Extraction of sample with ether; filtration through anhydrous sodium sulfate and evaporation of solvent; acid/base/neutral liquid-liquid partition.	GC/MS	1–3 ng/sample	No data	Rotard and Mailahn 1987
Coal tar creosote	Dissolution of sample in cyclohexane and extraction with 90% ethanol; evaporation of extract to dryness; dissolution of residue in cyclohexane, extraction with nitromethane; evaporation of extract to dryness and dissolution of residue with small amount of benzene.	GC	10 ppm	No data	Lijinsky et al. 1963
	Dissolution of sample in methylene chloride at a concentration of . 10% (w/w).	GC	No data	No data	Nestler 1974a
River sediments	Digestion of wet sediment sample in boiling EtOH/KOH; extraction of hydrocarbons into cyclohexane; extract concentration and Florisil column cleanup; elution of PAH complex with 50% methylene chloride/hexane; concentration of sample.	HPLC	No data	No data	Black 1982

Table 7-2. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Contaminated groundwater	Filtration through prebaked glass-fiber filters to remove suspended sediments; cleanup with bonded-phase extraction column; elution of organics from column with acetonitrile followed by methylene chloride; water removal (Na_2SO_4); concentration by nitrogen blow-down.	GC/MS	50 µg/L	95%	Rostad et al. 1984
Groundwater	pH to 12. Extraction with CH_2Cl_2. Drying and concentration of organic phase (containing neutral and bases). Adjustment of aqueous phase pH to 7 and extraction; then to pH 2 and extraction. Both extracts derivatized to TMS esters/ethers.	GC/FID	100 ppb	>90% for PAHs; .30–50% for phenols; .>70% for bases	Mueller et al. 1991
Impregnated wood (workplace)	Heating of sample at 60 EC in a chamber; cleanup with XAD-2 column; extraction with ether.	GC/MS	0.07–0 µg/L using ITMS (α, β, and sulfate)	116–128%	Heikkilä et al. 1987
	Collection of heated sample on a prewashed (cyclohexane) glass fiber filter; extraction of sample with cyclohexane and evaporation to dryness; dissolution of residue in acetonitrile/water (85/15).	HPLC	8 ng/m^3	No data	

Table 7-2. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Creosote treated wood	Heating of sample in injection port of GC.	GC	No data	No data	Lorenz and Gjovik 1972
Gas and particulate matter (workplace)	Pumping sample through a glass fiber filter-XAD-2 adsorbent sampling system; extraction with ether in ultrasonic bath; concentration of extract and dilution with acetonitrile.	HPLC	0.005–2.5 mg/m^3	87–102%	Andersson et al. 1983
Breathing zone air (workplace)	Pumping air through Teflon filters and sorbent tubes. Extraction of particulate and tubes with benzene. Concentration of extracts.	GC	0.05 mg/sample	No data	Tolos et al. 1990
Breathing zone air (workplace)	No information.	HPLC/Fl	No data	No data	Rogaczewska and Ligocka 1991
Breathing zone air (workplace)	Pumping air through filters and XAD resin. Extraction of both with benzene. Concentration.	HPLC/UV-Fl	No data	No data	Ny et al. 1993
Creosote	Dissolution in cyclohexane; washing with H_2SO_4; neutralization of acid fraction and extraction with cyclo-hexane; alumina column cleanup.	HPLC/UV or GC/MS	No data	No data	Galceran et al. 1994

Table 7-2. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water and sediment	Extraction (Soxhlet for sediment only) of PAHs with methylene chloride.	HPLC/ spectro-fluorometric detection	No data	Water - 74.4± 7.8% to 103± 1.1%; Sediment - 71.3± 2.9% to 105± 3.1%	Bestari et al. 1998
Creosote-treated wood	Soxhlet extraction of PAHs with dichloromethane; concentration of extracts and cleanup on silica column eluted with hexane; drying with anhydrous sodium sulfate; extraction in series with hexane, hexane: DCM (60:40); elution with hexane: DCM (60:40).	GC/FID	No data	HMW PAHs - 104±0.9% LMW PAHs - 84±5%	Gevao and Jones 1998
Sediment pore water and elutriate	Drying with anhydrous sodium sulfate; Soxhlet extraction with acetone:hexane (59:41); concen-tration of extract; cleanup on silica column eluted in series with hexane and dichloro-methane; concen-tration and redissolution in hexane.	GC/FID	2–5 ng/g	No data	Hyötyläinen and Oikari 1999b

Table 7-2. Analytical Methods for Determining Creosote/Coal Tar-Derived PAH Components in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Coal tar pitch volatiles on glass filters	Soxhlet extraction with dichloro-methane; cleanup on silica columns eluted with cyclohexane; concentration; HPLC separation using backflush.	GC/S-selective AED	4 ng/m^3	Cleanup recoveries were estimated at 97–100%	Becker et al. 1999

AED = atomic emission detection; Fl = fluorescence; FID = flame ionization detection; GC = gas chromatography; HMW = high molecular weight; HPLC = high-performance liquid chromatography; LMW = low molecular weight; MS = mass spectrometry; PAH = polycyclic aromatic hydrocarbon; UV = ultraviolet

methods also include on-line purification and coupling of extraction and chromatography. These authors found that MS use has increased, especially since ion traps and mass selective detectors have become more available. Other increasingly common methods are HPLC with fluorescence and diode array UV; and C-, S-, and N-selective GC detectors. The use of HPLC with fluorescence detection allows for a lower limit of detection for some PAHs than does GC/FID.

GC/FID or GC/MS are the most widely employed analytical techniques for the determination of coal-derived PAHs in contaminated ground water, railroad cross ties, and impregnated wood (Gevao and Jones 1998; Heikkilä et al. 1987; King and Barker 1999; Lijinski et al. 1963; Lorenz and Gjovik 1972; Nestler 1974a; Rostad et al. 1984; Rotard and Mailahn 1987). GC/FID is one of the methods recommended by EPA for detection of PAHs in waste water and solid waste (EPA 1986c). GC/FID was utilized by Bieniek (1997) to determine the breathing-zone air concentration of naphthalene in a coking plant. Hyötyäinen and Oikari (1999b) utilized GC/FID to determine PAHs in sediment pore water and elutriates.

Heikkilä et al. (1987; 1997), employed GC/MS to determine creosote levels in workplace air from impregnated wood. Detection limits of $10x10^{-6}$ to $50x10^{-6}$ g of creosote per m^3 of sample and recoveries of 82 and 102% were achieved. Heikkilä and co-workers measured the components of PAHs with reverse-phase HPLC using fluorescence detection. A similar study was conducted by Heikkilä et al. (1995) for a worker exposed to coal tar pitch. For the detection of creosote vapors, naphthalene was used as an indicator since it constitutes about 18% by weight of total PAHs in creosote (Andersson et al. 1983; Heikkilä et al. 1987). Rotard and Mailahn (1987) used a modified sample extraction procedure to identify various components of creosote extracts in railroad cross ties. The procedure involved the separation of compounds by functional group using acid, base, and neutral conditions. Detected compounds included phenanthrene, anthracene, and naphthalene (neutral extractions), quinoline, and isoquinoline (basic extraction), cresols, and phenols (acidic extraction). Mohammed et al. (1998) used GC/MS to determine creosote-derived PAHs in aquifer materials. Recent literature has shown that GC with (sulfur selective) atomic emission detection (CG/AED) is successful in determining the thiaarene fraction of total PAHs in the atmosphere without prior separation of the thiaarenes from the PAHs (Becker et al. 1999).

Grimmer et al. (1997) developed a technique using GC/MS for simultaneously determining 25 urinary metabolites as a measure for exposure to individual PAHs. Samples are treated enzymatically with glucuronidase and arylsulfatase and extracted with benzene or toluene; the extract is then divided and one part is treated with diazomethane to convert phenols into methylethers and the other part is used to convert dihydrodiols into phenols. Following further purification, individual metabolites are determined

using GC/MS. The detection limit for various compounds is approximately 0.01 ng. Inter-individual variation was significant. These authors determined that the correlation between inhaled PAHs to their urinary metabolites will vary with the individual, but appeared to be linear for an individual.

Rostad et al. (1984) developed a method for the isolation and detection of creosote in contaminated ground water. This method involved passage of the sample through a small column containing a solid-bonded phase sorbent, which retained the organic compounds. The authors indicated that this method is simple, faster, and cheaper to perform than the acid/base/neutral extraction procedure. It effectively isolated all organic compounds from contaminated ground water regardless of polarity, functional group, or water solubility in one step, thereby minimizing hazardous exposure to sample.

A study on the spatial and temporal distribution of PAHs from various sources (wood-preserving facilities, refineries, chemical manufacturers, etc.) was reported by Huntley et al. (1995). The concentrations of PAHs were shown to increase with sediment depth from analysis of core samples. Samples were analyzed using EPA Method 8310 (GC/MS).

HPLC with fluorescence detection has been used to identify coal-derived PAHs in river sediments (Black 1982). Andersson et al. (1983) employed an Amberlite XAD-2 adsorbent for isolating organic compounds from gas and particulate matter in a creosote impregnating plant. Good sample recoveries and detection limits were achieved. HPLC, with either fluorescence or UV detection, is an EPA-recommended method for the analysis of both solid and liquid hazardous waste (EPA 1986c). At present, HPLC cannot achieve the high resolution capability of capillary GC. HPLC, however, does offer some advantages for the determination of coal-derived PAHs in environmental samples. HPLC offers a variety of stationary phases capable of providing unique selectivity for the separation of PAH components and/or isomers that are often difficult to separate by GC. In addition, UV absorption and fluorescence detection provide sensitive and selective detection of PAHs. Rogaczeska and Ligocka (1991) reported results of a study of occupational exposure to coal tar pitch volatiles, including benzo[a]pyrene (B[a]P), by measuring B[a]P in air using HPLC with fluorescence detection.

An acid partition and alumina column clean-up procedures were used to analyze for several acridines (HPLC/UV) in creosote by Galceran et al. (1994). HPLC with fluorescence detection was used for analysis of the PAH components from a coal tar sample (NIST SRM 1597) as reported in a review article by Wise et al. (1993). Since fluorescence detection affords more selectivity than UV absorbance detection, less clean-up is required for certain sample types. This study also showed the utility of a multi-dimensional approach to PAH analysis from complex samples. This methodology involves use of normal

phase liquid chromatography (LC) to separate PAH fractions, which can then be analyzed by reverse phase LC with fluorescence. Coal tar pitch has also been analyzed using planar chromatography as an initial fractionation technique (Herod and Kandiyoti 1995). The resultant fractions were analyzed either directly on the silica by MS, or were extracted from the silica for further fractionation using size exclusion chromatography. The approach yielded structural information not readily available from direct characterization of the original mixture.

7.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of creosote is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of creosote.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Wood creosote and coal-derived tars are complex mixtures of organic compounds. Virtually all potential human and ecological exposures in the natural environment are limited to the coal-derived tars and not wood creosote, which is used medicinally. Sensitive methods exist for measuring components of the coal-derived mixtures in biological media. Most of these methods involve detection of PAHs, the predominant components of creosote, and their metabolites (Amin et al. 1982; Harris et al. 1985; Haugen et al. 1986; Newman et al.

1988; Ny et al. 1993; Perera et al. 1988; Tolos et al. 1990). These analytical methods can reliably detect trace levels of PAHs in human tissues and body fluids, making them sensitive enough to measure background levels in the population, as well as levels at which biological effects might occur. PAHs, however, are not unique to creosote exposure. Analytical methods currently exist which are sensitive and selective enough to measure possibly unique or unusual components of creosote, and are capable of yielding a unique "fingerprint" for the mixture. These would be useful in monitoring exposures that might occur in work environments and near hazardous waste sites where creosote has been detected. Although these capabilities exist, they have not been applied except in the case of the pyrene biomarker discussed earlier.

The analytical methods for measuring PAHs and their metabolites in biological tissues and fluids are sensitive enough to measure levels at which health effects might occur, as well as background levels in the population. Methods also exist for measuring PAH-DNA adducts (Harris et al. 1985; Phillips et al. 1988), and research efforts are underway to develop methods that will detect ultratrace levels of these adducts in biological media. The increased sensitivity may allow correlation between levels of these adducts and observed health effects of PAH exposure related to coal products. There is also a need for methods to quantitatively correlate monitored levels of various PAHs in biological tissues or fluids to toxic effects in humans. Methods dependent on monitoring PAHs, however, are not specific for coal-derived products exposure. Methods sensitive and selective enough to detect a unique component or group of components making up the mixture would allow a more accurate assessment of the health effects associated with exposure to monitored levels of creosote and tars. The use of 1-pyrenol as illustrated above is an example of such an approach. Additional methods, targeting the detection of unique components of coal tar, coal tar creosote, and coal tar pitch in biological samples, would facilitate detection of exposure to these mixtures.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Reliable and sensitive methods are available for measuring PAHs from creosote and tars in soil or sediments (Black 1982), water (Mueller et al. 1991; Rostad et al. 1984), air (Ny et al. 1993; Rogaczewska and Ligocka 1991; Tolos et al. 1990), and other environmental media. Exposure to such materials is most likely to occur in industrial settings where coal-derived tars are manufactured or used. Creosote-contaminated water and soil are a concern in areas near hazardous waste sites and other areas where creosote might be concentrated. The analytical methods available are accurate and sensitive enough to quantitatively detect PAHs from creosote and tars in these and other environmental media, and are effective for estimating creosote levels in media known to be contaminated with this substance. There is a lack of sensitive and reliable methods for detecting and measuring creosote and coal tar degradation

products in environmental media. Development of such methods would allow assessment of the potential exposure to these products.

The minimal use of wood creosote for other than medicinal purposes probably argues against a pressing need for analytical methods for environmental monitoring of this substance. The rather short half-life of phenolic substances under most environmental conditions increases the difficulty of developing such assay methods.

7.3.2 Ongoing Studies

No ongoing studies concerning techniques for measuring and determining creosote in biological and environmental samples were reported.

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding coal tars, coal tar pitch, and creosote in air, water, and other media are summarized in Table 8-1. ATSDR has derived no MRLs for any of the creosotes, in part because creosote is a mixture that can vary in chemical components and concentrations. No EPA reference concentration or reference dose exists for the compound.

The EPA has determined that creosote is a class B1 carcinogen (probable human carcinogen) (IRIS 2001). A potency factor was not provided in IRIS. IARC classifies creosote as Group 2A (probably carcinogenic to humans) and coal tars as Group 1 (carcinogenic to humans) (IARC 2001). The National Toxicology Program classifies coal tar (coke oven emissions, coal tar, coal tar pitch, and creosotes) as a known human carcinogen (NTP 1998).

Coal tar creosote is on the list of chemicals appearing in "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 1987b). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to coal tar pitch volatiles to institute engineering controls and work practices to reduce employee exposure to, and maintain employee exposure at or below permissible exposure limits (PEL). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 0.2 mg/m^3. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1999a).

Table 8-1. Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles

Agency	Description	Information	Reference
INTERNATIONAL Guidelines:			
IARC	Carcinogenicity classification Creosotes Coal-tars	 Group 2A[a] Group 1[b]	IARC 2001
NATIONAL Regulations and Guidelines:			
a. Air:			
ACGIH	TWA—coal tar pitch volatiles[c]	0.2 mg/m^3	ACGIH 2001
NIOSH	REL—coal tar pitch volatiles[d] IDLH	0.1 mg/m^3 80 mg/m^3	NIOSH 2001
OSHA	8-Hour TWA for general industry—coal tar pitch volatiles[e]	0.2 mg/m^3	OSHA 2001b 29CFR1910.1000 Table Z-1
	8-Hour TWA for construction industry—coal tar pitch volatiles[e]	0.2 mg/m^3	OSHA 2001a 29CFR1926.55
	8-Hour TWA for shipyard industry—coal tar pitch volatiles[e]	0.2 mg/m^3	OSHA 2001c 29CFR1915.1000
b. Water		No data	
c. Food			
ATF	Denaturant authorized for denatured spirits—coal tar		ATF 2001 27CFR21.151
FDA	Active ingredient for the control of dandruff, seborrheic dermatitis, and psoriasis—coal tar	0.5–5%	FDA 2001a 21CFR358.710
	Synthetic flavoring substance and adjuvants—beechwood creosote	Used in the minimum quantity required to produce their intended effect, and in accordance with all principles of good manufacturing practice	FDA 2001d 21CFR172.515

Table 8-1. Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
FDA	Based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses		FDA 2001b 21CFR310.545
	Coal tar	Topical acne drug products and diaper rash drug products	
	Beechwood creosote	Expectorant drug products	
	Creosote (beechwood) and creosote	Poison ivy, oak, and sumac drug products	
	Creosote (beechwood), oral and topical	Nasal decongestant drug products	
	Drugs, recommended warning and caution statements—creosote		FDA 2001c 21CFR369.20
	External use	Caution—do not apply to large areas of the body	
	Douche preparations	Warning—use of solutions stronger than recommended may result in severe local irritation, burns, or serious poisoning; do not use more than twice weekly	
d. Other			
ACGIH	Carcinogenicity classification—coal tar pitch volatiles[c]	A1[f]	ACGIH 2001
EPA	RfC RfD Carcinogenicity classification—creosote	No data No data B1[g]	IRIS 2001

Table 8-1. Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	CERCLA Section 102 and RCRA Section 3001 reportable quantity—creosote and coal tar	1 pound	EPA 2001b 40CFR302.4
	Identification and listing of hazardous waste—creosote identified as a toxic waste	U051	EPA 2001c 40CFR261.33
	Toxic chemical release reporting: Community right-to-know; effective date—creosote	01/01/90	EPA 2001d 40CFR372.65
	TSD facilities; Henry's law constant less than 0.1 atm m^3/mol—creosote		EPA 2001a 40CFR265 Appendix VI
NTP	Carcinogenicity classification—coal tar and coal tar aerosols	Known to be a human carcinogen	NTP 1998
STATE Regulations and Guidelines:		No data	

[a]Group 2A: Probably carcinogenic to humans
[b]Group 1: Carcinogenic to humans
[c]Coal tar pitch volatiles: benzene soluble aerosol
[d]Coal tar pitch volatiles: cyclohexane-extractable fraction
[e]Coal tar pitch volatiles: benzene soluble fraction, anthracene, benzo[a]pyrene, phenanthrene, acridine, chrysene, pyrene
[f]A1: Confirmed human carcinogen
[g]B1: Probable human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; ATF = Alcohol, Tobacco, and Firearms; CERCLA = Comprehensive Environmental Response Compensation and Liability Act; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicological Program; OSHA = Occupational Safety and Health Administration; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TSD = transport, storage, and disposal; TWA = time-weighted average

9. REFERENCES

Abu-Hilal AH, Khordagui HK. 1993. Assessment of tar pollution on the United Arab Emirates beaches. Environ Int 19:589-596.

ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH. 1992. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH. 1994. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

*ACGIH. 1999. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

*ACGIH. 2001. Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

*Acharya P, Ives P. 1994. Incineration at Bayou Bounfouca remediation project. Waste Management 14(1):13-26.

Adams J, Giam CS. 1984. Polynuclear azaarenes in wood preservative wastewater. Environ Sci Technol 18(5):391-394.

*Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Dev Med Child Neurol 27:532-537.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112.

Agency for Toxic Substances and Disease Registry. 1989a. Toxicological profile for pentachlorophenol. Atlanta, GA. Agency for Toxic Substances and Disease Registry.

Agency for Toxic Substances and Disease Registry. 1989b. Toxicological profile for phenol. Atlanta, GA. Agency for Toxic Substances and Disease Registry.

*Agency for Toxic Substances and Disease Registry. 1989c. Decision guide for identifying substance-specific data needs related to toxicological profiles. Atlanta, GA. Agency for Toxic Substances and Disease Registry, Division of Toxicology.

*Agency for Toxic Substances and Disease Registry. 1992. Toxicological profile for creosols. Atlanta, GA. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.

---

*Cited in text

9. REFERENCES

*Agency for Toxic Substances and Disease Registry. 1993a. Polycyclic aromatic hydrocarbon toxicity; Environmental medicine. Agency for Toxic Substances and Disease Registry. Am Family Physician 47(3):623-629.

Agency for Toxic Substances and Disease Registry. 1993b. Toxicological profile for polycyclic aromatic hydrocarbons. Atlanta, GA. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.

*Agency for Toxic Substances and Disease Registry. 1994. Final Report: Site specific surveillance project at the Koppers Company, Inc. National Priorities List Site Texarkana, Texas.

*Agency for Toxic Substances and Disease Registry. 1995. Toxicological profile for polycyclic aromatic hydrocarbons. Atlanta, GA. Agency for Toxic Substances and Disease Registry.

*Agency for Toxic Substances and Disease Registry. 1998. Toxicological profile for phenol. Atlanta, GA. Agency for Toxic Substances and Disease Registry.

*Agency for Toxic Substances and Disease Registry. 1999. Toxicological profile for pentachlorophenol: Draft for public comment. Atlanta, GA. Agency for Toxic Substances and Disease Registry.

*Agency for Toxic Substances and Disease Registry/Centers for Disease Control and Prevention. 1990. Subcommittee report on biological indicators of organ damage. Atlanta, GA. Agency for Toxic Substances and Disease Registry/Centers for Disease Control and Prevention.

*Agurell E, Stensman C. 1992. Salmonella mutagenicity of three complex mixtures assayed with the microsuspension technique. A WHO/IPCS/CSCM study. Mutat Res 276:87-91.

Ahrens W, Jockel KH, Patzak W, et al. 1991. Alcohol, smoking, and occupational factors in cancer of the larynx: a case-control study. Bremen Institute for Prevention Research and Social Medicine, Federal Republic of Germany. Am J Ind Med 20(4):477-493.

*Akkineni KL, Zeisig M, Baranczewski P, et al. 2001. Formation of DNA adducts from oil-derived products analyzed by 32P-HPLC. Arch Toxicol 74(11):720-731.

*Alderman S, Kailas S, Goldfarb S, et al. 1994. Cholestatic hepatitis after ingestion of chaparral leaf: Confirmation by endoscopic retrograde cholangiopancreatography and liver biopsy. J Clin Gastroenterol 19(3):242-247.

Alderson MR, Clarke JA. 1983. Cancer incidence in patients with psoriasis. Br J Cancer 47:857-859.

*Altman PL, Dittmer DS. 1974. In: Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

*Amdur MO, Doull J, Klaasen CD. 1991. Casarett and Doull's toxicology: the basic science of poisons. 4th edition. New York, NY: Pergamon Press, 478-479.

*American Wood Preservers' Association. 1988. AWPA book of standards. Washington, DC: American Wood Preservers' Association.

American Wood Preservers Institute. 1988. Questions and answers about pressure treated wood. Vienna, VA: American Wood Preservers Institute.

9. REFERENCES

*Amin S, LaVoie EJ, Hecht SS. 1982. Identification of metabolites of benzo[b]fluoranthene. Carcinogenesis 3:171-174.

*Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ III, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205

*Anderson A, Dahlberg BE, Magnus K, et al. 1982. Risk of cancer in the Norwegian aluminum industry. Int J Cancer 29:295-298.

*Andersson K, Levin JO, Nilsson CA. 1983. Sampling and analysis of particulate and gaseous polycyclic aromatic hydrocarbons from coal tar sources in the working environment. Chemosphere 12(2):197-207.

Andersson K, Levin JO, Nilsson CA. 1992. Groundwater pollution arising from the disposal of creosote waste. J Water Environ Manage 6:646-652.

Angerer J. 1999. Das Biological Monitoring bei der Beurteilung der Belastung/Beanspruchung durch PAH-Aufnahme in Wohnungen mit teerhaltigem Parkettkleber. Umweltmed Forsch Prax 4(2):65-72.

Armknecht SL, Kaattari SL, Van Veld PA. 1998. An elevated glutathione S-transferase in creosote-resistant mummichog (*Fudulus heteroclitus*). Aquat Toxicol 41:1-16.

Armstrong B, Theriault G. 1996. Compensating lung cancer patients occupationally exposed to coal tar pitch volatiles. Occup Environ Med 53:160-167.

*Armstrong B, Tremblay C, Baris D, et al. 1994. Lung cancer mortality and polynuclear aromatic hydrocarbons: A case-cohort study of aluminum production workers in Arvida, Quebec, Canada. Am J Epidemiol 139(3):250-262.

Arnold WP. 1997. Tar. Clin Dermatol 15:739-744.

*Arvin E, Flyvbjerg J. 1992. Groundwater pollution arising from the disposal of creosote waste. J Water Environ Manage 6:646-652.

*ATF. 2001. List of denaturants authorized for denatured spirits. Washington, DC. Bureau of Alcohol, Tobacco, and Firearms. Treasury. Code of Federal Regulations. 27 CFR 21.151. http://www.frwebgate.access.gpo.gov/cgi.bin/...&PART=21&SECTION=151&YEAR=2001& TYPE=TEXT. September 17, 2001.

*Ataka K, Ogata N, Kuge T, et al. 1996. Suppression of enterotoxin-induced intestinal fluid secretion by wood creosote. Res Comm Chem Pathol Pharmacol 93(2):219-224.

Ataka H, Ogata N, Morino H. 1999. [Creosote as a chloride ion secretion inhibitor]. Japan Kokai 99335290, issued 7 Dec 1999. (Japanese).

*Atkinson R. 1989. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. New York, NY: American Institute of Physics. 3-7.

9. REFERENCES

*Atkinson R, Aschmann SM, Winer AM. 1987. Kinetics of the reactions of NO_3 radicals with a series of aromatic compounds. Environ Sci Technol 21:1123-1126.

*Attalla MN. 1968. Effect of beechwood creosote and chloramine on periapical tissue of dogs. J Can Dent Assoc 34:190-195.

*Autrup H, Seremet T. 1986. Excretion of benzo[a]pyrene-Gua adduct in the urine of benzo[a]pyrene-treated rats. Chem Biol Interact 60:217-226.

Baileys RT, Webb DA. 1987. 1958 Cooperative creosote project--XII: an analysis of creosotes from posts after 26 years in test. Am Wood Preserve Assoc:163-171.

*Ball J. 1987. Soil and groundwater contamination at wood preserving plants. In: Bell JM, ed. Proceedings of the 41st Industrial Waste Conference. May 1986. Purdue University. Chelsea, MI: Lewis Publishers, Inc, 347-351.

*Ball J, Norton CM, Andrews JW. 1985. Environmental feasibility of using creosote contaminated soil and sludges in roadway paving structures. In: Bell JM, ed. Proceedings of the 39th Industrial Waste Conference. May 1984. Purdue University. Chelsea, MI: Lewis Publishers, Inc, 361-368.

*Baranski B, Palus J, Rogaczewska T, et al. 1992. Correlation between polycyclic aromatic hydrocarbons concentration and airborne particle mutagenicity in the rubber factory. Pol J Occup Med Environ Health 5(4):357-362.

Barbee GC, Brown KW, Thomas JC, et al. 1996. Mutagenic activity (Ames test) of wood-preserving waste sludge applied to soil. Bull Environ Contam Toxicol 57:54-62.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Barnhill RL, Wiles JC. 1989. Malignant melanoma associated with multiple therapies for psoriasis. J Am Acad Dermatol 21(1):148-50.

*Bartosek I, Guaitani A, Modica R. 1984. Comparative kinetics of oral benz(a)anthracene, chrysene and triphenylene in rats: Study with hydrocarbon mixtures. Toxicol Lett 23:333-339.

*BATF. 1999. List of denaturants authorized for denatured spirits. Bureau of Alcohol, Tobacco and Firearms, Treasury. 27 CFR 21.151.

Baumann PC. 1998. Epizootics of cancer in fish associated with genotoxins in sediment and water. Mutat Res 411:227-233.

*Becker G, Colmsjo A, Ostman C. 1999. Determination of thiaarenes and polycyclic aromatic hydrocarbons in workplace air of an aluminum reduction plant. Environ Sci Technol 33(9):1321-1327.

*Bedient PB, Rodgers AC, Bouvette TC, et al. 1984. Groundwater quality at a creosote waste site. Groundwater 22:318-329.

*Bender MA, Leonard RC, White O Jr, et al. 1988. Chromosomal aberrations and sister-chromatid exchanges in lymphocytes from coke oven workers. Mutat Res 206:11-16.

9. REFERENCES

*Bennett JL, Updegraff DM, Pereira WE, et al. 1985. Isolation and identification of four species of quinoline-degrading pseudomonads from a creosote-contaminated site at Pensacola, Florida. Microbios Letters 29:147-154.

*Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. Endometriosis: Advanced management and surgical techniques. New York, NY: Springer-Verlag.

Bermejo J, Fernandez AL, Prada V, et al. 1999. Monitoring the synthesis of new pitches from coal tar and its fractions by chromatography and related techniques. J Chromatogr 849:507-519.

Berth-Jones J. 1994. Prescribing in psoriasis. Practitioner 238:231-234.

*Bertrand JP, Chau N, Patris A, et al. 1987. Mortality due to respiratory cancers in the coke oven plants of the Lorraine coal mining industry (Houilleres du Bassin de Lorraine). Br J Ind Med 44:559-565.

*Bestari KTJ, Robinson RD, Solomon KR, et al. 1998. Distribution and composition of polycylic aromatic hydrocarbons within experimental microcosms treated with creosote-impregnated Douglas fir pilings. Environ Toxicol Chem 17(12):2369-2377.

*Bhate SM, Sharpe GR, Marks JM, et al. 1993. Prevalence of skin and other cancers in patients with psoriasis. Clin Exp Dermatol 18:401-404.

*Bickers DR, Kappas A. 1978. Human skin aryl hydrocarbon hydroxylase induction by coal tar. J Clin Invest 62:1061-1068.

*Bieniek G. 1997. Urinary naphthols as an indicator of exposure to napthalene. Scand J Work Environ Health 23:414-420.

*Birdwood GT. 1938. Keratitis from working with creosote. J Brit Med 2:18.

*Black JJ. 1982. Movement and identification of a creosote-derived PAH complex below a river pollution point source. Arch Environ Contam Toxicol 11:161-166.

*Blair A, Linos A, Stewart PA, et al. 1993. Evaluation of risks for non-Hodgkin's lymphoma by occupational and industry exposure from a case-control study. Am J Ind Med 23(2):301-312.

*Blanco CG, Canga JS, Dominguez A, et al. 1992. Flame ionization detection relative response factors of some polycyclic aromatic compounds: Determination of the main components of the coal tar pitch volatile fraction. J Chromatography 607:295-302.

Boffetta P, Cardis E, Vainio H, et al. 1991. Cancer risks related to electricity production. International Agency for Research on Cancer (IARC). Eur J Cancer 27(11):1504-1519.

*Bolt HM, Golka K. 1993. Cases of lung cancer and tar-related skin changes in an aluminum reduction plant (letter). Med Lav 84(2):178-181.

*Bonser GM, Manch MD. 1932. Tumors of the skin produced by blast-furnace tar. Lancet April 9,1932:775-776.

*Bordelon NR, Donnelly KC, King LC, et al. 2000. Bioavailability of the Genotoxic Components in Coal Tar Contaminated Soils in Fischer 344 Rats. Toxicol Sci 56:37-48.

9. REFERENCES

*Borden RC. 1986. Influence of adsorption and oxygen limited biodegradation on the transport and fate of a creosote plume: Field methods and simulation techniques [abstract]. Diss Abstracts Int 47:204.

*Borthwick PW, Patrick JM. 1982. Use of aquatic toxicology and quantitative chemistry to estimate environmental deactivation of marine-grade creosote in seawater. Environ Toxicol Chem 1:281-288.

*Bos RP, Jongeneelen FJ. 1988. Nonselective and selective methods for biological monitoring of exposure to coal-tar products. IARC Scientific Publications 89:389-395.

*Bos RP, Hulshof CTJ, Theuws JLG. 1983. Mutagenicity of creosote in the Salmonella/microsome assay. Mutat Res 119:21-25.

*Bos RP, Hulshof CTJ, Theuws JLG. 1984a. Genotoxic exposure of workers creosoting wood. Br J Ind Med 41:260-262.

*Bos RP, Jongeneelen FJ, Theuws JLG. 1985. Detection of volatile mutagens in creosote and coal-tar. Mutat Res 156:195-198.

*Bos RP, Jongeneelen FJ, Theuws JLG, et al. 1984c. Exposure to mutagenic aromatic hydrocarbons of workers creosoting wood. IARC Sci Publ, ISS59, 1984, 279-288.

*Bos RP, Prinsen WJC, van Rooy JGM. 1987. Fluoranthene, a volatile mutagenic compound, present in creosote and coal-tar. Mutat Res 187:119-125.

*Bos RP, Theuws JL, Leijdekkers Ch. M. 1984b. The presence of the mutagenic polycyclic aromatic hydrocarbons benzo[a]pyrene and benz[a]anthracene in creosote P_1. Mutat Res 130:153-158.

Botello AV, Villanueva S, Diaz G. 1997. Petroleum pollution in the Gulf of Mexico and Caribbean Sea. Rev Environ Contam Toxicol 153:91-118.

*Boutwell RK, Bosch DK. 1958. The carcinogenicity of creosote oil: Its role in the induction of skin tumors in mice. Cancer Res 18:1171-1175.

*Bowman CE, Muhleman MF, Walters E. 1984. A fatal case of creosote poisoning. Postgrad Med J 60:499-500.

*Bowman ED, Rothman N, Hackl C, et al. 1997. Interindividual variation in the levels of certain urinary polycyclic aromatic hydrocarbon metabolites following medicinal exposure to coal tar ointment. Biomarkers 2:321-327.

Brender J, Suarez L, Hendricks K, et al. 1994. Health risks among residents living at the former site of a creosote wood treatment facility. Am J Epidemiol 139:S50.

*Brooks LR, Hughes TJ, Claxton LD, et al. 1998. Bioassay-directed fractionation and chemical identification of mutagens in bioremediated soils. Environ Health Perspect Suppl 106(6):1435-1440.

Burak W, Sroczynski J. 1992. [Assessment of the immune system in people employed at the production of carbon derivatives]. Med Pr 43(4):315-320. (Polish).

*Burden AD, Muston H, Beck MH. 1994. Intolerance and contact allergy to tar and dithranol in psoriasis. Contact Dermatitis 31(3):185-186.

Bureau of the Census. 1984a. U.S. imports for consumption and general imports 1984. Washington, DC: Government Printing Office, 1-327.

Bureau of the Census. 1984b. U.S. exports, schedule E. Washington, DC: Government Printing Office, 2-66.

*Burgaz S, Erdem O, Karahalil B, et al. 1998. Cytogenetic biomonitoring of workers exposed to bitument fumes. Mutat Res 419(1-1):123-130.

Butala JH. 1990. Creosote council II. Written communication. Public comment on Toxicological profile for creosote. Pittsburgh, PA, Feb 16.

*Cabot S, Shear N, Shear MJ. 1940. Studies in carcinogenesis. XI. Development of skin tumors in mice painted with 34-benzpyrene and creosote oil fractions. Am J Pathol 16:301-312.

*Calabrese EJ. 1978. Pollutants and high-risk groups. The biological basis of increased human susceptibility to environmental and occupational pollutants. New York: John Wiley and Sons, 24, 79-80, 187, 193.

Callen M, Maranon E, Mastral A, et al. 1998. Ecotoxicological assessment of ashes and particulate matter from fluidized bed combustion of coal. Ecotoxicol Environ Saf 41:59-61.

*Camel V, Tambut A, Caude M. 1993. Analytical scale supercritical fluid extraction: A promising technique for the determination of pollutants in environmental matrices. J Chromatogr 642:263-281.

*Cammer P. 1982. Current trends follow-up on pentachlorophenol in log homes. Morbidity and Mortality Weekly Report Transfer file. MMWR 31(13):170-171. http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00000238.htm.

Casey P, Vale JA. 1994. Deaths from pesticide poisoning in England and Wales: 1945-1989. Human Exp Toxicol 13(2):95-101.

CELDs. 1993. Computer-aided Environmental Legislative Database. Urbana, IL: University of Illinois at Urbana.

*CEOH. 1997. Case-control study of lung cancer in coal-tar exposed workers. Consultants in Epidemiology and Occupational Health. FYI-OTS-0998-0385. OTS0000385-1.

*Cernikova M, Dubsky H, Horacek J. 1983. Detection of acridine in human urine after topical coal-tar treatment. J Chromatog 273:202-206.

*Chadwick RW, George SE, Kohan MJ, et al. 1995. Potentiation of 2,6-dinitrotoluene genotoxicity in Fischer 344 rats by pretreatment with coal tar creosote. J Toxicol Environ Health 44(3):319-336.

*Chang F, Wang L, Zhao Q, et al. 1992. Investigation on the carcinogenic effects of coal tar pitch in rat respiratory tract by intratracheal instillations. Carcinogenesis 13(2):233-239.

*Chang LH. 1943. The fecal excretion of polycyclic hydrocarbons following their administration to the rat. J Biol Chem 151:93-99.

Chasey KL, McKee RH. 1993. Evaluation of the dermal carcinogenicity of lubricant base oils by the mouse skin painting bioassay and other proposed methods. J Appl Toxicol 13(1):57-65.

Cheng Y, Liu L, Huang J. 1994. [Coal tar pitch and membrane lipid peroxidation]. Gongye Weisheng Yu Zhiyebing 20(2):72-76. (Chinese).

Cheng Y, Yu S, Huang J, et al. 1995. [Etiological study of rat lung cancer induced by coal tar pitch]. Zhonghua Laodong Weiheng Zhiyebing Zazhi 13(3):131-134. (Chinese).

Chong JP, Haines AT, Verma DK. 1989. A pragmatic approach to standard setting--the example of coal tar products and asphalt. Ann Occup Hyg 33(2):197-208.

*Clark F, Reed R. 1992. Chaparral-induced toxic hepatitis--California and Texas. Morbidity and Mortality Weekly Report Transfer file, MMWR 41(43):812-814.

Claxton LD, Creason J, Lerouz B, et al. 1992. Results of the IPCS collaborative study on complex mixtures. Mutat Res 276:23-32.

*Clayton GD, Clayton FE. 1981. Patty's industrial hygiene and toxicology. Vol. 2A, 3rd ed. New York: John Wiley Sons, 2603.

*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

*Clonfero E, Jongeneelen F, Zordan M, et al. 1990. Biological monitoring of human exposure to coal tar. Urinary mutagenicity assays and analytical determination of polycyclic aromatic hydrocarbon metabolites in urine. Institute of Occupational Health, University of Padua, Italy. IARC Sci Publ (104):215-222.

*Clonfero E, Zordan M, Venier P, et al. 1989. Biological monitoring of human exposure to coal tar. Urinary excretion of total polycyclic hydrocarbons, 1-hydroxypyrene and mutagens in psoriatic patients. Institute of Occupational Health, University of Padua, Italy. Int Arch Environ Health 61:363-368.

Cohn BNE. 1932. Absorption of compound solution of iodine from the gastro-intestinal tract. Arch Intern Med 49:950-956.

*Colborn T, Clement C, eds. 1992. Chemically-induced alterations in sexual and functional development: The wildlife-human connection. In: Advances in modern environmental toxicology, Vol. XXI. Princeton, NJ: Princeton Scientific Publishing.

Cole P, Green LC, Lash TL. 1999. Lifestyle determinants of cancer among Danish Mastic asphalt workers. Regul Toxicol Pharmacol 30:1-8.

Cooke M, Dennis AJ, Fisher GL, eds. 1982. Polynuclear aromatic hydrocarbons: Physical and biological chemistry. New York, NY: Springer-Verlag.

*Cookson HA. 1924. Epithelioma of the skin after prolonged exposure to creosote. Br Med J 68:368.

Cordier S, Poisson M, Gerin M, et al. 1988. Gliomas and exposure to wood preservatives. Br J Ind Med 45:705-709

*Costantino JP, Redmond CK, Bearden A. 1995. Occupationally related cancer risk among coke oven workers: 30 years of follow-up. J Occup Environ Med 37(5):597-604.

Crawford DW, Bonnevie NL, Wenning RJ. 1995. Sources of pollution and sediment contamination in Newark Bay, New Jersey. Ecotoxicol Environ Saf 30:85-100.

*Cribb PH. 1968. Creosote poisoning in cattle (letter). Vet Rec 82:555.

*Culp SJ, Beland FA. 1994. Comparison of DNA adduct formation in mice fed coal tar or benzo[a]pyrene. Carcinogenesis 15(2):247-252.

*Culp SJ, Gaylor DW, Sheldon WG, et al. 1996a. DNA adduct measurements in relation to small intestine and forestomach tumor incidence during the chronic feeding of coal tar or benzo(A)pyrene to mice. Polycyclic Aromat Compd 11:161-168.

*Culp SJ, Gaylor DW, Sheldon WG, et al. 1996b. Relationship between DNA adduct levels and tumor incidence in mice fed coal tar or benzo[a]pyrene for two years [Abstract]. Proc Am Assoc Cancer Res 37:101.

*Culp SJ, Gaylor DW, Sheldon WG, et al. 1998. A comparison of the tumors induced by coal tar and benzo[a]pyrene in a 2-year bioassay. Carcinogenesis 19(1):117-124.

Culp SJ, Kaderlik PA, Beland FA. 1992. Comparison of DNA adduct formation in mice fed benzo(a)pyrene and coal tar. Proc Am Assoc Cancer Res 33:147.

Culp SJ, Warbritton AR, Norton DR, et al. 1993. Cell proliferation in mice fed coal tar or benzo(a)pyrene. Proc Am Assoc Cancer Res 34:159.

*Culp SJ, Warbritton AR, Smith BA, et al. 2000. DNA adduct measurements, cell proliferation and tumor mutation induction in relation to tumor formation in B6C3F1 mice fed coal tar or benzo[a]pyrene. Carcinogenesis 21(7):1433-1440.

*Cusano F, Capozzi M, Errico G. 1992. Allergic contact dermatitis from coal tar. Contact Dermatitis 27(1):51-52.

*Dahl AR, Coslett DS, Bond JA. 1985. Metabolism of benzo[a]pyrene on the nasal mucosa of Syrian hamsters: Comparison to metabolism by other extrahepatic tissues and possible role of nasally produced metabolites in carcinogenesis. J Natl Cancer Inst 75:135-139.

*Dao TL. 1964. Carcinogenesis of mammary gland in rats. Prog Exp Tumor Res 5:157-216.

*Dao TL, Sunderland H. 1959. Mammary carcinogenesis by 3-methylcholanthrene. I. Hormonal aspects in tumor induction and growth. J Natl Cancer Inst 23:567-585.

Davies GM. 1977. A mortality study of coke oven workers in two South Wales integrated steelworks. Br J Int Med 34:291-297.

*Davis JW, Libke KG. 1968. Hematologic studies in pigs fed clay pigeon targets. JAVMA 152:382-384.

9. REFERENCES

*Davis MW, Glaser JA, Evans JW, et al. 1993. Field evaluation of the lignin-degrading fungus Phanerochaete Sordida to treat creosote-contaminated soil. Environ Sci Technol 27:2572-2576.

*Dean AG, Imrey HH, Dusich K. 1988. Adjusting morbidity ratios in two communities using risk factor prevalence in cases. Am J Epidemiol 127:654-662.

*Dean BS, Lopez G, Kreyelok EP. 1992. Environmentally induced methemoglobinemia in an infant. J. Toxicol: Clin Toxicol 30:(1)127-133.

*Deelman HT. 1962. Induction and other problems of tar cancer. Laboratory of Morbid Anatomy, University of Amsterdam, Holland, 69-73.

*DeLeon IR, Ferrairo JB, Byrne CJ. 1988. Bioaccumulation of polynuclear aromatic hydrocarbons by the clam, Rangia Cuneata, in the vicinity of a creosote spill. Bull Environ Contam Toxicol 41:872-879.

*De Meo MP, Dumenil G, Botta AH et al. 1987. Urine mutagenicity of steel workers exposed to coke oven emissions. Carcinogenesis 8(3):363-367.

Dickman M, Brindle I, Benson M. 1992. Evidence of teratogens in sediments of the Niagara River watershed as reflected by chironomid (Diptera: Chironomidae) deformaties. J Great Lakes Res 18(3):467-480.

*Diette KM, Gange RW, Stern RS, et al. 1983. Coal tar phototoxicity: Kinetics and exposure parameters. J Invest Derm 81:347-350.

DOE. 1981. Epidermal carcinogenicity of some crude fossil fuels in mice: A preliminary report. In: Mahlum DD, Gray RH, Felix WD, ed. Coal conversion and the environment: Chemical, biomedical, and ecological considerations: Proceedings of the 20th annual Hanford Life Sciences Symposium at Richland, Washington, October 19-23, 1980. DOE Symposium Series 54. Oakridge, TN: U.S. Department of Energy, 471-481.

Donnelly KC, Huebner HJ. 1996. Bioassay-based risk assessment of complex mixtures. In: Hoddinott KB, ed. Superfund risk assessment in soil contamination studies. Conshohocken,PA: ASTM STP, 132-145.

*Donnelly KC, Brown KW, Markiewicz KV, et al. 1993. The use of short-term bioassays to evaluate the health and environmental risk posed by an abandoned coal gasification site. Haz Waste Haz Mater 10(1):59-70.

*Donnelly KC, Phillips TD, Onufrock AM, et al. 1996. Genotoxicity of model and complex mixtures of polycyclic aromatic hydrocarbons. In: Bengtson DA, Henshel DS, eds. Environmental toxicology and risk assessment: Biomarkers and risk assessment. ASTM STP. Conshohocken, PA: ASTM, 138-148.

*DOT. 1985. Chemical hazard response information system (CHRIS) hazard assessment handbook. Washington, DC: Department of Transportation, U.S. Coast Guard.

Druzhinin VG et al. 2000. Cytogenic disorders in workers of coal-tar chemical industry. Medistina Truda i Promyschlennaya Ekologiya 10:22-23.

*Dunn BP, Stich HF. 1976. Monitoring procedures for chemical carcinogens in coastal waters. J Fish Res Board Canada 33:2040-2046.

9. REFERENCES

*Dusich K, Sigurdson E, Hall WN, et al. 1980. Cancer rates in a community exposed to low levels of creosote components in municipal water. Minnesota Med 803-806.

Dutton CB, Pigeon MJ, Renzi PM, et al. 1993. Lung function in workers refining phosphorus rock to obtain elementary phosphorus. J Occup Med 35(10):1028-1033.

*Ehrlich GG, Godsy EM, Goerlitz DF, et al. 1983. Microbial ecology of a creosote-contaminated aquifer at St. Louis Park, MN. Developments in industrial microbiology, Proc 39th Gen Meet Soc Ind Microbiol 24:235-245.

*Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15(1):30-38.

*Eisler R. 1987. Polycyclic aromatic hydrocarbon hazards to fish, wildlife, and invertebrates: A synoptic review. Washington, DC: U.S. Fish and Wildlife Service, U.S. Department of the Interior. Biological Report 85, Contaminant Hazard Review Report No. 11.

*Elder JF, Dresler PV. 1988. Accumulation and bioconcentration of polycyclic aromatic hydrocarbons in a nearshore estuarine environment near a Pensacola (Florida) creosote contamination site. Environ Pollut 49:117-132.

Ellenhorn MJ, Barceloux DG, eds. 1988. Phenol. In: Medical toxicology: diagnosis and treatment of human poisoning. New York, NY: Elsevier, 951-952.

*Ellenhorn MJ, ed. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. New York, NY: Elsevier Publishing.

*Elovaara E, Heikkilä P, Pyy L, et al. 1995. Significance of dermal and respiratory uptake in creosote workers: exposure to polycyclic aromatic hydrocarbons and urinary excretion of 1-hydroxypyrene. Occup Environ Med 52(3):196-203.

*Emmett EA. 1986. Cutaneous and ocular hazards of roofers. Occupational Medicine: State of the Art Reviews. 1(2):307-322.

*Emmett EA, Bingham EM, Barkley W. 1981. A carcinogenic bioassay of certain roofing materials. Am J Ind Med 2:59-64.

EPA. 1971. Standards of performance for new stationary sources. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60.

*EPA. 1975. Case study no. 20: Creosote. Production, distribution and environmental impact potential of selected pesticides. Washington, DC: U.S. Environmental Protection Agency. EPA-540/1-74-001.

*EPA. 1978a. Coal-tar, creosote, coal-tar neutral oil: Position document 1. Washington, DC: U.S. Environmental Protection Agency, Special Pesticide Review Division. EPA/SPRD-80/82.

*EPA. 1978b. Investigation of selected potential environmental contaminants: Asphalt and coal tar pitch. Final Report. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA-560/2-77-005.

9. REFERENCES

*EPA. 1980. Identification and listing of hazardous waste. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.

*EPA. 1981a. Wood preservative pesticides. Creosote, pentachlorophenol and the inorganic arsenicals (wood uses). Position Document 2/3. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs. EPA-540/9-82-004.

*EPA. 1981b. Creosote, pentachlorophenol, and the inorganic arsenicals: Preliminary notice of determination concluding the rebuttable presumption against registration of the wood-preservative uses of pesticide products. Fed Reg 46:13020-13036.

EPA. 1981c. Identification and listing of hazardous waste. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.

*EPA. 1984a. Coal tar, creosote, and coal tar neutral oil: Non-wood preservative uses. U.S. Environmental Protection Agency. EPA/540/09-87/110.

EPA. 1984b. Wood preservative pesticides: Creosote, pentachlorophenol and the inorganic arsenicals. Position document 4. U.S. Washington, DC: Environmental Protection Agency, Office of Pesticide Programs. EPA-540/9/84-003.

EPA. 1985. Designation, reportable quantities, and notification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.

EPA. 1986a. Land disposal restrictions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.

*EPA. 1986b. Creosote, pentachlorophenols, and inorganic arsenicals: Amendment of notice of intent to cancel registrations. U.S. Environmental Protection Agency. Fed Reg 51:1334-1348.

*EPA. 1986d. Emissions test report air toxics sampling at Wyckoff, Inc., Bainbridge Island, Washington. U.S. Environmental Protection Agency, Seattle, WA. EPA-910/9-86-149.

*EPA. 1986c. Methods 8100 and 8310. Polynuclear aromatic hydrocarbons. In: Test methods for evaluating solid waste. Volume IB: Laboratory manual physical/chemical methods. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. SW-846.

EPA. 1987a. Health effects assessment for creosote. Cincinnati, OH. U.S. Environmental Protection Agency. EPA/600/8-88/025.

*EPA. 1987b. U.S. production of manufactures gases: Assessment of past disposal practices. Research Triangle Park, NC: Research Triangle Institute prepared for U.S. Environmental Protection Agency. Hazardous Waste Engineering Research Laboratory. EPA/600/2-88/012.

*EPA. 1988a. Evaluation of the potential carcinogenicity of creosote (8001-58-9), final report. Syracuse Research Corp., NY: U.S. Environmental Protection Agency. EPA/600/8-91/096.

*EPA. 1988b. Toxic chemical release reporting: Community right-to-know. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.

EPA. 1988c. Land disposal restrictions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.

EPA. 1988d. Guidance for the reregistration of pesticide products containing coal tar/creosote as the active ingredient. U.S. Environmental Protection Agency. NTIS PB88-225255. EPA/540/RS-88/066.

EPA. 1989. Designation, reportable quantities, and notification. U.S. Environmental Protection Agency. 54 FR 33418.

EPA. 1990a. Interim methods for development of inhalation reference concentrations. U.S. Environmental Protection Agency. EPA/600/8-90-066A.

EPA. 1990b. National oil and hazardous substances pollution contingency plan. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 300.

*EPA. 1990c. Land disposal restrictions for third scheduled wastes. U.S. Environmental Protection Agency. Fed Reg 55(106):22520-22720.

EPA. 1992. Drinking water regulations and health advisories. U.S. Environmental Protection Agency, Office of Water. April, 1992.

*EPA. 1993. Guidance for assessing chemical contaminant data for use in fish advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology. EPA-823-R-93-002.

*EPA. 1995. National listing of state fish and shellfish consumption advisories. Washington DC: U. S. Environmental Protection Agency, Office of Science and Technology. EPA 823-C-95-001.

*EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA/630/R-96/012.

*EPA. 1999a. Chemicals and chemical categories to which this part applies. U.S. Environmental Protection Agency. 40 CFR 372.65.

*EPA. 1999b. Designation of hazardous substances. U.S. Environmental Protection Agency. 40 CFR 302.4.

EPA. 1999c. Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof. U.S. Environmental Protection Agency. 40 CFR 261.33.

*EPA. 1999d. Special monitoring for sodium. U.S. Environmental Protection Agency. 40 CFR 141.42.

*EPA. 2001a. Compounds with Henry's law constant less than 0.1 Y/X. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 265, Appendix VI. http://ecfrback.access.gpo.gov/otcgi/cfr...4&RGN=BAPPCT&SUBSET=SUBSET&FROM =1&ITEM=1. September 17, 2001

*EPA. 2001b. Designation of hazardous substances. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. http://frwebgate.access.gpo. gov/cgi.bin/...&PART=21&SECTION=151&YEAR=2001&TYPE=TEXT. September 17, 2001.

*EPA. 2001c. Identification and listing of hazardous waste. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33. http://frwebgate.access.gpo.gov/cgi-bin/...&PART=261&SECTION=33&YEAR=2–1&TYPE= TEXT. Accessed September 17, 2001.

*EPA. 2001d. Toxic chemical release report; Community right-to-know. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. http://ecfr.access.gpo.gov/otcgi/cfr/otf...4&RGN=BSECCT&SUBSET=SUBSET&FROM=1& ITEM=1. September 17, 2001.

*Ericson G, Liewenborg B, Naf C, et al. 1998. DNA adducts in perch, Perca fluviatilis, from a creosote contaminated site and in perch exposed to an organic solvent extract of creosote contaminated sediment. Mar Environ Res 46:341-344.

*Ericson G, Liewenborg B, Lindesjoo E, et al. 1999. DNA adducts in perch (*Perca fluviatilis*) from a creosote contaminated site in the River Angermanalven, Sweden. Aquat Toxicol 45:181-193.

*Evan AP, Gardner KD. 1979. Nephron obstruction in nordihydroguaiaretic acid-induced renal cystic disease. Kidney Int 15:7-19.

Fader DJ, Metzman MS. 1994. Hazards of smoking during therapy for psoriasis. N Engl J Med 330(21):1541.

Farant J-P, Gariepy M. 1998. Relationship between benzo[a]pyrene and individual polycyclic aromatic hydrocarbons in a Söderberg primary aluminum smelter. Am Ind Hyg Assoc J 59:758-765.

*FDA. 1999a. Active ingredients for the control of dandruff, seborrheic dermatitis, or psoriasis. U.S. Food and Drug Administration. 21 CFR 358.710.

*FDA. 1999b. Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. U.S. Food and Drug Administration. 21 CFR 310.545.

*FDA. 1999c. Drugs; Recommended warning and caution statements. U.S. Food and Drug Administration. 21 CFR 369.20.

*FDA. 1999d. Synthetic flavoring substances and adjuvants. U.S. Food and Drug Administration. 21 CFR 172.515.

*FDA. 2001a. Active ingredients for the control of dandruff, seborrheic dermatitis, or psoriasis. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 358.710. http://frwebgate.access.gpo.gov/cgi-bin/...PART=358&SECTION=710&YEAR=2001&TYPE=TEXT. September 17, 2001.

*FDA. 2001b. Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 310.545. http://frwebgate.access.gpo.gov/cgi-bin/...SECTION=545&YEAR=2001&YEAR=2001&TYPE=TEXT. September 17, 2001.

*FDA. 2001c. Drugs; Recommended warning and caution statements. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 369.20. http://frwebgate.access.gpo.gov/cgi-bin/...&PART=369&SECTION=20&YEAR=2001&TYPE=TEXT. September 17, 2001.

*FDA. 2001d. Synthetic flavoring substances and adjuvants. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 172.515. http://frwebgate.access.gpo.gov/cgi-bin/...PART=172&SECTION=515&YEAR=2001&TYPE=TEXT. September 17, 2001.

Federman DG, Froelich CW, Kirsner RS. 1999. Topical psoriasis therapy. Am Fam Physician 59(4):957-962.

FEDRIP. 1996. Summary of federal research. Federal Research in Progress (FEDRIP) data base, 1996.

*FEDRIP. 2000. Summary of federal research. Federal Research in Progress (FEDRIP) data base, 2000.

*Fellows EJ. 1937. Studies on calcium creosotate: III. The elimination of volatile phenols in rabbit urine after the administration of "calcium creosotate solution" and after creosote solution. J Pharmacol Exp Ther 60:183-188.

*Fellows EJ. 1939a. Studies on calcium creosotate. IV. Observations on its use in pulmonary tuberculosis. Am J Med Sci 197:683-690.

*Fellows EJ. 1939b. Calcium creosotate: V. Nature of phenols eliminated in urine. Proc Society Exp Biol Med 42:103-107.

*Fielden MR, Wu Z-F, Sinal CJ, et al. 2000. Estrogen receptor- and aryl hydrocarbon receptor-mediated activities of a coal-tar creosote. Environ Toxicol Chem 19(5):1262-1271.

Finkelstein MM. 1989. Mortality among employees of an Ontario factory that manufactured construction materials using chrysotile asbestos and coal tar pitch. Health Studies Service, Ontario Ministry of Labour, Toronto. Canada Am J Ind Med 16(3):281-287.

*Fisher REW. 1953. Occupational skin cancer in a group of tar workers. Arch Ind Hyg Occup Med 7:12-18.

Flodin U, Fredriksson M, Persson B. 1987. Multiple myeloma and engine exhausts, fresh wood, and creosote: a case-referent study. Am J Ind Med 12:519-529.

*Flyvbjerg J, Arvin E, Jensen BK, et al. 1993. Microbial degradation of phenols and aromatic hydrocarbons in creosote-contaminated groundwater under nitrate-reducing conditions. J Contam Hydrol 12:133-150.

*Fomon SJ. 1966. Body composition of the infant: Part I: The male “reference infant”. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

*Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35:1169-1175.

*Franssen ME, van der Wilt GJ, de Jong PC, et al. 1999. A retrospective study of the teratogenicity of dermatological coal tar products. Acta Derm Venereol (Stockh) 79(5):390-391.

Fraumeni JF Jr, ed. 1975. Persons at high risk of cancer. An approach to cancer etiology and control. New York, NY: Academic Press, Inc., 172, 187-189.

FSTRAC. 1988. Summary of state and federal drinking water standards and guidelines. Chemical Communication Subcommittee, Federal-State Toxicology and Regulatory Alliance Committee (FSTRAC) data base, Washington, DC.

*Gabbani G, Pavanello S, Nardini B, et al. 1999. Influence of metabolic genotype GSTM1 on levels of urinary mutagens in patients treated topically with coal tar. Mutat Res 440:27-33.

Gagne F, Trottier S, Blaise C, et al. 1995. Genotoxicity of sediment extracts obtained in the vicinity of a creosote-treated wharf to rainbow trout hepatocytes. Toxicol Lett 78:175-182.

*Galceran MT, Curto MJ, Puignou L, et al. 1994. Determination of acridine derived compounds in charcoal-grilled meat and creosote oils by liquid chromatographic and gas chromatographic analysis. Anal Chim Acta 295:307-313.

Gardosová D, Kalina I, Hejj F, et al. 1994. [Mutagenic Activity of urine of psoriatic patients with pharmaceutical black coal tar]. Cas Lek Cesk 133(15):463-466. (Slovak).

Gardosova D, Mezencevova V, Kalina I, et al. 1997a. [Mutagenic effects of coal tar used in the treatment of psoriasis]. Bratisl Lek Listy 98(3):146-149. (Russian).

Gaylor DW, Moolgavkar S, Krewski D, et al. 1998. Recent bioassay results on coal tars and benzo(a)pyrene: Implications for risk assessment. Regul Toxicol Pharmacol 28:178-179.

*Gaylor DW, Culp SJ, Goldstein LS, et al. 2000. Cancer risk estimation for mixtures of coal tars and benzo(a)pyrene. Risk Anal 20(1):81-85.

*Geddie JE, Amin S, Huie K, et al. 1987. Formation and tumorigenicity of benzo[b]fluoranthene metabolites in mouse epidermis. Carcinogenesis 8:1579-1584.

*Genevois C, Brandt HCA, Bartsch H, et al. 1996. Formation of DNA adducts in skin, lung and lymphocytes after skim painting of rats with undiluted bitumen of coal-tar fume condensates. Polycyclic Aromat Compd 8:75-92.

*Genevois C, Pfohl-Leszkowicz A, Boillot K, et al. 1998. Implication of cytochrome P-450 1A isoforms and the AH receptor in the genotoxicity of coal-tar fume condensate and bitumen fume condensates. Environ Toxicol Pharmacol 5:283-294.

*Gevao B, Jones KC. 1998. Kinetics and potential significance of polycyclic aromatic hydrocarbon desorption form creosote-treated wood. Environ Sci Technol 32:640-646.

Ghoshal S, Weber WJ, Rummel AM, et al. 1999. Epigenetic toxicity of a mixture of polycyclic aromatic hydrocarbons on gap junctional intercellular communication before and after biodegredation. Environ Sci Technol 33:1044-1050.

*Gibbs GW. 1985. Mortality of aluminum reduction plant workers, 1950 through 1977. J Occup Med 27:761-770.

*Gibbs GW, Horowitz I. 1979. Lung cancer mortality in aluminum reduction plant workers. J Occup Med 21(5):347-353.

*Giffee JW. 1945. Clay pigeon poisoning in swine. Vet Med 40:97.

9. REFERENCES

*Gile JD, Collins JC, Gillett JW. 1982. Fate and impact of wood preservatives in a terrestrial microcosm. J Agric Food Chem 30:295-301.

*Gilmour JW, Vestey JP, Norval M. 1993. The effect of UV therapy on immune function in patients with psoriasis. Br J Dermatol 129(1):28-38.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect Suppl 101(2):65-71.

*Godschalk RWL, Ostertag JU, Moonen EJC, et al. 1998. Aromatic DNA adducts in human white blood cells and skin after dermal application of coal tar. Cancer Epidemiol Biomarkers Prev 7:767-773.

*Godschalk RWL, Ostertag JU, Zandsteeg AMG, et al. 2001. Impact of GSTM1 on aromatic-DNA adducts and P53 accumulation in human skin and lymphocytes. Pharmacogenetics 11:537-543.

*Goerlitz DF, Troutman DE, Godsy EM, et al. 1985. Migration of wood-preserving chemicals in contaminated groundwater in a sand aquifer at Pensacola, Florida. Environ Sci Technol 19:955-961.

Goldman WJ. 1995. Carcinogenicity of coal-tar shampoo. Lancet 345:326.

Goldstein LS, Safe S, Weyand EH. 1994. Carcinogenicity of coal tars: A multidisciplinary approach. Polycyclic Aromat Compd 7:161-174.

*Goldstein LS, Weyland EH, Safe S, et al. 1998. Tumors and DNA adducts in mice exposed to benzo[a]pyrene and coal tars: Implications for risk assessment. Environ Health Perspect Suppl 106(6):1325-1330.

*Goodman T, Grice HC, Becking GC, et al. 1970. A cystic nephropathy induced by nordihydroguaiaretic acid in the rat: Light and electron microscopic investigations. Lab Invest 23(1):93-107.

*Goon D, Hatoum NS, Klan MJ, et al. 1991. Oral bioavailability of *aged* soil-adsorbed benzo[a]pyrene (BaP) in rats. Toxicologist 11:1356.

*Gordon DW, Rosenthal G, Hart J, et al. 1995. Chaparral ingestion: The broadening spectrum of liver injury caused by herbal medications. JAMA 273(6):489-490.

Goto S, Endo O, Matsushita H. 1992. Results of a comparative study on the salmonella pre-incubation and plate incorporation assays using test samples for the IPCS collaborative study. Mutat Res 276:93-100.

*Goulden CB, Stallard HB. 1933. A case of tar epithelioma of the lid margins with pathological report. Proc Roy Soc Med 26:1477-1478.

Gowri MS, Reaven GM, Azhar S. 1999. Effect of mascoprocaol on glucose transport and lipolysis by isolated rat adipocytes. Metabolism 48(4):411-414.

*Graham R, Hester HR, Henderson JA. 1940. Coal-tar pitch poisoning in pigs. J Am Vet Med Assoc 96:135-140.

9. REFERENCES

*Granella M, Clonfero E. 1992. Sensitivity of different bacterial assays in detecting mutagens in urine of humans exposed to polycyclic aromatic hydrocarbons. Mutat Res 268:131-137.

Green Associates. 1982. Residential wood combustion study, Task 5, Emissions testing of wood stoves, Vol 1 and 2. EPA-910/9-82-089G.

*Greenwood-Van Meerveld B, Tyler K, Kuge T, et al. 1999. Anti-diarrhoeal effects of seirogan in the rat small intestine and colon examined *in vitro*. Aliment Pharmacol Ther 13:97-102.

*Grimmer G, Jacob J, Dettbarn G, et al. 1997. Determination of urinary metabolites of polycyclic aromatic hydrocarbons (PAH) for the risk assessment of PAH-exposed workers. Int Arch Occup Environ Health 69:231-239.

*Grosjean D. 1991. Atmospheric fate of toxic aromatic compounds. Sci Total Environ 100:367-414.

Gruner S, Zwirner A, Strunk D, et al. 1992. The influence of topical dermatological treatment modalities on epidermal Langerhans cells and contact sensitization in mice. Contact Derm 26(4):241-247.

*Guillen MD, Iglesias MJ, Dominguez A, et al. 1992. Polynuclear aromatic hydrocarbon retention indices on SE-54 stationary phase of the volatile components of a coal tar pitch: Relationships between chromatographic retention and thermal reactivity. J Chromatog 591:287-295.

*Gunster DG, Bonnevie NL, Gillis CA, et al. 1993. Assessment of chemical loadings to Newark Bay, New Jersey from petroleum and hazardous chemical accidents occurring from 1986 to 1991.

*Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

*Hackett PL, Rommereim DN, Sikov MR. 1984. Developmental toxicity following oral administration of a high-boiling coal liquid to pregnant rats. J Appl Toxicol 4(1):57-62.

Haddad LM. 1990. Phenol and related agents. In: Haddad LM and Winchester JF, eds. Clinical management of poisoning and drug overdose, 2nd edition. Philadelphia, PA: W.B. Saunders Company, 1290-1291.

*Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose, 2nd edition. Philadelphia, PA: W.B. Saunders Company, 1126,956-958.

*Haldin-Davis H. 1935. Multiple warts in a creosote worker. Proc Royal Soc Med 29:89-90.

*Hale RC, Aneiro KM. 1997. Determinatio of coal tar and creosote in the aquatic environment. J Chromatogr 774:79-95.

Haller JS Jr. 1990. Creosote: short history of its medicinal uses. University of Colorado, Boulder. Conn Med 54(9):502-507.

*Hanlon G. 1938. Creosote poisoning of cattle. Aust Vet J 14:73.

*Hansen AM, Poulsen OM, Menne T. 1993. Longitudinal study of excretion of metabolites of polycyclic aromatic hydrocarbons in urine from two psoriatic patients. Acta Derm Venereol 73(3):188-190.

*Harris C, Vahakangs K, Newman MJ, et al. 1985. Detection of benzo[a]pyrene diol epoxide-DNA adducts in peripheral blood lymphocytes and antibodies to the adducts in serum from coke oven workers. Proc Natl Acad Sci USA 82:6672-6676.

*Harrison DL. 1959. The toxicity of wood preservatives to stock. Part 2: Coal tar creosote. New Zealand Vet J 7:89-98.

*Hathaway GJ, Protor NH, Hughes. 1991. Proctor and Hughes' chemical hazards of the workplace. New York, NY: Van Nostrand Reinhold, 14-15.

*Haugen A, Becher G, Benestad C, et al. 1986. Determination of polycyclic aromatic hydrocarbons in the urine, benzo[a]pyrene diol epoxide-DNA adducts in lymphocyte DNA, and antibodies to the adducts in sera from coke oven workers exposed to measure amounts of polycyclic aromatic hydrocarbons in the work atmosphere. Cancer Res 46:4178-4183.

*Hawley GG. 1977. The condensed chemical dictionary. New York, NY: Van Nostrand Reinhold Company.

*Hawley GG. 1981. The condensed chemical dictionary. 10th ed. New York, NY: Van Nostrand Reinhold Company.

Hawley GG. 1987. The condensed chemical dictionary. 11th ed. New York, NY: Van Nostrand Reinhold Company.

HazDat. 1996. Agency for Toxic Substances and Disease Registry (ATSDR), database, Atlanta, GA.

HazDat. 2000. Agency for Toxic Substances and Disease Registry (ATSDR), database, Atlanta, GA.

HazDat. 2001. Agency for Toxic Substances and Disease Registry (ATSDR), database, Atlanta, GA.

*HazDat. 2002. Agency for Toxic Substances and Disease Registry (ATSDR), database, Atlanta, GA.

*Hecht SS, Grabowski W, Groth K. 1979. Analysis of feces for benzo[a]pyrene after consumption of charcoal-broiled beef by rats and humans. Food Cosmet Toxicol 17:223-227.

*Heikkilä P, Luotamo M, Pyy L, et al. 1995. Urinary 1-naphthol and 1-pyrenol as indicators of exposure to coal tar products. Int Arch Occup Environ Health 67(3):211-217.

*Heikkilä PR, Hameila M, Pyy L, et al. 1987. Exposure to creosote in the impregnation and handling of impregnated wood. Scand J Work Environ Health 13:431-437.

*Heikkilä PR, Luotamo M, Riihimaki V. 1997. Urinary 1-napthanol excretion in the assessment of exposure to creosote in a impregnation facility. Scand J Work Environ Health 23:199-205.

Heineman EF, Olsen JH, Pottern LM, et al. 1992. Occupational risk factors for multiple myeloma among Danish men. Cancer Causes Control 3:555-568.

Heinrich U. 1994. On the carcinogenicity of soot and carbon black. Proc Am Assoc Cancer Res 35:162.

*Heinrich U, Dungworth DL, Pott F, et al. 1994b. The carcinogenic effects of carbon black particles and tar-pitch condensation aerosol after inhalation exposure of rats. Ann Occup Hyg 38(Suppl. 1):351-356.

9. REFERENCES

*Heinrich U, Pott F, Roller M. 1994a. Estimation of a lifetime unit lung cancer risk for benzo(a)pyrene (BAP) based on tumor rates in rats exposed to coal tar/pitch condensation aerosol (CTP). Zentral Hyg Umwelt 195:155-156.

Heinrich U, Roller M, Pott F. 1994c. Estimation of a lifetime unit lung cancer risk for benzo(a)pyrene based on tumour rates in rats exposed to coal tar/pitch condensation aerosol. Toxicol Lett 72(1-3):155-161.

*Hekmat M, Latawiec A, Smith R. 1994. Determination of coal tar pitch volatile materials on air sampling filters: Comparison of gravimetric and spectroscopic methods. J Am Ind Hyg Assoc 55(10):942-945.

*Helmrich SP, Shapiro S, Rosenberg L, et al. 1983. Risk factors for breast cancer. Am J Epidemiol 117:35-45.

Henderson HM, Eskin NAM, Pinsky C, et al. 1992. Pyridine and other coal tar constituents as inhibitors of potato polyphenol oxidase: A non-animal model for neurochemical studies. Life Sci 51:207-210.

*Henningsson B. 1983. Environmental protection and health risks in connection with the use of creosote. Holz als Roh- und Werkstoff 41:471-475.

*Henry SA. 1946. Cancer of the scrotum in relation to occupation. London: Humphrey Milford Oxford University Press, 8-105.

*Henry SA. 1947. Occupational cutaneous cancer attributable to certain chemicals in industry. Br Med Bull 4:389-401.

*Hernandez C, Strassman-Sundy S. 1980. Pentachlorophenol in log homes-Kentucky. MMWR 29(36):431-433.

*Herod AA, Kandiyoti R. 1995. Fractionation by planar chromatography of a coal tar pitch for characterization by size exclusion chromatography, UV fluorescence and direct probe mass spectrometry. J Chromatogr 708:143-160.

*Heron S, Yarnell E. 2001. The safety of low-dose Larrea tridentata (DC) Coville (creosote bush or chaparral): a retrospective clinical study. J Altern Complement Med 7(2):175-185.

Heudorf U, Angerer J. 1999. Urinary levels of 1-hydroxypyrene, 1,2,3, and 4-hydroxyphenanthrene in children living in residences with high PAH-contents of adhesive used for parquet floors - additional information. Umweltmed Forsch Prax 4(2):97-100.

Heudorf U, Angerer J. 2000. Humanbiomonitoring auf PAK-Metaboliten im Urin von Kindern aus Wohnungen mit PAK-haltigem Parkettkleber. Umweltmed Forsch Prax 5(4):218-226.

*Hickok EA, Erdmann JB, Simonett MJ, et al. 1982. Groundwater contamination with creosote wastes. In: Johnson WK, Martenson DR, eds. National Conference on Environmental Engineering. Minneapolis, Minnesota: American Society of Civil Engineers, 430-437.

Hochman H. 1970. Tailoring a wood treatment for the marine environment. Proceedings of the Am Wood Preserv Assoc 66:38-42.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

Holme JA, Refsnes M, Dybing E. 1999. [Possible carcinogenic risk associated with the production and use of creosote-treated wood]. Tidsskr Nor Laegeforen 119(18):2664-2666. (Norwegian).

*Hopkins RP, Brooks CJW, Young L. 1962. Biochemical studies of toxic agents. 13. The metabolism of acenaphthylene. Biochem J 82:457-466.

Horton AW, Tye R , Stemmer KL. 1963. Experimental carcinogenesis of the lung, inhalation of gaseous formaldehyde or an aerosol of coal tar by C3H mice. J Nat'l Cancer Inst 30(1):31-43.

Hours M, Fevotte J, Dananche B, et al. 1992. Lung cancer and occupational risk: Results of case-control study conducted in Lyon (France) 1984-1990. Rev Epidemiol Sante Publique 40(Suppl. 1):S90.

HSDB. 1996. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*HSDB. 2000. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*Hueper WC, Payne WW. 1960. Carcinogenic studies on petroleum asphalt, cooling oil, and coal tar. Arch Pathol 70:106-118.

*Hughes NC, Pfau W, Hewer A, et al. 1993. Covalent binding of polycyclic aromatic hydrocarbon components of coal tar to DNA in mouse skin. Carcinogenesis 14(1):135-144.

Hughes TJ, Claxton LD, Brooks L, et al. 1998a. Genotoxicity of bioremediated soils from the Reilly tar site, St. Louis Park, Minnesota. Environ Health Perspect Suppl 106(6):1427-1433.

Hughes TJ, Warren S, Matthews FK, et al. 1998b. Genotoxicity of bioremediated soils from two superfund sites. Environ Mol Mutagen Suppl 31(29):67.

*Huntley SL, Bonnevie NL, Wenning RJ. 1995. Polycyclic aromatic hydrocarbon and petroleum hydrocarbon contamination in sediment from the Newark Bay Estuary, New Jersey. Arch Environ Contam Toxicol 28:93-107.

*Huntley SL, Bonnevie NL, Wenning RJ, et al. 1993. Distribution of polycyclic aromatic hydrocarbons (PAHs) in three northern New Jersey waterways. Bull Environ Contam Toxicol 51:865-872.

Hyötyläinen T, Oikari A. 1999a. Assessment of the bioactivity of creosote-contaminated sediment by liver biotransformation system of rainbow trout. Ecotoxicol Environ Saf 44:253-258.

*Hyötyläinen T, Oikari A. 1999b. Assessment of toxicity hazards of dredged lake sediment contaminated by creosote. Sci Total Environ 243/244:97-105.

Hyötyläinen T, Oikari A. 1999c. The toxicity and concentrations of PAHs in creosote-contaminated lake sediment. Chemosphere 38(5):1135-1144.

*IARC. 1973. Monographs on the evaluation of carcinogenic risk of chemicals to man. Certain polycyclic aromatic hydrocarbons and heterocyclic compounds. Vol. 3, Lyon, France: World Health Organization, International Agency for Research on Cancer, 22-42.

*IARC. 1985. Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Polynuclear aromatic compounds, part 4, bitumens, coal-tars and derived products, shale oils and soots. Vol. 35, Lyon, France: World Health Organization, International Agency for Research on Cancer, 104-140.

*IARC. 1987. IARC monographs on the evaluation of carcinogenic risk to humans. International Agency for Research on Cancer, World Health Organization. Supplement 7, Vols 1 to 47.

*IARC. 2000. Coal-tars (group 1); Creosotes (group 2a). International Agency for Research on Cancer. http://193.51.164.11/htdocs/monographs/Suppl7/CoalTars.html.

*IARC. 2001. IARC monographs programme on the evaluation of carcinogenic risks to humans. Creosotes. Coal-tars. International Agency for Research on Cancer. http://monographs.iarc.fr/. September 17, 2001.

*Ibbotson SH, Stenton SC, Simpson NB. 1995. Acute severe bronchoconstriction precipitation by coal tar bandages. Clin Exp Dermatol 20(1):58-59.

Ikeshoji T. 1975. Chemical analysis of wood creosote for species-specific attraction of mosquito oviposition. Appl Ent Zool 10(4):302-308.

*Ingram LL Jr, McGinnis GD, Gjovik LR, et al. 1982. Migration of creosote and its components from treated piling sections in a marine environment. Proc Am Wood Preserv Assoc 78:120-128.

*IRIS. 1995. Integrated Risk Information System (IRIS), online. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. June 1995.

*IRIS. 2000. Creosote. Integrated Risk Information System. U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/0360.htm.

*IRIS. 2001. Creosote. Integrated Risk Information System. U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/0360.htm. September 17, 2001.

*IRIS. 2002. Creosote. Integrated Risk Information System. U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/0360.htm. June 6, 2002.

*Iyer PR, Irvin TR, Martin JE. 1993. Developmental effects of petroleum creosote on mice following oral exposure. Res Commun Chem Pathol Pharmacol 82(3):371-374.

Iyer P, Martin JE, Irvin TR. 1992. *In vitro* embryotoxicity of petroleum creosote monitored via mouse preimplantation embryo culture. J Toxicol Environ Health 37:231-245.

Jackson EM. 1995. Strong evidence supports coal tar shampoo safety despite European controversy. Cosmet Dermatol 8(6):29-32.

9. REFERENCES

*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

*Johnston N, Sadler R, Shaw GR, et al. 1993. Environmental modification of PAH composition in coal tar containing samples. Chemosphere 27(7):1151-1158.

*Jonas AD. 1943. Creosote burns. J Ind Hyg Toxicol 25:418-420.

*Jones SK, Mackie RM, Hole DJ, et al. 1985. Further evidence of the safety of tar in the management of psoriasis. Br J Dermatol 113:97-101.

*Jongeneelen FJ. 1992. Biological exposure limit for occupational exposure to coal tar pitch volatiles at coke ovens. Int Arch Occup Environ Health 63(8):511-516.

*Jongeneelen FJ, Anzion RB, Leijdekkers Ch. M. 1988. 1-Hydroxypyrene in human urine as a biological indicator of exposure to polycyclic aromatic hydrocarbons in several work environments. Ann Occup Hyg 32:34-43.

*Jongeneelen FJ, Anzion RBM, Scheepers PTJ, et al. 1985. 1-Hydroxypyrene in human urine after exposure to coal tar and a coal tar derived product. Int Arch Occup Environ Health 57:47-55.

*Jongeneelen FJ, Bos RP, Anzion, RB, et al. 1986. Biological monitoring of polycyclic aromatic hydrocarbons; metabolites in urine. Scand J Work Environ Health 12:137-143.

Kanzler MH, Gorsulowsky DC. 1993. Efficacy of topical 5% liquor carbonis detergens vs. its emollient base in the treatment of psoriasis. Br J Dermatol 129(3):310-314.

*Karlehagen S, Andersen A, Ohlson CG. 1992. Cancer incidence among creosote-exposed workers. Scand J Work Environ Health 18(1):26-29.

Karrow NA, Boermans HJ, Dixon DG, et al. 1999. Characterizing the immunotoxicity of creosote to rainbow trout (*Oncorhynchus mykiss*): a microcosm study. Aquat Toxicol 45:223-239.

*Kasai K. 1908. The effect of creosote on the intestine. Chem Abstract 2:2583.

*Katz M, Saibil F. 1990. Herbal hepatitis: Subacute hepatic necrosis secondary to chaparral leaf. J Clin Gastroenterol 12(2):203-206.

*Kerr MA, Nasca PC, Mundt KA, et al. 2000. Parental occupational exposures and risk of neuroblastoma: a case-control study (United States). Cancer Causes Control 11(7):635-643.

*Kesik K, Janik-Spiechowicz E. 1997. Comparison of the mutagenicity of chemical agents released during coke production. Int J Occup Med Environ Health 10(3):267-272.

*King MWG, Barker JF. 1999. Migration and natural fate of a coal tar creosote plume: 1. Overview and plume development. J Contam Hydrol 39:249-279.

*King MWG, Barker JF, Devlin JF, et al. 1999. Migration and natural fate of a coal tar creosote plume: 2. Mass balance and biodegredation indicators. J Contam Hydrol 39:281-307.

*Kligman AM, Kligman LH. 1994. Carcinogens show comedogenic activity: A potential animal screen for tumorigenic substances. Cancer Letters 87(2):171-178.

*Klingner TD, McCorkle T. 1994. The application and significance of wipe samples. AIHA Journal Short Communications 251-254.

*Kobayashi K, Akitake H, Manabe M. 1979. Relation between toxicity and accumulation of various chlorophenols in goldfish. Bull Japan Soc Sci Fish 45(2):173-175.

Kocan RM, Matta MB, Salazar SM. 1996. Toxicity of weathered coal tar for chortnose sturgeon (*Acipenser brevirostrum*) embryos and larvae. Arch Environ Contam Toxicol 31:161-165.

*Kock ND, Kock MD, Young KB. 1994. Hepatopathy in two black rhinoceroses (*diceros bicornis*) in Zimbabwe: Creosote toxicosis? J Zoo Wild Med 25(2):270-273.

*Koganti A, Singh R, Ma B, et al. 2001. Comparative Analysis of PAH:DNA Adducts Formed in Lung of Mice Exposed to Neat Coal Tar and Soils Contaminated with Coal Tar. Environ Sci Technol 35:2704-2709.

*Koganti A, Singh R, Rozett K, et al. 2000. 7H-benzo[c]fluorene: a major DNA adduct-forming component of coal tar. Carcinogenesis 21(8):1601-1609.

Koganti A, Spina DA, Ma B-L, et al. 1999. Comparative analysis of chemical: DNA adduct formation in mouse lung following the ingestion of neat MGP tar and soils contaminated with MGP tar. Toxicologist 38:52.

*Koganti A, Spina DA, Rozett K, et al. 1998. Studies on the applicability of biomarkers in estimating the systemic bioavailability of polynuclear aromatic hydrocarbons from manufactured gas plant tar-contaminated soils. Environ Sci Technol 32:3104-3112.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29:4430-4433.

Kongerud J, Gronnesby JK, Magnus P. 1990. Respiratory symptoms and lung function of aluminum potroom workers. Scan J Work Environ Health16:270-277.

Krewsi D, Leroux BG, Creason J, et al. 1992. Sources of variation in the mutagenic potency of complex chemical mixtures based on the salmonella/microsome assay. Mutat Res 276:33-59.

*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Kromhout H, Heederik D, Dalderup LM, et al. 1992. Performance of two general job-exposure matrices in a study of lung cancer morbidity in the zutphen cohort. Am J Epidemiol 136(6):698-711.

*Kuehl DW, Ankley GT, Burkhard LP, et al. 1990. Bioassay directed characterization of the acute aquatic toxicity of a creosote leachate.

*Kuge T, Shibata T, Willet MS, et al. 2001. Lack of oncogenicity of wood creosote, the principal active ingredient of seirogan, an herbal antidiarrheal medication, in sprague-dawley rats. Int J Toxicol 20:297-305.

Kumar B, Kumar R, Kaur I. 1997. Coal tar therapy in palmoplantar psoriasis: old wine in an old bottle? Int J Dermatol 36:309-312.

*Kunze E, Chang-Claude J, Frentzel-Beyme R. 1992. Life style and occupational risk factors for bladder cancer in Germany. Cancer 69:1776-1790.

Landrigan PJ. 1993. Health risks of creosotes. JAMA 269(10):1309.

Larrey D. 1997. Hepatotoxicity of herbal remedies. J Hepatol 26(Suppl. 1):47-51.

*Leach CW, Weinert JJ. 1976. A report to the Environmental Task Group, sub-group no. 5 (creosote) of the American Wood Preservers Institute.

Leadon SA. 1993. Production of oxidative DNA damage and DNA adducts during the metabolic activation of polycyclic aromatic hydrocarbons. Environ Mol Mutagen 21(Suppl. 22):38.

*Leadon SA, Sumerel J, Minton TA, et al. 1995. Coal tar residues produce both DNA adducts and oxidative DNA damage in human mammary epithelial cells. Carcinogenesis 16(12):3021-3026.

Lebwohl M, Matinez J, Weber P, et al. 1995. Effects of topical preparations on the erthemogenicity of UVB: Implications for psoriasis phototherapy. J Am Acad Dermatol 32:469-471.

*Lee LS, Suresh P, Rao C, et al. 1992. Equilibrium partitioning of polycyclic aromatic hydrocarbons form coal tar into water. Environ Sci Technol 26:2110-2115.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

Lei ZM. 1993. [The relationship between concentrations of B(a)P in blood, urine and immune function of coking workers]. Chin J Prev Med 27(4):212-214. (Japanese).

*Lenson N. 1956. Multiple cutaneous carcinoma after creosote exposure. N Engl J Med 254:520-522.

*Leonforte JF. 1986. Contact dermatitis from Larrea (creosote bush). J Am Acad Dermatol 14:202-207.

Letzel S, Drexler H, Lehnert G. 1992. [Tar-induced preccancerous stages and malignant tumors of the skin in tar refinery workers]. Derm Beruf Umwelt 40(3):94-101. (German).

*Leung H-W. 1993. Physiologically-based pharmacokinetic modeling. In: Ballentine B, Marro T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

*Lewin L. 1929. Gifte und Vergifungen. Stilke, Berlin.

Lewtas J, Claxton LD, Rosenkranz HS, et al. 1992. Design and implementation of a collaborative study of the mutagenicity of complex mixtures in Salmonella typhimurium. Mutat Res 276:3-9.

Lewtas J, Dobias L, Binkova B, et al. 1994. Exposure-dosimetry of PAH in humans using DNA adducts as the biomarker of dose and personal exposure monitors for PAH. Proc Am Assoc Cancer Res 35:95.

Lewtas J, Dooley K, Von Tungeln L, et al. 1993. Comparative tumorgenicity of complex environmental mixtures in the newborn mouse and mouse skim tumor assays. Proc Am Assoc Cancer Res 34:117.

*Lewtas J, Walsh D, Williams R, et al. 1997. Air pollution exposure-DNA adduct dosimetry in humans and rodents: evidence for non-linearity at high doses. Mutat Res 378:51-63.

Li EE, Culp SJ, Beland FA. 1994. Tumor mutational spectrum in relation to DNA adduct profile in forestomachs of mice fed coal tar or benzo[a]pyrene. Proc Am Assoc Cancer Res 35:148.

*Li X-Y, Astrom A, Duell EA, et al. 1995. Retinoic acid antagonizes basal as well as coal tar and glucocorticoid-induced cytochrome P4501A1 expression in human skin. Carcinogenesis 16(3):519-524.

Li X, Wang J, Wei L, et al. 1997. The experimental study on the induction of malignant lymphoma by coal tar pitch in mice. Proc Am Assoc Cancer Res 38:466-467.

*Liao W, Smith WD, Chiang TC. 1988. Rapid, low-cost cleanup procedure for determination of semivolatile organic compounds in human bovine adipose tissues. J Assoc Off Anal Chem 71:742-747.

*Lijinsky W, Domsky I, Mason G, et al. 1963. The chromatographic determination of trace amounts of polynuclear hydrocarbons in petrolatum, mineral oil, and coal-tar. Anal Chem 35:952-956.

*Lijinsky W, Saffiotti U, Shubik P. 1957. A study of the chemical constitution and carcinogenic action of creosote oil. J Natl Cancer Inst 18:687-692.

Lin AN, Moses K. 1985. Tar revisited. Int J Dermatol 24:216-218.

*Lindelof B, Sigurgeirsson B. 1993. PUVA and cancer: A case-control study. Br J Dermatol 129(1):39-41

*Linder G, Bergman HL, Meyer JS. 1985. Anthracene bioconcentration in rainbow trout during single-compound and complex-mixture exposures. Environ Toxicol Chem 4:549-558.

Lindhardt B, Christensen TH. 1996. Volatisation of aromatic hydrocarbons from soil: Part II, fluxes from coal tar contaminated soils residing below the soil surface. Water Air Soil Pollut 92:375-389.

*Liu N, Wang Z, Dong D, et al. 1997. Cancer mortality among carbon workers in China: Retrospective cohort study. J Occup Health 39(4):325-330.

*Livingston, AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301-324.

Lloyd JBF. 1975. Nitrogen heterocycle and polynuclear hydrocarbon fluorescence and adsorption effects in the presence of silica gel: Applications in high-pressure liquid and microcolumn chromatography. Analyst 100:529-539.

*Lloyd JW. 1971. Long-term mortality study of steelworkers V. Respiratory cancer in coke plant workers. J Occup Med 13(2):53-68.

*Lloyd JW, Lundin FE Jr, Redmond CK , et al. 1970. Long-term mortality study of steelworkers IV. Mortality by work area. J Occup Med 12(5):151-157

Loi A, Mariotti F, Turini L, et al. 1997. Oncogenic risk in a chemical plant: A methological approach and preliminary results. J Environ Pathol Toxicol Oncol 16:125-132.

*Lorenz LF, Gjovik LR. 1972. Analyzing creosote by gas chromatography: Relationship to creosote specifications. Proc Am Wood Preserv Assoc 68:32-42.

*Luke D. 1954. Liver dystrophy associated with coal tar pitch poisoning in the pig. Vet Rec 66(43):643-645.

*Luukkanen L, Elovaara E, Lautala P, et al. 1997. Characterization of 1-hydroxypyrene as a novel marker substrate of 3-methylcholanthrene-inducible phenol UDP-glucutonosyltransferase(s). Pharmacol Toxicol 80:152-158.

*MacEwen JD, Hall A III, Scheel LD. 1977. Experimental oncogenesis in rats and mice exposed to coal tar aerosols Proceedings of the annual conference on environmental toxicology. Aerospace Medical Research Lab, Wright-Patterson AFB, OH. AMRL-TR-76-125

*Machado ML, Beatty PW, Fetzer JC, et al. 1993. Evaluation of the relationship between PAH content and mutagenic activity of fumes from roofing and paving asphalts and coal tar pitch. Fundam Appl Toxicol 21:492-499.

*Mackenzie S. 1898. Yellow pigmentary stains of hemorrhagic origin and a case of tar eruption. Brit J Dermatol 10:416-417.

*Madhavan ND, Naidu KA. 1995. Polycyclic aromatic hydrocarbons in placenta, maternal blood, umbilical cord blood and milk of Indian women. Hum Exp Toxicol 14:503-506.

*Madsen EL, Bilotta-Best S, Sandoli RL, et al. 1993. Final electron acceptor limitations and sorption may explain the persistence of polycyclic aromatic hydrocarbons in coal-tar contaminated surface sediments. Abstr Gen Meet Am Soc Microbiol 93:407.

*Madsen EL, Mann CL, Bilotta SE. 1996. Oxygen limitations and aging as explanations for the field persistence of naphthalene in coal tar-contaminated surface sediments. Environ Toxicol Chem 15(11):1876-1882.

*Mahlum DD. 1983. Initiation/promotion studies with coal-derived liquids. J Appl Toxicol 3(1):31-34.

Maier M, Maier D, Lloyd BJ. 2000. Factors influencing the bobilization of polycyclic aromatic hydrocarbons (PAHS) from the coal-tar lining of water mains. Water Res 34(3):733-786.

*Malkin R, Kiefer M, Tolos W. 1996. 1-hydroxypyrene levels in coal-handling workers at a coke oven. J Occup Environ Med 38(11):1141-1144.

*Markel HL, Ligo RN, Lucas JB. 1977. Health hazard evaluation/toxicity determination report 75-117-372. North Little Rock, Arkansas: Koppers Company, Inc.

Marston CP, Baird WM. 1997. Polycyclic aromatic hydrocarbon (PAH)-DNA binding in the epidermis of mice treated with complex PAH mixtures. Proc Am Assoc Cancer Res 38:338.

*Marston CP, Pereira C, Ferguson J, et al. 2001. Effect of a complex environmental mixture from coal tar containing polycyclic aromatic hydrocarbons (PAH) on the tumor initiation, PAH-DNA binding and metabolic activation of carcinogenic PAH in mouse epidermis. Carcinogenesis 22(7):1077-1086.

*Martin J-C, Imbernon E, Goldberg M, et al. 2000. Occupational risk factors for lung cancer in the French electricity and gas industry: A case-control survey nested in a cohort of active employees. Am J Epidemiol 151(9):902-912.

Marvin CH, Lundrigan JA, McCarry BE, et al. 1995. Determination and genotoxicity of high molecular mass polycyclic aromatic hydrocarbons isolated from coal-tar-contaminated sediment. Environ Toxicol Chem 14(12):2059-2066.

Marvin CH, McCarry BE, Villella J, et al. 2000. Chemical and biological profiles of sediments as indicators of sources of contamination in Hamilton Harbour. Part II: Bioassay-directed fractionation using the Ames Salmonella/microsome assay. Chemosphere 41:989-999.

*Maugham WZ, Muller SA, Perry HO. 1980. Incidence of skin cancers in patients with atopic dermatitis treated with coal-tar: A 25-year follow-up study. J Am Acad Dermatol 3:612-615.

May WE, Benner BA, Wise SA, et al. 1992. Standard reference materials for chemical and biological studies of complex environmental samples. Mutat Res 276:11-22.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.

*Mayura K, Huebner HJ, Dwyer MR, et al. 1999. Multi-bioassay approach for assessing the potency of complex mixtures of polycyclic aromatic hydrocarbons. Chemosphere 38(8):1721-1732.

*Mazumdar S, Redmond C, Sollecito W, et al. 1975. An epidemiological study of exposure to coal tar pitch volatiles among coke oven workers. J Air Pollut Control Assoc 25(4):382-289.

McGarry GW, Robertson JR. 1989. Scrotal carcinoma following prolonged use of crude coal tar ointment. Br J Urol 63(2):211.

*McKinlay R. 1933. The creosote treatment of lobar pneumonia. J Royal Army Med Corps 61:54-55.

*Menter A, Cram DL. 1983. The Goeckerman regimen in two psoriasis day care centers. J Am Acad Dermatol 9(1):59-65.

*Merck. 1989. The Merck index: An encyclopedia of chemicals and drugs. 11th ed. Budavari S. ed. Rahway, NJ: Merck and Co., Inc.

*Merck. 1996. The Merck index: An encyclopedia of chemicals and drugs. 11th ed. Budavari S. ed. Rahway, NJ: Merck and Co., Inc. 435-437.

*Meylan WM, Howard PH. 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. Chemosphere 26(12):2293-2299.

*Meylan WM, Howard PH. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J Pharmaceut Sci 84(1):83-92.

*Middleton AC. 1984. Land disposal and spill site environments. Basic Life Sci 28:137-149.

*Mielzynska D, Snit M. 1992. Urine mutagenicity in workers directly employed in coke production. Pol J Occup Med Environ Health 5(4):363-371.

*Minnesota Department of Health. 1985. Feasibility of community-wide epidemiologic studies of drinking water and health: St. Louis Park and New Brighton: Final Report to the Minnesota Legislature.

*Mitchell AD, Tajiri DT. 1978. *In vitro* mammalian mutagenicity assays of creosote P_1 and P_2. SRI International. Unpublished report for EPA. 68-01-2458.

*Miyazato T, Matsumoto M, Uenishi C. 1981. Studies on the toxicity of beechwood creosote. I. Acute and subacute toxicity in mice and rats. Oyo Yakuri Pharmacometrics 21:899-919.

*Miyazato T, Suzuki A, Nohno M. 1984a. Studies on the toxicity of beechwood creosote. 2. Chronic toxicity and carcinogenicity in mice. Oyo Yakuri Pharmacometrics 28:909-924.

*Miyazato T, Suzuki A, Uenishi C. 1984b. Studies on the toxicity of beechwood creosote. 3. Chronic toxicity and carcinogenicity in rats. Oyo Yakuri Pharmacometrics 28:925-947.

*Modica R, Fiume M, Guaitani A. 1983. Comparative kinetics of benz(a)anthracene, chrysene, and triphenylene in rats after oral administration. I. Study with single compounds. Toxicol Lett 18:103-109.

*Mohammed SA, Sorensen DL, Sims DC, et al. 1998. Pentachlorophenol and phenanthrene biodegradation in creosote contaminated aquifer material. Chemosphere 37:(1)103-111.

Morse MA, Baird WM, Carlson GP. 1987. Distribution, covalent binding, and DNA adduct formation of 7-12- dimethylbenz(a)anthracene in SENCAR and BALB/c mice following topical and oral administration. Cancer Res 47:4571-4575.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokin 5:485-527.

*Mueller JG, Chapman PJ, Pritchard PH. 1989. Creosote-contaminated sites: Their potential for bioremediation. Environ Sci Technol 23(10):1197-1201.

*Mueller JG, Middaugh DP, Lantz SE, et al. 1991. Biodegradation of creosote and pentachlorophenol in contaminated groundwater: Chemical and biological assessment. Appl Environ Microbiol 57(5):1277-1285.

Muller C, Hausen BM. 1994. Contact allergy to a synthetic tannin in Tannosynt(r) liquid. Contact Derm 31:185-186.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 15-35.

NATICH. 1992. National Air Toxics Information Clearing House (NATICH) Data Base Report of Federal, State, and Local Air Toxic Activities. Research Triangle Park, NC. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-453\R-92-008.

Negrie E, Franzoi MG, La Vecchia C, et al. 1993. Tar yield of cigarettes and risk of acute myocardial infarction. Br Med J 306:1567-1570.

Nenoff P, Richter B, Will W, et al. 1997. [Longitudinal study of the excretion of 1-hydroxypyrene in urine after external treatment with coal tar]. Hautarzt 48(4):240-245. (German).

Nersessian AK, Arutyunyan RM. 1994. The comparative clastogenic activity of mainstream tobacco smoke from cigarettes widely consumed in Armenia. Mutat Res 321(1-2):89-92.

*Nestler FHM. 1974a. Characterization of wood-preserving coal-tar creosote by gas-liquid chromatography. Anal Chem 46:46-53.

Nestler FHM. 1974b. The characterization of wood-preserving creosote by physical and chemical methods of analysis. U.S. Forest Service Research Paper, FPL.

Neuman WR. 1988. Hazard review. Creosote. Health Information for Hazardous Materials Emergencies 4:1-3.

*Newman MJ, Light BA, Weston A, et al. 1988. Detection and characterization of human serum antibodies to polycyclic aromatic diol-epoxide DNA adducts. J Clin Invest 82:145-153.

Nicolas J-M, Vandermeulen JH. 1997. Estrogenic effect of coal-tar contamination on an estuarian population of male winter flounder (*Pleuronectes americanus*). Can Tech Rep Fish Aquat Sci 2192:10.

*Niemeier RW, Thayer PS, Menzies KT, et al. 1988. A comparison of skin carcinogenicity of condensed roofing asphalt and coal tar pitch fumes. In: Polynuclear Aromatic hydrocarbons: A decade of progress, 609-647.

*Nightingale SL. 1993. Instructional videos on food safety in nursing homes. JAMA 269(3):328.

*NIOSH. 1977. Criteria for recommended standard. Occupational exposure to coal-tar products. Cincinnati, OH. SRI International for U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. NIOSH-78-107.

NIOSH. 1979. Industrial hygiene report, preliminary survey of wood preservative treatment facility at Koppers Company, Inc, Forest Products Group, Florence, South Carolina. Cincinnati, OH. National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies. NTIS PB86-136652.

*NIOSH. 1980a. Health hazard evaluation determination report No. HE-79-43-663, Harbison- Walker refractories, Clearfield, Pennsylvania. Cincinnati, OH. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 1980b. Industrial hygiene report comprehensive survey of wood preservative treatment facility at Santa Fe Centralized Tie Plant, Somerville, Texas. Cincinnati, OH. National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies. NTIS PB83-133892.

9. REFERENCES

*NIOSH. 1981a. Health Hazard Evaluation: New York Port Authority, Brooklyn, New York. Cincinnati, OH. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. HHE 80-238-931.

*NIOSH. 1981b. Industrial hygiene report, comprehensive survey of wood preservative treatment facility at Cascade Pole Company, McFarland Cascade, Tacoma, Washington. Cincinnati, OH. National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies. NTIS PB82-174160.

*NIOSH. 1982. Health Hazard Evaluation Report. HETA No. 80-206-1164, Mid-South Terminals Memphis, Tennessee. Cincinnati, OH. U.S. National Institute for Occupational Safety and Health.

*NIOSH. 1983. Health Hazard Evaluation Report. HETA 82-324-1279, Chemical Leaman Tank Lines, Inc., Stockertown, Pennsylvania. Cincinnati, OH. National Institute for Occupational Safety and Health. PB84-149178.

NIOSH. 1990. Pocket guide to chemical hazards. Cincinnati, OH. National Institute of Occupational Safety and Health. Publication No. 90-117.

NIOSH. 1992. Recommendations for occupational safety and health. Cincinnati, OH. National Institute of Occupational Safety and Health. Compendium of Policy Documents and Statements, U.S. DHHS/NIOSH. 161-170.

*NIOSH. 2000. Creosote. NIOSH pocket guide to chemical hazards. Cincinnati, OH. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/npg/npgd0145.html.

*NIOSH. 2001. Coal tar pitch volatiles. NIOSH pocket guide to chemical hazards. Cincinnati, OH. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/npg/npgd0145.html. September 17, 2001.

*NOES. 1990. National occupational exposure survey 1981-83. Cincinnati, OH. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. July 1, 1990.

*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.

*NTDB. 1994. National Trade Data Bank, the export connection. U.S. Department of Commerce.

*NTDB. 1995. National Trade Data Bank, the export connection. U.S. Department of Commerce.

*NTP. 1998. Report on carcinogens; 8th edition; summary. Research Triangle Park, NC: National Toxicology Program. U.S. Department of Health and Human Services. 31-46.

Nurminen T, Rantala K, Kurppa K, et al. 1995. Agricultural work during pregnancy and selected structural malformations in Finland. Epidemiology 6(1):23-30.

*Ny ET, Heederik D, Kromhout H, et al. 1993. The relationship between polycyclic aromatic hydrocarbons in air and in urine of workers in a Soderberg potroom. Am Ind Hyg Assoc J 54 (6):277-284.

Nylund L, Heikkilä P, Hameila M, et al. 1992. Genotoxic effects and chemical compositions of four creosotes. Mutat Res 265(2):223-236.

*Obana H, Hori S, Kashimoto T, et al. 1981. Polycyclic aromatic hydrocarbons in human fat and liver. Bull Environ Contam Toxicol 27:23-27.

*O'Donovan WJ. 1920. Epitheliomatous ulceration among tar workers. Br J Dermatol Syphilis 32:215-252.

Ogata N, Ataka H. 1998. [Drugs containing creosote for bacterial toxin-induced symptoms]. Japan Kokai 98147536, issued 2 Jun 1998. (Japanese).

*Ogata N, Baba T. 1989. Analysis of beechwood creosote by gas chromatography-mass spectrometry and high-performance liquid chromatography. Res Comm Chem Pathol Pharmacol 66(3):411-423.

Ogata N, Ataka H 1998. [Drugs containing creosote for bacterial toxin-induced symptoms.] Japan Kokai 98147536, issued 2 Jun 1998. (Japanese)

*Ogata N, Ataka K, Morino H, et al. 1999. Effect of wood creosote and loperamide on propulsive motility of mouse colon and small intestine. Pharmacology 59:212-220.

*Ogata N, Baba T, Shibata T. 1993. Demonstration of antidiarrheal and antimotility effects of wood creosote. Pharmacology 46(3):173-180

*Ogata N, Matsushima N, Shibata T. 1995. Pharmacokinetics of wood creosote: Glucuronic acid and sulfate conjugation of phenolic compounds. Pharmacology 51(3):195-204.

Ogata N, Shibata T. 2000. Binding of alkyl- and alkoxy-substituted simple phenolic compounds to human serum proteins. Res Commun Mol Pathol Pharmacol 107(1-2):167-173.

*Okaygun MS. 1988. Identification of toxic components in Beechwood and Petroleum Creosotes. Thesis submitted to the Graduate College of Texas A & M University.

Olafson P, Leutritz J Jr, 1958. The toxicity of creosote and creosote-pentachlorophenol mixtures to cattle. Am Wood Preserv Assoc 55:54-57.

OSHA. 1974. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*OSHA. 1999a. Air contaminants. Occupational Safety and Health Administration. 29 CFR 1910.1000.

*OSHA. 1999b. Air contaminants. Occupational Safety and Health Administration. 29 CFR 1915.1000.

*OSHA. 1999c. Gases, vapors, fumes, dusts, and mists. Occupational Safety and Health Administration. 29 CFR 1926.55.

*OSHA. 2001a. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. http://www.osha-slc.gov/OshStd_data/1915_1000.html. September 17, 2001.

*OSHA. 2001b. Limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. http://www.osha-slc.gov/OshStd_data/1910_1000_Table_Z-1.html. September 17, 2001.

*OSHA. 2001c. Gases, vapors, fumes, dusts, and mists. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55. http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=29&PART=1926&SECTION=55&YEAR=2001&TYPE=TEXT. September 17, 2001.

*Osol A, ed. 1980. Remington's pharmaceutical sciences. 16th ed. Easton, PA: Mack Publishing Co.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-438, April 1990.

*Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

Padma TA, Hale RC, Roberts MH. 1998. Toxicity of water-soluble fractions derived from whole creosote and creosote-contaminated sediments. Environ Toxicol Chem 17(8):1606-1610.

*Paleologo M, van Schooten FJ, Pavanello S, et al. 1992. Detection of benzo[a]pyrene-diol-epoxide-DNA adducts in white blood cells of psoriatic patients treated with coal tar. Mutat Res 281:11-16.

Panja D. 1941. Treatment of tuberculosis verrucosa cutis by local application of creosote and salicylic acid. Ind Med Gazette 76:70-72.

*Park RM, Mirer FE. 1996. A survey of mortality at two automotive engine manufacturing plants. Am J Ind Med 30:664-673.

Pauly JL, Jezewski HM, Rodriquez MI, et al. 1993. Human lung tumor immunology cigarette filter fibers identified in the lungs of patients with cancer. Joint Meeting of the American Association of Immunologist and the Clinical Immunology Society, Denver, Colorado, USA May 21-25, 1993. J Immunol 150(8)part 2:1770.

*Pavanello S, Levis AG. 1992. Coal tar therapy does not influence in vitro benzo[a]pyrene metabolism and DNA adduct formation in peripheral blood lymphocytes of psoriatic patients. Carcinogenesis 13(9):1569-1573.

*Pavanello S, Levis AG. 1994. Human peripheral blood lymphocytes as a cell model to evaluate the genotoxic effect of coal tar treatment. Environ Health Perspect 102(9):95-99.

*Pereira WE, Rostad CE, Garbarino JR, et al. 1983. Groundwater contamination by organic bases derived from coal-tar wastes. Environ Toxicol Chem 2:283-294.

*Perera FP, Hemminki K, Young TL, et al. 1988. Detection of polycyclic aromatic hydrocarbon-DNA adducts in white blood cells of foundry workers. Cancer Res 48:2288-2291.

Perry HO, Soderstrom CW, Schulze RW. 1968. The Goeckerman Treatment of Psoriasis. Arch Dermatol 98:178-182.

*Persson B, Dahlander A, Fredriksson M et al. 1989. Malignant lymphomas and occupational exposures. Br J Ind Med 46:516-520.

Persson B, Fredriksson M, Olsen K, et al. 1993. Some occupational exposures as risk factors for malignant lymphomas. Cancer 72(5):1773-1778.

Peters CA, Knightes CD, Brown DG. 1999. Long-term composition dynamics of PAH-containing NAPLs and implications for risk assessment. Environ Sci Technol 33:4499-4507.

*Petridou-Fischer J, Whaley SL, Dahl AR. 1988. *In vivo* metabolism of nasally instilled benzo[a]pyrene in dogs and monkeys. Toxicology 48:31-40.

*Petsonk EL, Storey E, Becker PE , et al. 1988. Pneumoconiosis in carbon electrode workers. J Occup Med 30(11):887-891.

Pfitzer EA, Gross P. 1964. Range-finding toxicity tests on creosote (64-451B) for Koppers Company, Inc. Industrial Hygiene Foundation of America, Inc., Mellon Institute, Pittsburgh, PA. (Unpublished report).

*Pfitzer EA, Gross P, Kaschak M. 1965. Range-finding toxicity tests on creosote (64-451B) for Koppers Company, Inc. Pittsburgh: Industrial Hygiene Foundation of America, Inc. for Koppers Company, Inc.

Phillips DH. 1993. Analysis of polycyclic aromatic hydrocarbon-DNA adducts by 32P-postlabelling. Environ Mol Mutagen 21(Suppl. 22):54.

*Phillips DH, Alldrick AJ. 1994. Tumorigenicity of a combination of psoriasis therapies. Br J Cancer 69(6):1043-1045

*Philips DH, Hemminki K, Alhonen A, et al. 1988. Monitoring occupational exposure to carcinogens: detection by ^{32}P-postlabeling of aromatic DNA adducts in white blood cells from iron foundry workers. Mutat Res 204:531-541.

Phillips DH, Schoket B, Hewer A, et al. 1990. DNA adduct formation in human and mouse skin by mixtures of polycyclic aromatic hydrocarbons. IARC Sci Publ No.104, 223-229.

Pickering RW. 1999. A toxicological review of polycyclic aromatic hydrocarbons. J Toxicol Cutaneous Ocul Toxicol 18(2):101-135.

*Pittelkow MR, Perry HO, Muller SA. 1981. Skin cancer in patients with psoriasis treated with coal-tar. Arch Dermatol 117:465-468.

Plato N, Steineck G. 1993. Methodology and utility of a job-exposure matrix. Am J Ind Med 23:491-502.

*Poel WE, Kammer AG. 1957. Experimental carcinogenicity of coal-tar fractions: The carcinogenicity of creosote oils. JNCI 18:41-55.

Pollard SJ, Hrudey SE, Fuhr BJ, et al. 1992. Hydrocarbon wastes at petroleum- and creosote-contaminated sites: Rapid characterization of component classes by thin-layer chromatography with flame ionization detection. Environ Sci Technol 26(12):2528-2534.

*Povey AC, Brouet I, Bartsch H. 1987. Binding of benzo[a]pyrene metabolites in the rat intestinal lumen by magnetic polyethyleneimine microcapsules following an intragastric dose of [^{14}C]benzo[a]pyrene. Carcinogenesis 8:825-831.

Prichard FD, Obermeyer W, Bradlaw J, et al. 1994. Primary rat hepatocyte cultures aid in the chemical identification of toxic chaparral (larrea tridentata). In Vitro Cell Develop Biol 30A(3 PT 2):91-92.

Prigoda YG, Obukhan EI. 1993. [Experimental substantiation of the maximum permissible concentration of a volatile fraction of coal tar STU-3]. Gig Sanit 4:11-14. (Russian).

Pylev LN, Vasil'eva LA, Azarova MA, et al. 1999. [The carcinogenic activity of the pesticide kreokhin (leptocide)]. Gig Sanit :54-57.

Raftos D, Hutchinson A. 1997. Effects of common estuarine pollutants on the immune reactions of tunicates. Biol Bull 192:62-72.

*Rahman A, Barrowman JA, Rahimtula A. 1986. The influence of bile on the bioavailability of polynuclear aromatic hydrocarbons from the rat intestine. Can J Physiol Pharmacol 64:1214-1218.

*Randerath E, Zhou G-D, Donnelly KC, et al. 1996. DNA damage induced in mouse tissues by organic wood preserving waste extracts as assayed by ^{32}P-postlabeling. Arch Toxicol 70:683-695.

*Reddy MV, Blackburn GR, Schreiner CA, et al. 1997. Correlation of mutagenic potencies of various petroleum oils and oil coal tar mixtures with DNA adduct levels *in vitro*. Mutat Res 378:89-95.

*Redmond CK. 1976. Epidemiological studies of cancer mortality in coke plant workers Proceedings of the annual conference on environmental toxicology. Aerospace Medical Research Lab, Wright-Patterson AFB, OH. AMRL-TR-76-125.

*Redmond CK, Ciocco A, Lloyd JW, et al. 1972. Long-term mortality study of steelworkers VI. Mortality from malignant neoplasms among coke oven workers. JOM 14(8):621-629.

*Redmond CK, Strobino BR, Cypess RH. 1976. Cancer experience among coke by-product workers. Ann NY Acad Sci 271:102-115.

*Rees ED, Mandelstam P, Lowry JQ. 1971. A study of the mechanism of intestinal absorption of benzo(a)pyrene. Biochim Biophys Acta 225:96-107.

*Reeves WR, Barhoumi R, Burghardt RC, et al. 2001. Evaluation of Methods for Predicting the Toxicity of Polycyclic Aromatic Hydrocarbon Mixtures. Environ Sci Technol 35:1630-1636.

Reid DD, Buck C. 1956. Cancer in coking plant workers. Brit J Ind Med 13:265-269

Rhomundstad P, Haldorsen T, Andersen A. 2000. Lung and bladder cancer among workers in a Norwegian aluminum reduction plant. Occup Environ Med 57(7):495-499.

Riala R, Heikkila P, Kaverva L. 1998. A questionnaire study of road pavers' and roofers' work-related skin problems and bitumen exposure. Int J Dermatol 37:27-30.

*Rice E, Hosted TJ Jr, DeFloria MC, et al. 1986. Tumor-initiating activity of major *in vivo* metabolites of indeno[1,2,3-cd]pyrene on mouse skin. Carcinogenesis 7:1761-1764.

Rittinghausen S, Dungworth DL, Dasenbrock C, et al. 1997a. Cystic squamous cell carcinoma in the lungs of Syrian golden hamsters induced by coal oven flue exhaust mixed with pyrolized tar pitch in combination with benzo(a)pyrene. Exp Toxicol Pathol 49:11-14.

Rittinghausen S, Mohr U, Dungworth DL. 1997b. Pulmonary cystic keratinizing squamous cell lesions of rats after inhalation/instillation of different particles. Exp Toxicol Pathol 49(6):433-446.

*Rivers PM. 1990. Comments on toxicological profile on creosote submitted by Paul M. Rivers, Reilly Industries, Inc., February 16, 1990.

Roberts SJ, Hedrick HG. 1979. Degradation of creosote phenolic compounds by selected bacterial isolates. Dev Ind Microbiol 20:471-478.

*Robinson SK. 1938. An instance of hypertension apparently due to the taking of creosote for a period of nine years. ILL Med J 74:278-279.

*Rockette HE, Arena VC. 1983. Mortality studies of aluminum reduction plant workers: Potroom and carbon department. J Occup Med 25(7):549-557.

Rodriguez LV, Dunsford HA, Steinberg M, et al. 1997. Carcinogenicity of benzo[a]pyrene and manufacture gas plant residues in infant mice. Carcinogenesis 18(1):127-135.

*Roe FJC, Bosch D, Boutwell RK. 1958. The carcinogenicity of creosote oil: the induction of lung tumors in mice. Cancer Res 18:1176-1178.

*Rogaczewska T, Ligocka D. 1991. Occupational exposure to polycyclic aromatic hydrocarbons (coal tar pitch volatiles) and benzo(a)pyrene in tyre production. Sci Total Environ 101:171.

*Rogaczewska T, Ligocka D. 1994. Occupational exposure to coal tar pitch volatiles, benzo/a/pyrene and dust in tyre production. Int J Occup Med Environ Health 7(4):379-386.

*Rojas M, Godschalk R, Alexandrov K, et al. 2001. Myeloperoxidase--463A varient reduces benzo[alpha]pyrene diol epoxide DNA adducts in skin of coal tar treated patients. Carcinogenesis 22(7):1015-1018.

*Romundstad P, Haldorsen T, Andersen A. 2000. Lung and bladder cancer among workers in a Norwegian aluminium reduction plant. Occup Environ Med 57:495-499.

Rönneberg A. 1995a. Mortality and cancer morbidity in workers from an aluminum smelter with prebaked carbon anodes-Part I: Exposure assessment. Occup Environ Med 52(4):242-249.

*Rönneberg A. 1995b. Mortality and cancer morbidity in workers from an aluminum smelter with prebaked carbon anodes-Part III: Mortality from circulatory and respiratory diseases. Occup Environ Med 52(4):255-261.

*Rönneberg A, Andersen A. 1995. Mortality and cancer morbidity in workers from an aluminum smelter with prebaked carbon anodes-Part II: Cancer morbidity. Occup Environ Med 52(4):250-254.

Rönneberg A, Langmark F. 1992. Epidemiologic evidence of cancer in aluminum reduction plant workers. Am J Ind Med 22:573-590.

Rooij GM, van Lieshout EMA, van Bodelier-Bade MM, et al. 1993. Effect of the reduction of skin contamination on the internal dose of creosote workers exposed to polycyclic aromatic hydrocarbons. Scand J Work Environ Health 19(3):200-207.

*Rostad CE, Pereira WE. 1987. Creosote compounds in snails obtained from Pensacola Bay, Florida, near an onshore hazardous-waste site. Chemosphere 16:10-12.

*Rostad CE, Pereira WE, Ratcliff SM. 1984. Bonded-phase extraction column isolation of organic compounds in groundwater at a hazardous waste site. Anal Chem 56:2856-2860.

*Rotard W, Mailahn W. 1987. Gas chromatographic-mass spectrometric analysis of creosote extracted from wooden sleepers installed in playgrounds. Anal Chem 59:65-69.

Roy TA, Johnson SW, Blackburn GR, et al. 1988. Correlation of mutagenic and dermal carcinogenic activities of mineral oils with polycyclic aromatic compound content. Fundam Appl Toxicol 10:466-476.

Roy TA, Krueger AJ, Mackerer CR, et al. 1998. SAR models for estimating the percutaneous absorption of polynuclear aromatic hydrocarbons. Environ Res 9(3-4):171-185.

*RTECS. 1994. Registry of Toxic Effects of Chemical Substances Database. National Institute of Occupational Safety and Health. National Library of Medicine Bethesda MD.

*RTECS. 1998. Registry of Toxic Effects of Chemical Substances Database. National Institute of Occupational Safety and Health. National Library of Medicine Bethesda MD.

*R.U.P. 1994. EPA Restricted Use Products File. Washington DC: U.S. Environmental Protection Agency, Office of Pesticide Programs (on-line BBS database).

*Sakabe H, Tsuchiya K, Takekura N, et al. 1975. Lung cancer among coke oven workers: A report to Labour Standard Bureau, Ministry of Labour, Japan Ind. Health 13:57-68.

Salim ASM (1994): Pharmaceutical compositions containing methylsulfonylmethane. (to and oxypurinol or allopurinol for skin cancer treatment) PCT Int. Appl. Patent 94 05291, issued 17 Mar 1994.

*Sall RD, Shear MJ. 1940. Studies in carcinogenesis. XII. Effect of the basic fraction of creosote oil on the production of tumors in mice by chemical carcinogens. JNCI 1:45-55.

*Samson JG, Limkako G. 1923. Preliminary report on creosote as an adjuvant in leprosy treatment. Philippine J Sci 23:515-529.

Sanders CL, Skinner C, Gelman RA. 1986. Percutaneous absorption of 7,10[^{14}C]benzo[a]pyrene and 7,12[^{14}C]- dimethylbenz[a]anthracene in mice. J Environ Pathol Toxicol 7:25-34.

Santella RM. 1993. Immunologic methods for quantitation of polycyclic aromatic hydrocarbon-DNA adducts. Environ Mol Mutagen 21(Suppl. 22):61.

*Santella RM, Nunes MG, Blaskovic R, et al. 1994. Quantitation of polycyclic aromatic hydrocarbons, 1-hydroxypyrene, and mutagenicity in urine of coal tar-treated psoriasis patients and untreated volunteers. Cancer Epidemiol Biomarkers Prev 3(2):137-140.

*Santella RM, Perera FP, Young TL, et al. 1995. Polycyclic aromatic hydrocarbon-DNA and protein adducts in coal tar treated patients and controls and their relationship to glutathione S-transferase genotype. Mutat Res 334(2):117-224.

*Santodonato J, Bosch S, Meylan W, et al. 1985. Monographs on human exposure to chemicals in the workplace: Creosote. National Cancer Institute, Division of Cancer Etiology, Bethesda, MD. PB86-147303.

*Sarto F, Zordan M, Tomanin R, et al. 1989. Chromosomal alterations in peripheral blood lymphocytes, urinary mutagenicity and excretion of polycyclic aromatic hydrocarbons in six psoriatic patients undergoing coal tar therapy. Carcinogenesis 10(2):329-341.

*Sasser LB, Lundstrom DL, Zangar RC, et al. 1989. Elevated blood pressure and heart rate in rats exposed to a coal-derived complex organic mixture. J Appl Toxicol 9 (1):47-52.

Saunders JCJ, Davis HJ, Coetzee L, et al. 1999. A Novel Skin Penetration Enhancer: Evaluation by Membrane Diffusion and Confocal Microscopy. J Pharm Pharmaceut Sci 2(3):99-107. http://www.ualberta.ca/~csps/JPPS2(3)/J.Saunders/microscopy.htm.

Schabad L. 1928. [Primative pulmonary tumors in the offspring of mice treated externally with tar]. C R Seances Soc Biol Fil 99:1550-1551. (French).

*Schildt E-B, Eriksson M, Hardell L, et al. 1999. Occupational exposures as risk factors for oral cancer evaluated in a Swedish case-control study. Oncol Rep 6:317-320.

*Schipper IA. 1961. Toxicity of wood preservatives for swine. Am J Vet Res 22:401-405.

Schirmer K, Herbrick JS, Greenberg BM, et al. 1997. An evaluation of the cytotoxicity and photocytotoxicity of intact and photomodified creosote through the use of a rainbow trout gill cell line, TRGILL-W1, and two flourescent indicator dyes, alamar blue and 5-carboxyfluorescein diacetate acetoxymethyleste. Can Tech Rep Fish Aquat Sci 2192:4.

*Schirmer K, Herbrick J, Greenberg BM, et al. 1999. Use of fish gill cells in culture to evaluate the cytotoxicity and photocytotoxicity of intact and photomodified creosote. Environ Toxicol Chem 18(6):1277-1288.

*Schoket B, Horkay I, Kosa A, et al. 1990. Formation of DNA adducts in the skin of psoriasis patients, in human skin in organ culture. and in mouse skin and lung following topical application of coal- tar and juniper tar. J Invest Dermatol 94(2):241-246.

*Schwartz L. 1942. Dermatitis from creosote-treated wooden floors. Ind Med 11,No.8:387.

*Schweikert H, Schnyder UW. 1972a. [Tar-induced acanthosis of the guinea pig nipple. I. Histological observations.] Arch Derm Forsch 243:31-38. (German).

*Schweikert H, Schnyder UW. 1972b. [Tar-induced acanthosis of the guinea pig nipple. II. Enzymehistochemical observations.] Arch Derm Forsch 243:39-46. (German).

Scobbie E, Dabill DW, Groves JA. 1998. The development of an improved method for the determination of coal tar pitch volatiles (CTPV) in air. Ann Occup Hyg 42(1):45-59.

Scribner KA, Gadbois TM, Gowri M, et al. 2000. Masoprocol Decreases Serum Triglyceride Concentrations in Rats with Fructose-Induced Hypertriglyceridemia. Metabolism 49(9):1106-1110.

Seidler A, Heiskel H, Bickeboller R, et al. 1998. Association between diesel exposure at work and prostrate cancer. Scand J Work Environ Health 24(6):486-494.

*Setchell BP, Waites GMH. 1975. The blood-testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society.

*Shambaugh P. 1935. Tar cancer of the lip in fishermen. JAMA 104:2326-2329.

*Shimauchi T, Rikihisa W, Yasuda H, et al. 2000. [A case of squamous cell carcinoma that developed on chronic tar dermatosis.] J UOEH 22(2):183-187. (Japanese)

*Siemiatycki J, Dewar R, Nadon L, et al. 1994. Occupational risk factors for bladder cancer: Results from a case-control study in Montreal, Quebec, Canada. Am J Epidemiol 140(12):1061-1080.

*Simmon VF, Shepherd S. 1978. *In vitro* microbiological mutagenicity assay of creosote P_1 and creosote P_2. Final Report. SRI International, Menlo Park, California. Project LSU-7558. Contract No. 68-02-2947.

Skowronski GA, Abdel-Rahman MS, Turkall RM. 1994. Effects of gender, route of administration, and soil on the bioavailability of coal tar components. In: Wise DL, Trantolo DJ, eds. Remediation of hazardous waste contaminated soils. New York: M. Dekker, 299-315.

Smale BC. 1977. Coal-tar creosote and coal-tar pesticides as candidates for RPAR. Unpublished EPA report.

*Smith AY, Feddersen RM, Gardner KD, et al. 1994. Cystic renal cell carcinoma and acquired renal cystic disease associated with consumption of chaparral tea: A case report. J Urol 152:2089-2091.

*Smith GA, Nickels JS, Davis JD. 1985. Indices identifying subsurface microbial communities that are adapted to organic pollution. Ada, OK. U.S. Environmental Protection Agency, Office of Research and Development. EPA/600/D-85/055.

*Smith LM. 1937. Dermatitis caused by creosote bush. J Allergy 8:187-188.

Snit M. 1993. [Concentration of carcinoembryonic antigen, alpha-fetoprotein and beta-subunit of human chorionic gonadotropin in serum of coke oven workers]. Med Pr 44(1):21-28. (Polish)

*Spinelli JJ, Band PR, Svirchev LM, et al. 1991. Mortality and cancer incidence in aluminum reduction plant workers. J Occup Med 33(11):1150-1155.

*Springer DL, Hackett PL, Miller RA, et al. 1986a. Lung development and postnatal survival for rats exposed *in utero* to a high-boiling coal liquid. J Appl Toxicol 6:129-133.

*Springer DL, Mann DB, Dankovic DA, et al. 1989. Influences of complex organic mixtures on tumor-initiating activity, DNA binding and adducts of benzo[a]pyrene. Carcinogenesis 10(1):131-137.

*Springer DL, Miller RA, Weimer WC, et al. 1986b. Effects of inhalation exposure to a high-boiling (288 to 454ºC) coal liquid. Toxicol Appl Pharmacol 82:112-131.

*Springer DL, Miller RA, Wright CW, et al. 1987. Effects of subchronic inhalation exposure of mice to a high-boiling coal liquid. Fundam Appl Toxicol 9:277-286.

*Springer DL, Poston KA, Mahlum DD, et al. 1982. Teratogenicity following inhalation exposure of rats to a high-boiling coal liquid. J Appl Toxicol 5(2):261-265.

*SRI. 1993. Directory of chemical producers: United States of America. SRI International, Menlo Park, CA.

*Srivastava VK, Chauhan SS, Srivastava PK, et al. 1986. Fetal translocation and metabolism of PAH obtained from coal fly ash given intratracheally to pregnant rats. J Toxicol Environ Health 18:459-469.

*Stangroom SJ, Collins CD, Lester JN. 1998. Sources of organic micropollutants to lowland rivers. Environ Tech 19(7):643-666.

Stavric B, Klassen R. 1994. Dietary effects on the uptake of benzo[alpha]pyrene. Food Chem Toxicol 32(8):727-734.

Steinberg MA. 1996. The role of polycyclic aromatic hydrocarbons in coal tar-induced genotoxicity and carcinogenicity. Doctor of Philosophy Thesis, Texas A & M University, College Station. 154 p.

Steineck G, Plato N, Norell SE, et al. 1990. Urothelial cancer and some industry-related chemicals: An evaluation of the epidemiologic literature. Am J Ind Med 17(3):371-391.

*Stern FB, Ruder AM, Chen G. 2000. Proportionate mortality among unionized roofers and waterproofers. Am J Ind Med 37(5):478-492.

*Stern RS, Zietler S, Parrish JA. 1980. Skin cancer in outpatients treated with topical tar and artificial ultraviolet radiation. Lancet 1:732-734.

*Stevens ME, Ronan AK, Sourkes TS, et al. 1943. On the expectorant action of creosote and the guaiacols. Can Med Assoc J 48:124-127.

*Stjernsward J. 1966. Effect of noncarcinogenic and carcinogenic hydrocarbons on antibody-forming cells measured at the cellular level *in vitro*. JNCI 36:1189-1195.

*Stjernsward J. 1969. Immunosuppression by carcinogens. Antibiot Chemother (Basel) 15:213-233.

Story WC, Caruso JA. 1993. Gas chromatographic determination of phosphorus, sulfur and halogens using a water-cooled torch with reduced-pressure helium microwave-induced plasma mass spectrometry. J Anal Atomic Spectrom 8:571-575.

*Strickland P, Kang D, Sithisarankul P. 1996. Polycyclic aromatic hydrocarbon metabolites in urin as biomarkers of exposure and effect. Environ Health Perspect Suppl 104(5):927-932.

Stucker I, Bouyer J, Mandereau L, et al. 1993. Retrospective evaluation of the exposure to polycyclic aromatic hydrocarbons: Comparative assessments with a job exposure matrix and by experts in industrial hygiene. Int J Epidemiol 22(6)(Suppl. 2):S106-S112.

*Swaen GMH, Slangen JMM. 1997. Mortality in a group of tar distillery workers and roofers. Int Arch Occup Environ Health 70(2):133-137.

*Swann RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Res Rev 85:17-28.

*Swartz RC, Kemp PF, Schults DW, et al. 1989. Acute toxicity of sediment from Eagle Harbor, Washington, to the infaunal amphipod Rhepoxynius abronius. Environ Toxicol Chem 8:215-222.

*Szakal A, Hanna M. 1972. Immune suppression and carcinogenesis in hamsters during topical application of 7,12-dimethylbenz(a)anthracene. Oak Ridge, TN. Conference on Immunology of Carcinogenesis at Oak Ridge National Laboratory.

Taylor JM, Jenner PM, Jones WI. 1964. A comparison of the toxicity of some allyl, propenyl, and propyl compounds in the rat. Toxicol Appl Pharmacol 6:378-387.

*Tham SN, Lun KC, Cheong WK. 1994. A comparative study of calcipotriol ointment and tar in chronic plaque psoriasis. Br J Dermatol 131(5):673-677.

Theriault GP, Tremblay CG, Armstrong BG. 1990. Bladder cancer screening among primary aluminum production workers in Quebec. J Occup Med 32(9):869-872.

Thompson JP, Casey PB, Vale JA. 1994. Suspected paediatric pesticide poisoning in the UK. II-Home Accident Surveillance System 1989-1991. Hum Exp Toxicol 13(8):534-536.

Tigalonova M, Bjerke JR, Gallati H, et al. 1994. Serum levels of interferons and TNF-α are not correlated to psoriasis activity and therapy. Acta Derm Venereol Suppl (Stockh) 186:25-27.

Todd WA. 1993. TARS. Their role in the treatment of psoriasis. Dermatol Clin (United States) 11(1):131-135.

*Tolos WP, Shaw PB, Lowry LK, et al. 1990. 1-Pyrenol: A biomarker for occupational exposure to polycyclic aromatic hydrocarbons. Appl Occup Environ Hyg 5(5):303-309.

*TOMA. 1979. Cross-sectional health study of workers of four forest products plants of Koppers Company Inc. Volume A. Tabershaw Occupational Medicine Associates (TOMA). EPA/OTS number: FYI-OTS 0285 0385. U.S. EPA/OPTS Public Files.

*TOMA. 1980. Summary of health findings from the examination of 329 creosote workers. Report prepared for the Forest Products Group of Koppers Company, Inc., Pittsburgh, PA. Tabershaw Occupational Medicine Associates (TOMA). February 28, 1980.

*TOMA. 1981. Cross-sectional health study of workers of four forest products plants of Koppers Company Inc. Volume A. Tabershaw Occupational Medicine Associates (TOMA). EPA/OTS number: FYI-OTS-0285-0385. U.S. EPA/OPTS Public Files.

*TOMA. 1982. Mortality among Koppers workers employed at eight coal tar facilities, with cover letter dated 01/25/85. Tabershaw Occupational Medicine Associates (TOMA). EPA/OTS number FYI-OTS 0285 0385. U.S. EPA/OPTS Public Files.

*TOMES. 1994. (Toxicology, Occupational Medicine and Environment Series) electronic database. Creosote: Phenol and related agents. Micromedex, Inc. Vol 78.

*Torinuki W, Tagami H. 1988. Incidence of skin cancer in Japanese psoriatic patients treated with either methoxsalen phototherapy, Goeckerman regimen, or both therapies. J Am Acad Dermatol 18(6):1278-1281.

*Tremblay C, Armstrong B, Theriault G, et al. 1995. Estimation of risk of developing bladder cancer among workers exposed to coal tar pitch volatiles in the primary aluminum industry. Am J Ind Med 27(3):335-348.

TRI93. 1995. Toxics Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*TRI97. 2000. Toxics Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*TRI99. 2001. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access, Offices of Environmental Information, U.S. Environmental Protection Agency. Toxic Release Inventory. http://www.epa.gov/triexplorer/. October 24, 2001.

Tynes T, Jynge H, Vistnes AI. 1994. Leukemia and brain tumors in Norwegian railway workers, a nested case-control study. Am J Epidemiology 139(7):645-653.

*USDA. 1980. The biologic and economic assessment of pentachlorophenol, inorganic arsenicals, creosote. Volume 1: Wood preservatives. Washington, DC: U.S. Department of Agriculture. Technical Bulletin number 1658-1, 193-227.

*US Department of Energy. 1994. Toxicity studies of mild gasification products. Morgantown, WV: Office of Fossil Energy, U.S. Department of Energy. DOE/MC/26018-3730. DE94004113.

USGS. 1984. Phenolic contamination in the sand-and-gravel aquifer from a surface impoundment of wood treatment wastes, Pensacola, Florida. US Geological Survey Water-Resources Investigations Report, 82-4230.

*USGS. 1986. Investigations of organic contaminants derived from wood-treatment processes in a sand and gravel aquifer near Pensacola, Florida. Selected Papers in the Hydrologic Sciences 1986. U.S. Geological Survey, Washington, DC. U.S. Geological Survey Water-Supply Paper 2290, 65-80.

*USGS. 1988a. Geochemistry of a shallow aquifer contaminated with creosote products. In: Ragone SE, ed. U.S. Geological Survey Program on Toxic Waste -- Ground-water Contamination: Proc. Second Technical Meeting, Cape Cod, MA, Oct. 21-25, 1985. Reston, VA: U.S. Geological Survey, Open-File Report 86-481, A17-A20.

USGS. 1988b. Reexamination of the occurrence and distribution of creosote contaminants in the ground water at Pensacola, Fl. U.S. Geological Survey program on toxic waste--ground water contamination. Proceedings of the second technical meeting, Cape Cod, MA, Oct. 21-25, 1985. US Geological Survey open file report., 86-481.

*USITC. 1987. Synthetic organic chemicals. United States production and sales, 1986. Washington, DC: United States International Trade Commission. USITC Publication 2009.

9. REFERENCES

*USITC. 1988. Synthetic organic chemicals. United States production and sales, 1987. Washington, DC: United States International Trade Commission. USITC Publication 2118.

USITC. 1991. Harmonized tariff schedule of the United States (1991). Washington, DC: U.S. International Trade Commission.

USITC. 1992. Preliminary report on U.S. production of selected synthetic organic chemicals (including synthetic plastics and resin materials) first quarter, second quarter, and cumulative totals, 1992. Washington, DC: U.S. International Trade Commission.

*USITC. 1994. Synthetic organic chemicals. United States production and sales, 1992. Washington, DC: United States International Trade Commission. USITC Publication 2720.

van de Kerkhof PC, Timmerman MG. 1990. The effect of clobetasol-17-propionate and crude coal tar on dithranol-induced inflammation. A clinical and biochemical study. Acta Derm Venereol (Stockh) 70(5):434-437.

*Van Rooij JGM, De Roos JHC, Bodelier-Bade MM et al. 1993a. Absorption of polycyclic aromatic hydrocarbons through human skin: Differences between anatomical sites and individuals. J Toxicol Environ Health 38(4):355-368.

*Van Rooij JGM, Van Lieshout EMA, Bodelier Bade MM, et al. 1993b. Effect of the reduction of skin contamination on the internal dose of creosote workers exposed to polycyclic aromatic hydrocarbons. Scand J Work Environ Health 19(3):200-207.

*Van Rooij JGM, Vinke E, De Lange J, et al. 1995. Dermal absorption of polycyclic aromatic hydrocarbons in the blood-perfused pig ear. J Appl Toxicol 15(3):193-200.

van Schooten F-J. 1995. Carcinogenic consequences of coal-tar shampoo. Lancet 345:1635.

van Schooten F-J, Godschalk R. 1996. Coal tar therapy: Is it carcinogenic? Drug Saf 15(6):374-377.

*van Schooten F-J, Moonen EJC, Rhijnsburger E, et al. 1994. Dermal uptake of polycyclic aromatic hydrocarbons after hairwash with coal-tar shampoo. Lancet 344:1505-1506.

*van Schooten FJ, Moonen EJC, van der Wal L, et al. 1997. Determination of polycyclic aromatic hydrocarbons (PAH) and their metabolites in blood, feces, and urine of rats orally exposed to PAH contaminated soils. Arch Environ Contam Toxicol 33:317-322.

van Schooten FJ, Van Maanen JMS, Moonen EJC, et al. 1995. High urinary excretion of 1-hydroxypyrene after dermal uptake of polycyclic aromatic hydrocarbons via a single hairwash with coal tar-containing shampoo. Proc Am Assoc Cancer Res 36:109.

*Viau C, Vyskocil A. 1995. Patterns of 1-hydroxypyrene excretion in volunteers exposed to pyrene by the dermal route. Sci Total Environ 163:187-190.

*Viau C, Vyskocil A, Martel L. 1995. Background urinary 1-hydroxypyrene levels in non-occupationally exposed individual in the province of Quebec, Canada, and comparison with its excretion in workers exposed to PAH mixtures. Sci Total Environ 163:191-194.

9. REFERENCES

*Viccellio P, Bania T, Brent J, et al. 1998. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers. 356-357.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of *CYP2E1* in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

*Vogel U, Thein N, Moller P, et al. 2001. Pharmacological coal tar induces G:C to T:A transversion mutations in the skin of mutaTM mouse. Pharmacol Toxicol 89(1):30-34.

Vogelbein WK. 1993. Ultrastructural and histological characterization of hepatic neoplasms in mummichog fundulus heteroclitus inhabiting a creosote-contaminated environment. Mar Environ Res 35:197-231.

*Vogelbein WK, Fournie JW, Van Veld PA, et al. 1990. Hepatic neoplasms in the Mummichog Fundulus Heteroclitus from a creosote-contaminated site. Cancer Research 50:5978-5986.

*von Burg R, Stout T. 1992. Creosote: Toxicology update. J Appl Toxicol 12(2):153-156.

*Wallcave L, Garcia H, Feldman R, et al. 1971. Skin tumorigenesis in mice by petroleum asphalts and coal-tar pitches of known polynuclear aromatic hydrocarbon content. Toxicol Appl Pharmacol 18:41-52.

Walsh D, Hudgens E, Heinrich U, et al. 1996. Characterization of DNA adducts in humans and rats resulting from inhalation of particulate matter containing polycyclic aromatic compounds. Proc Am Assoc Cancer Res 37:114.

*Walter JF, Stoughton RB, Dequoy PR. 1978. Suppression of epidermal DNA synthesis by ultraviolet light, coal tar and anthralin. Br J Dermatol 99:89-96.

Wang X, Chen S, Wu Y, et al. 1998a. [Detection of sister chromatid exchange in workers exposed to coal tar pitch and to coke oven volatiles]. Wei Sheng Yen Chiu 27(4):220-221. (Chinese).

Wang X, Wu Y, Chen C. 1998b. Studies on the ras p21 serum levels in workers exposed to coal tar pitch and coke oven volatiles. Wei Sheng Yen Chiu 27(5):292-294.

Wang X, Wu Y, Chen C. 1998. [Studies on the ras p21 serum levels in workers exposed to coal tar pitch and coke oven volatiles.]. Wei Sheng Yen Chiu 27(5):292-294. (Chinese).

Wang Z, Zhang W-Q, Chaloupka K, et al. 1996. H-ras activation in liver tumors induced in B6C3F1 mice by manufactured gas plant residue (MGPs). Proc Am Assoc Cancer Res 37:142.

Wang Z, Zhang W-Q, Safe S, et al. 1997. Mutation frequency and spectrum in relation to dose and exposure length in coal tar carcinogenesis. Proc Am Assoc Cancer Res 38:461.

*Ward JB, Jr. 1988. Sperm evaluation in human genetic monitoring. Repro Toxicol 12:77-182.

*Warshawsky D, Barkley W, Bingham E. 1993. Factors affecting carcinogenic potential of mixtures. Fundam Appl Toxicol 20(3):376-382.

Warshawsky D, Livingston GK, Fonouni-Fard M, et al. 1995. Induction of micronuclei and sister chromatid exchanges by polycyclic and n-heterocyclic aromatic hydrocarbons in cultured human lymphocytes. Environ Mol Mutagen 26:109-118.

*Watson AF, Mellanby E. 1930. Tar cancer in mice II: The condition of the skin when modified by external treatment or diet, as a factor in influencing the cancerous reaction. Brit J Exp Path 11:311-322.

Watts P, Stables GS, Akhurst RJ, et al. 1994. Localization of transforming growth factor-alpha RNA and protein in the ski of psoriatic patients receiving therapy. Br J Dermatol 131(1):64-71.

Webb DA. 1975. Some environmental aspects of creosote. Proc Am Wood Preserv Assoc 71:176-181.

Wehner TA, Woodrow JE, Kim YH, et al. 1984. Multiresidue analysis of trace organic pesticides in air. Identification & Analysis of Organic Pollutants 273-290.

*Weiner MA. 1986. Stomach cancer in Japan: Relationship to a common folk remedy? Medical Hypotheses 20:357-358.

*Weiss G. 1986. Hazardous chemicals data book. 2nd ed. Park Ridge, NJ: Noyes Data Corp, 306.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

*Weston A, Santella RM, Bowman ED. 1994. Detection of polycyclic aromatic hydrocarbon metabolites in urine from coal tar treated psoriasis patients and controls. Polycyclic Aromat Compd 5:241-247.

*Weyand EH, Bevan DR. 1987. Covalent binding of benzo[a]pyrene to macromolecules in lung and liver of rats following intratracheal instillation. Cancer Lett 36:149-159.

*Weyand EH, Wu Y. 1995. Covalent binding of polycyclic aromatic hydrocarbon components of manufactured gas plant residue to mouse lung and forestomach DNA. Chem Res Toxicol 8:955-962.

*Weyand EH, Chen Y-C, Wu Y, et al. 1995. Differences in the tumorigenic activity of a pure hydrocarbon and a complex mixture following ingestion: Benzo[a]pyrene vs manufactured gas plant residue. Chem Res Toxicol 8:949-954.

Weyand EH, Rozett K, Koganti A, et al. 1996. Effect of soil on the genotoxicity of manufactured gas plant residue. Toxicologist 30:1644.

*Weyand EH, Wu Y, Patel S, et al. 1991. Urinary excretion and DNA binding of coal tar components in B6C3FI mice following ingestion. Chem Res Toxicol 4(4):466-473.

*Weyand EH, Wu Y, Patel S, et al. 1994. Biochemical effects of manufactured gas plant residue following ingestion by B6C3F1 mice. J Toxicol Env Health 42(1):89-107.

White PA, Rasmussen JB, Blaise C. 1996. A semi-automated, microplate version of the SOS chromotest for the analysis of complex environmental extracts. Mutat Res 360:51-74.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise. Volume II: The elements Part A. New York: Academic Press.

*Wilson JT, McNabb JF, Cochran JW, et al. 1985. Influence of microbial adaptation on the fate of organic pollutants in ground water. Environ Toxicol Chem 4:721-726.

Winston GW, Church DF, Cueto R, et al. 1993. Oxygen consumption and oxyradical production from microsomal reduction of aqueous extracts of cigarette tar. Arch Biochem Biophys 304(2):371-378.

*Wise SA, Sander LC, May WE. 1993. Determination of polycyclic aromatic hydrocarbons by liquid chromatography. J Chromatogr 642:329-349.

Wormhoudt LW, Commandeur JNM, Vermeulen NPE. 1999. Genetic polymorphisms of human N-acetyltransferase, cytochrome P450, glutathione-S-transferase, and epoxide hydrolase enzymes: Relevance to xenobiotic metabolism and toxicity. Crit Rev Toxicol 29(1):59-124.

*Wrench R, Britten AZ. 1975. Evaluation of coal-tar fractions for use in psoriasiform diseases using the mouse tail test. III. High boiling tar oil acids. Br J Dermatol 93:67-74.

*Wright CW, Later DW, Pelroy RA, et al. 1985. Comparative chemical and biological analysis of coal-tar based therapeutic agents to other coal-derived materials. J Appl Toxicol 5(2):80-89.

Wright MC, Kaufhold A, Hevert F, et al. 1992a. [Investigations into possible nephrotoxicity of a coal tar preparation]. Hautarzt 43(8):483-486. (German).

*Wright MC, Kaufhold A, Hevert F, et al. 1992b. Investigations into possible nephrotoxicity of a coal tar preparation. Hautarzt 43(8):483-486. (Translation).

*Wu Y, Wang X, Chen C, et al. 1998. [Serum ras P21 level and peripheral blood lymphocyte sister chromosome exchange frequency in workers exposed to coal tar pitch]. Henan Yike Daxue Xuebao 33(5):59-61. (Chinese).

*Yadav JS, Seth N. 1998. Effect of polycyclic aromatic hydrocarbons on somatic chromosomes of coal tar workers. Cytobios 93(374):165-173.

*Yamazaki H, Terada M, Tsuboi A. 1987. Distribution and binding pattern of benzo(a)pyrene in rat liver, lung and kidney constituents after oral administration. Toxicol Environ Chem 15:71-81.

*Zangar RC, Springer DL, Buschbom RL, et al. 1989. Comparison of fetotoxic effects of a dermally applied complex organic mixture in rats and mice. Fundam Appl Toxicol 13:662-669.

*Zeiger E, Anderson B, Haworth S, et al. 1992. Salmonella Mutagenicity Tests: V. Results from the Testing of 311 Chemicals. Environ Mol Mutagen 19(Suppl. 21):2-141.

*Zepp RG, Schlotzhauer PF. 1979. Photoreactivity of selected aromatic hydrocarbons in water. In: Jones PW, Leber P, eds. Polynuclear aromatic hydrocarbons: Third international symposium on chemistry and biology – Carcinogenesis and mutagenesis. Ann Arbor, MI: Ann Arbor Science Publishers Inc., 141-158.

*Zhang YJ, Li Y, DeLeo VA, et al. 1990. Detection of DNA adducts in skin biopsies of coal tar-treated psoriasis patients: Immunofluorescence and ^{32}P-postlabeling. Skin Pharmacol 3(3):171-179.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

*Zitko V. 1975. Aromatic hydrocarbons in aquatic fauna. Bull Environ Contam Toxicol 14:621-631.

10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Heterocyclic—A molecular configuration in which one of the atoms in a ring is not a carbon atom. Heterocyclic oxygen refers to a ring in which the non-carbon atom is oxygen. Other elements such as nitrogen and sulfur are frequently found in heterocyclic rings.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 6

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

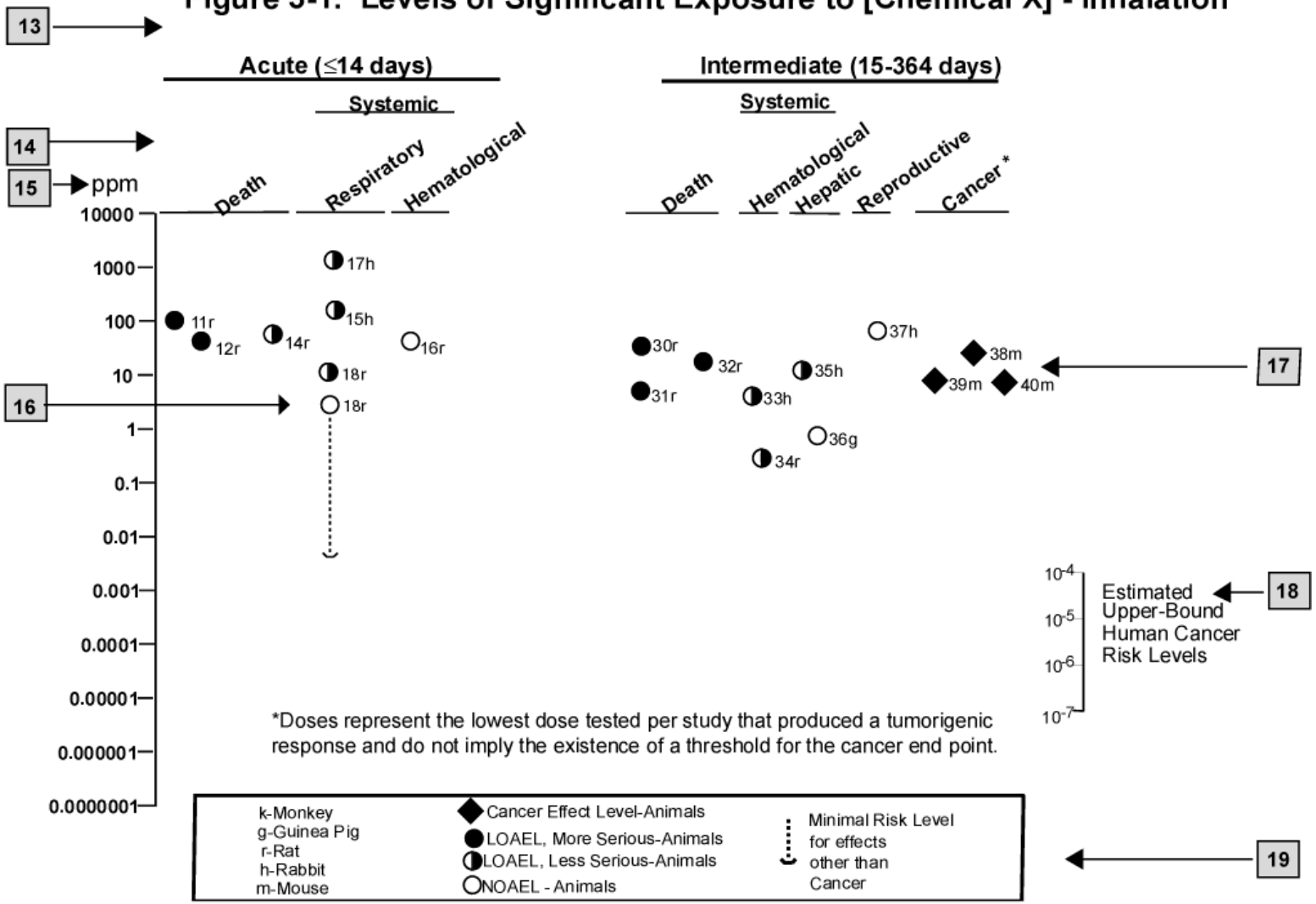
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
						11	
Cancer						9	
38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 3-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/NA/IMCO	Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal

MFO	mixed function oxidase
mg	milligram
MGP	manufactured gas plant
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
$	greater than or equal to
=	equal to

<	less than
#	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

INDEX

acute dermal exposure 198
adenocarcinoma 20, 107, 108
adipose tissue 164, 284, 285
adrenal gland 188
adrenal glands 20, 51, 56, 58, 98, 104, 105, 124, 134, 135, 188, 190
adsorption 263, 271, 273, 277, 280
aerobic 255-257, 276
AHH 161, 162, 167, 172, 173, 184, 186, 192, 199, 200
air 2-4, 6-9, 14, 15, 44, 52, 53, 63, 126, 130, 141, 156, 157, 168, 172, 174, 175, 191, 202, 223, 225, 231, 244, 246-248, 250, 254, 258, 265, 266, 268, 270, 271, 275, 278, 284, 287, 290, 293, 294, 297-299
alanine aminotransferase (see ALT) 92
ALT 92, 94, 95
ambient air 126, 254
anaerobic 255, 276
aryl hydrocarbon hydroxylase (see AHH) 161
aspartate aminotransferase (see AST) 50
AST 50, 92, 94
bioaccumulation 19, 202, 253, 258, 261, 262, 273, 274, 277
bioavailability 255, 273, 277, 279-282
bioconcentration 253, 276, 277
bioconcentration factors 253
biodegradation 255-257, 262, 272, 280-282
biomagnification 19, 261, 262, 277
biomarker 195, 196, 211, 212, 215, 263, 268-270, 284, 296
birth weight 57, 134
blood 13, 47-49, 89-91, 93, 95, 96, 121, 122, 132, 147, 148, 151, 152, 158, 160, 162, 163, 165, 167, 169, 184, 191, 195, 197, 211, 270, 272, 284, 285
body weight effects 45, 54, 87, 98, 113, 131
breast cancer 108-110, 188
breast milk 7, 9, 12, 163, 173, 184, 185, 195, 270, 273
cancer 7-9, 11, 20, 22, 28, 42-44, 58-64, 107-112, 124, 127, 136-139, 147, 159, 186, 188, 191, 193, 198, 199, 201, 207, 208, 211, 219, 220, 258, 268, 269, 301
carcinogen 8, 22, 24, 112, 211, 298, 301
carcinogenic 8, 22, 24, 27-29, 64, 108, 138-140, 144-147, 186, 198, 199, 208, 247, 255, 269, 270, 298, 301
carcinogenicity 22, 24, 108, 110, 139, 185, 186, 208, 212, 265, 299-301
carcinoma 63, 64, 132, 136, 140, 141, 200
cardiovascular effects 47, 48, 89, 120, 121
chloracne 52, 127
chromosomal abnormalities 147
crustaceans 262, 277
deoxyribonucleic acid (see DNA) 152, 154
dermal effects 20-23, 52, 53, 87, 98, 124, 127, 128, 211
DNA 99, 147-154, 159-161, 165, 167, 173, 196, 197, 201, 208, 211, 212, 270, 273, 284-287, 296
endocrine effects 51, 97, 113, 124
EROD 170
estrogen receptor 188
estrogenic 22, 105, 188, 189
ethoxyresorufin-O-deethylase (see EROD) 170
FDA 14, 299-301
FEDRIP 214, 280
fetus 7, 9, 190, 192, 200
fish 8, 12, 19, 20, 253, 258, 261, 273, 274, 278, 279
fish consumption 274, 278
Food and Drug Administration (see FDA) 14, 301
friable 95
gastrointestinal effects 48, 89, 90, 121

general population 5, 21, 42, 52, 133, 137, 138, 195, 200, 262, 274
groundwater 4, 6, 7, 19, 46, 53, 120, 238, 243, 248, 249, 257, 259, 276, 289
half-life 195, 254, 297
hematological effects 49, 91, 121
Henry's law 253, 301
hepatic effects 21, 50, 92, 122, 198
hydrolysis 277, 286
hydroxyl radical 254
IgG 93
immune system 210
immunoglobulin G (see IgG) 93
immunological effects 132, 210, 280
Integrated Risk Information System 301
kidney 7, 8, 20, 22, 43, 51, 56, 58, 87, 96, 97, 107, 123, 134, 135, 152, 192, 199, 205, 274
lake 251, 257, 262
LD50 . . . . . 64, 85, 86, 91, 112, 205
leukemia 22, 43, 58, 85
liver 7, 8, 20, 21, 50, 56, 58, 60, 87, 92-96, 104, 105, 111, 122, 134, 135, 149, 151, 152, 159, 162-165, 167, 169, 170, 172, 183, 184, 188, 193-195, 199, 205, 208, 285
lung 8, 22, 23, 42-47, 57, 58, 60-63, 88, 105, 106, 110, 111, 135, 139, 143, 144, 149-152, 157, 158, 162-165, 184, 195, 205, 208, 209, 268
lymph 20, 146
lymphatic 138
lymphoreticular effects 54, 101, 102, 131, 132
marine 234, 247, 249, 257, 258, 262, 271
milk 7, 9, 12, 163, 173, 184, 185, 195, 270, 273
Minimal Risk Levels (see MRL) 23, 28
MRL 23, 24, 206, 207
MRLs 23, 25, 28, 298
musculoskeletal effects 45, 206, 207
National Institute for Occupational Safety and Health (see NIOSH) 14
National Occupational Exposure Survey (see NOES) 267
National Priorities List (see NPL) 1, 17, 46, 241, 243
neoplastic 108, 136
neurobehavioral 187
NHL 138
NIOSH 14, 29, 30, 52, 53, 126-128, 130, 132, 172, 210, 218-220, 224, 265, 267, 283, 299, 301
nitrophenol 167, 169, 170
NOAEL 27, 45, 87, 101-105, 107, 113
NOAELs 27, 28
NOES 267
non-Hodgkin's lymphoma (see NHL) 138
no-observed-adverse-effect levels (see NOAEL) 27
NPL 1, 17, 46, 53, 120, 241-244, 247-251, 255, 259, 260, 262, 272, 280
ocean 52, 53, 126
ocular effects 53, 130
odds ratio 62
particulate 156, 157, 174, 175, 254, 265, 266, 270, 284, 290, 294
particulates 251, 265, 266
partition coefficients 223, 225, 231
PBPD 181
PBPK 180-183, 191, 214
pharmacodynamic 180, 181
pharmacokinetic 155, 180-183, 206-209, 212, 213
photolysis 252, 255, 277
physiologically based pharmacodynamic (see PBPD) 181
physiologically based pharmacokinetic (see PBPK) 180, 183
playground equipment 9, 12
protective gloves 156, 174, 267
public health 1, 8, 14, 17, 20, 27, 28, 187, 203, 274, 275, 283, 295
RCRA 238, 280, 301

reference dose 298, 301
regulations 14, 15, 25, 298-301
renal effects 20, 50, 51, 96, 122, 123
Resource Conservation and Recovery Act (see RCRA) 238, 280, 301
Restricted-use pesticide 2, 12, 15
salivation 100
salmon 153
sea 249, 252
sediment 238, 244, 250-252, 255-257, 259-261, 288, 291, 293, 294
selenium 195
serum 21, 50, 92-96, 132, 148, 158, 165, 169, 284
SMR 43, 60
soil 3-10, 14, 22, 46, 53, 57, 108, 120, 128, 129, 176, 201, 244, 248-253, 255-257, 259, 260, 262, 271-273, 275, 277, 279, 280, 297
solubility 158, 164, 184, 223, 225, 231, 251, 255, 262, 275, 294
Standardized mortality ratio (see SMR) 43
Superfund 251, 252, 255, 257, 280, 282
surface water 244, 247-250, 255, 256, 259, 276, 278, 280
thyroid 20, 51, 97
time-weighted average (see TWA) 59, 298, 301
toxicokinetic 27, 155
Toxics Release Inventory (see TRI) 234, 244
transport 52, 184, 186, 187, 201, 250, 251, 258, 276, 277, 280, 301
TRI 234, 238, 244, 246, 248-250, 276
tumors 20, 22, 44, 63, 64, 108-111, 126, 129, 140-147, 162, 185, 186, 205, 208
TWA 59, 298, 299, 301
U.S. Department of Agriculture (see USDA) 244
USDA 244, 247, 248, 256, 258, 262, 264, 266, 267, 274, 280, 282
vapor phase 157, 175, 254, 266
vapor pressure 223, 225, 231, 275
volatility 256
volatilization 244, 247, 250, 252, 253, 256, 267, 271, 272, 287
water 2-8, 10, 12, 14, 19, 90, 108, 109, 125, 158, 159, 164, 165, 169, 177, 184, 185, 188, 191, 196, 201, 202, 206, 207, 211, 223-225, 231, 234, 238, 244-252, 255-257, 259-263, 271, 272, 274-278, 280-282, 285, 289, 291, 293, 294, 297-299