SECTION 5

TOXICOLOGICAL PROFILE SUMMARIES FOR TARGET ANALYTES

5.1 INTRODUCTION

This section presents toxicological profile summaries for the target analytes in the same order in which they are listed in Table 1-1. Toxicity data were collected for the target analytes from a variety of sources. Major sources used were IRIS, HSDB, ATSDR Toxicological Profiles, the Office of Pesticide Programs toxicological database, and recent toxicological reviews. The EPA risk values discussed in this section were used along with exposure data (e.g., meal size and fish contaminant concentration) to calculate the fish consumption limits provided in Section 4. Primary literature searches and reviews were not conducted for the development of this section due to time and resource constraints.

EPA evaluates dose-response data for chemicals of environmental concern on an ongoing basis. However, new toxicological data are continually being generated. Consequently, there may be recent information that is not yet incorporated into the EPA risk values. This may be particularly relevant for developmental toxicity, which is the subject of much current research. The toxicological summaries provide the reader with information that can be used to calculate alternative health-based risk values and fish consumption limits. The methods for carrying this out are described in Sections 2 and 3.

Risk values are also provided in the individual profiles, accompanied by a discussion of a number of toxicity studies for each target analyte, which yield various dose-response results. These give some indication of the variability in the types of effects and doses at which various effects were observed.

5.1.1 Categories of Information Provided for Target Analytes

Specific types of information were sought for all target analytes to address health and risk concerns for carcinogenic, developmental, and chronic exposure (noncarcinogenic) effects. These include pharmacokinetics, acute and chronic toxicity, reproductive and developmental toxicity, mutagenicity, carcinogenicity, special susceptibilities, interactive effects, and critical data gaps. The categories of information provided for each target analyte are listed in Table 5-1. Although the same types of information were sought for all analytes, the information presented for the contaminants

Table 5-1. Health and Toxicological Data Reviewed for Target Analytes

Category	Specific Information
Background	Chemical structure/group Use and occurrence
Pharmacokinetics	Target tissues Absorption Deposition-bioaccumulation potential/half-life/body burden Metabolism Excretion Susceptible subgroups
Acute toxicity	Quantitation Susceptible subgroups
Chronic toxicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Database quality Susceptible subgroups Current risk values
Reproductive and developmental toxicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Database quality Susceptible subgroups Current risk values
Mutagenicity	Type Quantitation Source Database quality
Carcinogenicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Database quality Outstanding issues
Special susceptibilities	Subgroups of concern
Interactive effects	Qualitative Quantitative MIXTOX results
Critical data gaps	Description
Summary of EPA risk values	Cancer slope factor and reference dose

varies, depending on the types of data available. Many of the analytes listed have been recognized as environmental contaminants for a number of years and have a fairly comprehensive toxicological database. Others have been introduced into the environment relatively recently; consequently, only limited information is available on these chemicals.

When a substantial amount of information was available on a contaminant, the information included in the discussions focused on areas relevant to the toxicities under evaluation. For example, a significant amount of pharmacokinetic data is available for some chemicals in the ATSDR Toxicological Profiles. In this document, most information was briefly synopsized; however, detailed information on human milk bioconcentration was included for developmental toxicants if lactational exposure was of concern. In addition, when the toxicological data indicated that a particular type of information, not reported, was required for full exploration of relevant toxic effects, additional information was identified in the Data Gaps Section (e.g., the interaction of DDT with pharmaceutical efficacy arising from DDT-induced increases in levels of microsomal enzymes).

The information collected is categorized by the temporal nature of the exposure (e.g., acute, chronic). These groupings are most applicable to the standard risk assessment methods that were employed to calculate risk values. The temporal groupings and methods of evaluating dose-response data are briefly discussed in Section 2, with a description of uncertainties and assumptions associated with dose-response evaluation.

5.1.1.1 Pharmacokinetics—

A brief summary of the pharmacokinetic data is presented for many chemicals. The information was included if it had a bearing on the development of fish consumption limits or would be useful to the reader in evaluating the toxicological characteristics of a chemical. For more detailed information on pharmacokinetics, the reader is referred to the ATSDR profiles and the primary literature.

For most chemicals there was not sufficient quantitative information, such as absorption, uptake, distribution, metabolism, excretion, and metabolite toxicity, in the data reviewed to recommend modifications in exposure to yield an altered internal dose. Some chemicals contained in the IRIS database have risk values that have incorporated pharmacokinetic considerations. If additional information relevant to quantitative risk assessment becomes available, it will be included in future versions of this guidance document.

5.1.1.2 Acute Toxicity—

Very little acute exposure toxicity data were located that could have a quantitative bearing on the development of fish consumption limits. A qualitative description of acute effects is included. The minimum estimated lethal dose to humans and a brief discussion of the acute effects are included if the data were available.

5.1.1.3 Chronic Toxicity—

Under the chronic exposure heading, significant effects associated with long-term exposure are listed. These include effects on the major organs and systems: the liver, kidney, gastrointestinal, cardiovascular, and reproductive systems. The chronic exposure data for each analyte include a description of an RfD listed in IRIS or obtained from other sources and the critical study serving as the basis for that RfD, including the species tested, duration of the study, and critical effect noted. Information is provided on any special issues concerning the critical study or RfD (e.g., if the study is old or has very few subjects or if the confidence in the RfD is listed as "low").

Data are also provided on effects observed in recent dose-response studies or effects that were not the subject of the IRIS RfD critical study. This was done to provide a more comprehensive picture of the overall toxicological nature of the chemicals than could be obtained from reviewing the RfD critical study alone. For most analytes, the information is primarily a qualitative description of effects. For chemicals that have significant new toxicological data available, details are provided on NOAELs, LOAELs, some study characteristics, and the usual categories of uncertainty and modifying factors that should be considered for significant studies. These are provided to give readers the option of developing exposure limits as they deem necessary.

5.1.1.4 Redproductive and Developmental Toxicity—

Reproductive and developmental toxicity data were obtained for each target analyte. Section 2.3.2.3 contains general information on developmental toxicity, including definitions and special issues related to developmental toxicity.

For many chemicals, information is provided on the tendency of the chemical to accumulate in body tissue. Many of the target analytes bioaccumulate and/or preferentially seek fatty tissues. When such accumulation occurs, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing fetus. Any body burden may result in exposure, but lipid-seeking chemicals, such as organochlorines, are often rapidly mobilized at the onset of pregnancy and may result in elevated contaminant exposure to the developing fetus. As a result, it may be necessary to reduce the exposure of females of reproductive age in order to reduce their overall body burden. For example, if a female has been exposed to methylmercury, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected depending on the timing and extent of prior exposure. This is noted for bioaccumulative analytes in the individual toxicological profiles.

5.1.1.5 Mutagenicity—

Although there were many reported mutagenicity bioassays for target analytes, little in vivo mutagenicity dose-response data were located. In vivo studies are recommended by EPA for risk assessments of suspected mutagens. A brief summary of the results of the mutagenicity assays for the analytes is provided. There are numerous studies available for some of the contaminants; consequently, it was not feasible to list all results. To provide a more concise overview of the results of greatest concern, the nature of the positive studies is given. The direction of the majority of results is also given (e.g., primarily positive, negative, or mixed).

5.1.1.6 Carcinogenicity—

Cancer slope factors and descriptive data were obtained primarily from IRIS, HEAST, and OPP. Preference was given to IRIS values; however, when IRIS values were not available, values developed by Agency program offices (e.g., OPP) are provided. The program office values have not necessarily undergone the extensive interagency review required for inclusion in the IRIS database, although many have been reviewed by scientists within and outside of EPA.

There are often insufficient studies to evaluate the carcinogenicity of a chemical. EPA has recognized this and formalized the lack of data as classification D: "not classifiable as to human carcinogenicity" in EPA's cancer weight of evidence scheme (U.S. EPA, 1986a). Many target analytes fall into this category; for others, no data were found in the sources consulted regarding their carcinogenicity. For chemicals with insufficient or no data on carcinogenicity in the databases consulted, the text under the "Carcinogenicity" heading states that: "insufficient information is available to determine the carcinogenic status of the chemical." This statement is used for chemicals lacking a cancer slope factor unless an Agency-wide review has determined that there is evidence that the chemical is **not** carcinogenic (i.e., an E classification as provided in IRIS, 1999). For a complete description of EPA's weight-of-evidence classification scheme, see EPA's *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 1986a). EPA's proposed cancer guidelines have replaced this weight-of-evidence classification scheme with a narrative with descriptors in three categories: "known/likely," "cannot be determined," or "not likely" (U.S. EPA, 1996b).

5.1.1.7 Special Susceptibilities—

Toxicity data often indicate that some groups of individuals may be at greater risk from exposure to chemicals or chemical groups. For example, a chemical that causes a specific type of organ toxicity will usually pose a greater risk to individuals who have diseases of that organ system (e.g., immunotoxicity poses a greater risk to those with immunosuppression or with immature immune systems). Persons with some genetic diseases (e.g., enzyme disorders), nutritional deficiencies, and metabolic disorders may also be at greater risk due

to exposure to some chemicals. Qualitative data on special susceptibilities are provided for many of the target analytes. However, there are no quantitative data on subgroup susceptibilities for most chemicals that would enable the risk assessor to modify risk values.

The RfDs are designed to take into account the most susceptible individuals, and RfDs often incorporate an uncertainty factor to account for variability within the human species. Susceptible subgroups are those that exhibit a different or more enhanced response than most persons exposed to the same level of the chemical in the environment. Reasons include genetic makeup, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking).

5.1.1.8 Interactive Effects—

Data on interactive effects were located for many, but not all, of the target analytes. Most data on interactive effects were obtained from ATSDR Toxicological Profiles. Often the data indicate that certain classes of chemicals may be of concern. For example, most organochlorines induce the mixed function oxidase system. These chemicals may lead to unanticipated and exaggerated or diminished effects arising from simultaneous exposure to other chemicals that rely on the same metabolic system. In some cases this leads to potentiation (increased toxicity) and in others it hastens the process of detoxification.

The MIXTOX database, developed by EPA, was also used to obtain information on interactive effects (MIXTOX, 1992). The database provides a very brief summary of results of studies on combinations of chemicals. Most interactions are reported as "potentiation," "inhibition" or "antagonism" (decreased toxicity), "no apparent influence," or "additive." The interactions that differ from additive or no apparent influence are reported because it is assumed, in the absence of contrary information, that the toxicity of mixtures of chemicals will be additive for the same target tissue (see Section 2.3). The interactive terminology used in MIXTOX is used in this document.

5.1.1.9 Critical Data Gaps—

Data gaps noted in IRIS files, the OPP toxicological database, RfD summaries, and the ATSDR Toxicological Profiles are listed. In addition, data gaps that have been identified from a review of the studies are listed, along with the reasons that additional data are considered necessary.

5.1.1.10 Summary of EPA Levels of Concern—

The EPA risk values (RfDs and cancer slope factors) discussed in each section and used in the development of fish consumption limits are summarized in Table 3-1.

5.1.1.11 Major Sources—

At the end of each target analyte file is a list of the major sources of information consulted. Major sources are those that have been cited more than once. Within the text of each target analyte file, all information is provided with citations.

The IRIS files were consulted in early 1999 for cancer slope factors, chronic exposure RfDs, and additional study data. ATSDR Toxicological Profiles were also consulted when available. The profiles have extensive toxicity, pharmacokinetic, and epidemiological data reviews.

5.1.1.12 Statement Regarding Uncertainty—

There are always significant uncertainties associated with estimating health risks and safe exposure levels for human populations. Although these are discussed in Section 2, their importance warrants their mention in this section also. The risk values provided for each chemical in this section are based on human or animal studies that evaluated either a small subset of the human population or an entirely different species. In either case, we can only **estimate** the relevance of the study results to humans. Although a quantitative methodology is used to extrapolate from various types of studies to the general human population, there is considerable uncertainty in the estimated relationship between study populations and the human population.

The use of uncertainty factors and upper bound cancer risk estimates provides a margin of safety to account for some aspects of uncertainty in the extrapolation. However, our knowledge of response variability in the human population is very limited. The variations in response, which are engendered by age, sex, genetic heterogeneity, and preexisting disease states, may be considerable. Consequently, although current approaches to assessing risk involve estimating the upper bound values for deriving exposure or risk and are intended to be protective rather than predictive, the reader is urged to carefully review the information provided in this section on data gaps and uncertainties.

It is important to describe the uncertainties and assumptions when recommending fish consumption limits. With respect to toxicity, these include both uncertainties associated with specific chemicals and uncertainties and assumptions associated with the dose-response evaluation process (described in Section 2). In some cases, a variety of dose-response data will enable the reader to provide a quantitative estimation of the range of potential risk values that could be used to calculate exposure and fish consumption limits. A description of data gaps may also be useful to the risk manager in determining the best course of action. For chemicals having limited data, only a qualitative description may be possible.

5.1.2 Abbreviations Used and Scientific Notation

The glossary contains a description of additional terms and abbreviations used in this section.

Scientific notation is used where the values are less than 0.001 unless it would introduce confusion to the text (e.g., when presenting a range, the same format is used for both values in the range). In the summaries of risk values, all noncancer risk values are presented in scientific notation to facilitate comparison across health endpoints.

5.2 METALS

5.2.1 Arsenic

5.2.1.1 Background—

Arsenic is a naturally occurring element in the earth's crust that is usually found combined with other elements. Arsenic combined with elements such as oxygen, chlorine, and sulfur is referred to as inorganic arsenic; arsenic combined with carbon and hydrogen is referred to as organic arsenic. In this toxicological profile, arsenic refers to inorganic arsenic and its associated compounds. Organic arsenic compounds, such as arsenobetaine (an organic arsenic compound found in the edible parts of fish and shellfish) are not discussed, since these compounds are considered to be relatively nontoxic and not a threat to human health (ATSDR, 1999c).

5.2.1.2 Pharmacokinetics—

Pharmacokinetic studies show that water-soluble arsenic compounds are well-absorbed across the gastrointestinal tract. They appear to be transported throughout the body. Analysis of tissues taken at autopsy from people who were exposed to arsenic found arsenic present in all tissues of the body. The arsenic levels in hair and nails were the highest, with somewhat lower levels in internal organs (ATSDR, 1999c).

The metabolism of arsenic consists mainly of a reduction reaction, which converts pentavalent arsenic to trivalent arsenic, and methylation reactions, which convert arsenite to monomethylarsonic acid and dimethylarsenic acid. The primary excretion route for arsenic and metabolites is in the urine, with human studies showing that 45 to 85 percent is excreted in the urine within 1 to 3 days of ingestion. Very little is excreted in the feces (ATSDR, 1999c).

5.2.1.3 Acute Toxicity—

Arsenic is a recognized human poison. Single large doses, approximately 600 µg/kg-d or higher, taken orally have resulted in death. Acute oral exposure to lower levels of arsenic has resulted in effects on the gastrointestinal system (nausea, vomiting, diarrhea); central nervous system (headaches, weakness, lethargy, delirium); cardiovascular system (sinus tachycardia, hypotension, shock); and the liver, kidney, and blood (anemia, leukopenia). The limited available data have shown arsenic to have low to moderate acute toxicity to animals. Lethal oral doses to animals are higher than those in humans based on data showing that the oral LD_{50} values for arsenic range between 15 and 112 mg/kg (ATSDR, 1999c).

5.2.1.4 Chronic Toxicity—

The primary effects noted in humans from chronic exposure to arsenic are effects on the skin. Oral exposure has resulted in a pattern of skin changes that include the formation of warts or corns on the palms and soles along with areas of darkened skin on the face, neck, and back. Blackfoot disease, a disease characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene, is associated with arsenic exposure (ATSDR, 1999c). Other effects noted from chronic oral exposure include peripheral neuropathy, cardiovascular disorders, gastrointestinal disorders, hematological disorders, and liver and kidney disorders.

IRIS provides an RfD for inorganic arsenic of 3.0×10^{-4} mg/kg-d, based on a NOAEL (adjusted to include arsenic exposure from food) of 0.0008 mg/kg-d and an uncertainty factor of 3. This was based on two studies that showed that the prevalence of hyperpigmentation and skin lesions increased with both age and dose for individuals exposed to high levels of arsenic in drinking water. There were also some cardiovascular effects noted. Other human studies support these findings, with several studies noting an increase in skin lesions from chronic exposure to arsenic through the drinking water. An uncertainty factor of 3 was used to account for both the lack of data to preclude reproductive toxicity as a critical effect and for uncertainty as to whether the NOAEL of the critical studies accounts for all sensitive individuals (IRIS, 1999).

EPA has medium confidence in the studies on which the RfD was based and in the RfD. The key studies were extensive epidemiologic reports that examined the effects of arsenic in a large number of people. However, doses were not well-characterized, other contaminants were present, and potential exposure from food or other sources was not examined. The supporting studies suffer from other limitations, primarily the small populations studied. However, the general database on arsenic does support the findings in the key studies; this was the basis for EPA's "medium confidence" ranking of the RfD (IRIS, 1999).

5.2.1.5 Reproductive and Developmental Toxicity—

Limited information is available on the developmental effects of arsenic in humans. No overall association between arsenic in drinking water and congenital heart defects was detected in an epidemiological study, although an association with one specific lesion (coarctation of the aorta) was noted. In another study, a marginal association (not statistically significant) was found between detectable levels of arsenic in drinking water and spontaneous abortions. The odds ratio for the group with the highest arsenic concentration was statistically significant. However, a similar association was found for a number of compounds, which indicates that the association could be random or due to other risk factors (ATSDR, 1999c). A study of babies born to women exposed to arsenic dusts in a copper smelter in Sweden showed a higher-than-expected incidence of congenital malformations.

Minimal or no effects on fetal development have been observed in chronic oral exposure studies of pregnant rats or mice to low levels of arsenic in drinking water. Malformations were produced in 15-d hamster fetuses via intravenous injections of arsenic into pregnant dams on day 8 of gestation, while another study reported that very high single oral doses of arsenic were necessary to cause prenatal fetal toxicity (IRIS, 1999).

5.2.1.6 Mutagenicity—

Arsenic has not been reported to directly react with DNA in many studies. Studies have shown that arsenic chromosomal aberrations and sister chromatid exchange in human lymphocytes reported positive results, while others were negative. One study in mouse bone marrow cells reported an increase in micronuclei, while another did not report an increase in chromosomal breaks and exchanges (ATSDR, 1999c). In vitro studies have also reported both positive and negative results. Arsenic was negative in the bacterial colorimetric assay: SAS Chromotest (HSDB, 1999), and positive for reverse mutations in bacteria, morphological transformations, sister chromatid exchange, and chromosomal aberrations in Syrian hamster embryo cells. Arsenic was also positive for chromosomal aberrations in human leukocytes and lymphocytes, sister chromatid exchange, enhancement or inhibition of DNA synthesis, and hyperdiploidy and chromosomal breakage in human lymphocytes (ATSDR, 1999c).

5.2.1.7 Carcinogenicity—

EPA has classified inorganic arsenic in Group A—Known Human Carcinogen. This is based on the increased incidence in humans of lung cancer through inhalation exposure and the increased risk of nonmelanoma skin, bladder, liver, kidney, and lung cancer through drinking water exposure (IRIS, 1999).

Animal studies have not associated arsenic exposure, via ingestion, with cancer. All cancer studies in rodents with arsenic have reported negative results. However, the meaning of this nonpositive data is uncertain because the mechanism of action in causing human cancer is not known, and rodents may not be good models for arsenic-induced carcinogenicity (IRIS, 1999).

To estimate the risks posed by ingestion of arsenic, EPA uses data from Taiwan concerning skin cancer incidence, age, and level of exposure via drinking water. In 37 villages that had obtained drinking water for 45 years from artesian wells with various elevated levels of arsenic, more than 40,000 individuals were examined for hyperpigmentation, keratosis, skin cancer, and blackfoot disease. The local well waters were analyzed for arsenic, and the age-specific cancer prevalence rates were found to be correlated with both local arsenic concentrations and age (duration of exposure). The oral cancer potency is 1.5 per mg/kg-d (IRIS, 1999).

EPA's current regulation for arsenic in drinking water (50 μg/L) has recently been called into question. The conclusions of a recent National Research Council/National Academy of Sciences report on arsenic in drinking water suggest that the current drinking water regulation needs to be lowered based on risks of skin, lung, and bladder cancer (NRC, 1999).

5.2.1.8 Special Susceptibilities—

No studies regarding unusual susceptibility of any human subpopulation to arsenic are available. However, it is possible that some members of the population might be especially susceptible because of lower than normal methylating capacity. This could result from a dietary deficiency of methyl donors such as choline or methionine or a deficiency of the vitamin coenzymes (folacin, Vitamin B_{12}) involved in transmethylation reactions (ATSDR, 1999c; Rogers, 1995).

5.2.1.9 Interactive Effects—

Arsenic tends to reduce the effects of selenium, and selenium can decrease the effects of arsenic. No clear evidence exists for significant interactions between arsenic and other metals; the existing data do not suggest that arsenic toxicity is likely to be significantly influenced by concomitant exposure to other metals. Some evidence suggests that a positive interaction between arsenic and benzo(*a*)pyrene can occur for lung adenocarcinomas in animals. Other studies suggest that chemicals that interfere with the methylation process could increase the toxicity of arsenic (ATSDR, 1999c)

5.2.1.10 Critical Data Gaps—

There is a substantial database on the toxicity of arsenic, both in humans and in animals. However, there are some areas where studies are lacking. Further epidemiological studies on the health effects of arsenic at low doses would be valuable. Additional studies on developmental and reproductive effects of arsenic would also be useful (ATSDR, 1999c).

5.2.1.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3.0×10^{-4} mg/kg-d
Carcinogenicity	1.5 per mg/kg-d.

5.2.1.12 Major Sources—

ATSDR (1999c), HSDB (1999), IRIS (1999), Rogers (1995).

5.2.2 Cadmium

5.2.2.1 Background—

Cadmium is a heavy metal that occurs naturally in the earth's crust. It can be released into the environment through a wide variety of industrial and agricultural activities. It accumulates in human and other biological tissue and has been evaluated in both epidemiological and toxicological studies. ATSDR has determined that exposure conditions of most concern are long-term exposures to elevated levels in the diet (ATSDR, 1997).

The FDA has estimated that cadmium exposure among smokers is approximately 10 µg/d (0.01 mg/d). Passive exposure of nonsmokers may also be a source of exposure (U.S. FDA, 1993). This should be considered in evaluating the total exposure and risks associated with cadmium.

5.2.2.2 Pharmacokinetics—

Cadmium is not readily absorbed when exposure occurs via ingestion. Most ingested cadmium passes through the gastrointestinal (GI) tract without being absorbed. Studies in humans indicate that approximately 25 percent of cadmium consumed with food was retained in healthy adults after 3 to 5 days; this value fell to 6 percent after 20 days. Absorption may be much higher in iron-deficient individuals. Evaluations of the impact of cadmium complexation indicate that cadmium absorption from food is not dependent upon chemical complexation. However, some populations with high dietary cadmium intakes have elevated blood cadmium levels, which may be due to the particular forms of cadmium in their food (ATSDR, 1997).

Cadmium absorption studies in animals indicate that the proportion of an oral dose that is absorbed is lower in animals than in humans. Absorption is elevated during pregnancy, with whole-body retention in mice of 0.2 percent in those that had undergone pregnancy and lactation and 0.08 percent in those that had not. In rats, absorption decreased dramatically over the early lifetime, ranging from 12 percent at 2 hours to 0.5 percent at 6 weeks after birth. The placenta may act as a partial barrier to fetal exposure, with cord blood concentrations being approximately half those of maternal blood. The human data on placental concentrations are conflicting. Cadmium levels in human milk are approximately 5 to 10 percent of those found in blood (ATSDR, 1997).

Much of the cadmium absorbed into the blood is sequestered by metallothionein, and plasma cadmium is found primarily bound to this protein. This binding appears to protect the kidney from the otherwise toxic effects of cadmium. It has been suggested that kidney damage by cadmium occurs primarily due to unbound cadmium (ATSDR, 1997). Once cadmium is absorbed, it is eliminated slowly; the biological half-life has been estimated at 10 to 30 years (U.S. FDA, 1993).

Body stores of iron, zinc, and calcium may affect absorption and retention, although the retention may not be in readily available tissues (e.g., intestinal wall versus blood). The greatest concentrations of cadmium are typically found in the liver and kidney. Cadmium is not directly metabolized, although the cadmium ion binds to anionic groups in proteins, especially albumin and metallothionein (ATSDR, 1997).

5.2.2.3 Acute Toxicity—

Effects of acute oral exposure to cadmium include GI irritation, nausea, vomiting, abdominal pain, cramps, salivation, and diarrhea. In two human cases, lethal doses caused massive fluid loss, edema, and widespread organ destruction. The ingested doses that caused death were 25 mg cadmium/kg and 1,840 mg cadmium/kg (ATSDR, 1997).

5.2.2.4 Chronic Toxicity—

Kidney toxicity is a significant concern with cadmium exposure. Increased death rates from renal disease have been observed in exposed human populations in Belgium, England, and Japan (ATSDR, 1997). There are also extensive animal data indicating that the kidney is a target organ. IRIS contains an RfD of 0.001 mg/kg-d in food based upon a NOAEL of 0.01 mg/kg-d in multiple human studies. The critical effect was significant proteinuria (an indicator of kidney toxicity). To calculate the RfD, it was assumed that 2.5 percent of cadmium in food was absorbed and approximately 5 percent in water was absorbed. Using an uncertainty factor of 10 to account for intrahuman variability in cadmium sensitivity, the RfD for cadmium in food was calculated to be 0.001 mg/kg-d. The RfD was calculated using a toxicokinetic model to determine the highest level of cadmium in the human renal cortex not associated with significant proteinuria and therefore was not based on a single study. EPA's confidence in the database and the RfD is high (IRIS, 1999).

The FDA has calculated a tolerable daily intake of 55 µg/person-d, which is approximately equal to 0.78 µg/kg-d (7.8×10^{-4} mg/kg-d) in a 70-kg person and 5.5 µg/kg-d (0.005 mg/kg-d) in a 10-kg child (their example uses 2+ years of age). The FDA value is based upon a pharmacokinetic approach that utilized the critical body burden associated with kidney toxicity. See U.S. FDA (1993) for more details.

Cadmium causes many other types of toxic effects in addition to nephrotoxicity. In humans, some studies have suggested an association between neurotoxicity and cadmium exposure at levels below those that cause kidney toxicity (no additional details available). Cadmium exposure reduces the GI uptake of iron, which may cause anemia if iron intakes are low. Bone disorders including osteomalacia, osteoporosis, and spontaneous bone fracture have been observed in some chronically exposed individuals. Increased calcium excretion associated

with cadmium-induced renal damage may lead to increased risk of osteoporosis, especially in postmenopausal women, many of whom are already at risk of osteoporosis. Cardiovascular toxicity and elevated blood pressure have been suggested in some human studies; however, the results are conflicting (ATSDR, 1997).

Animal studies indicate that cadmium ingestion causes a wide variety of alterations in the function of the immune system. Some aspects of the system were enhanced and others were impaired (e.g., susceptibility to virally induced leukemia). In short-term studies, serious effects occurred at levels as low as 1.9 mg/kg-d and less serious effects (induction of antinuclear antibodies) at 0.75 mg/kg-d in a 10-wk study in mice (ATSDR, 1997). No longer-term studies were located.

5.2.2.5 Reproductive and Developmental Toxicity—

Reproductive and developmental toxicity has been associated with oral cadmium exposure both in short- and long-term studies. In 10-d prenatal dosing studies in rats at 18.4 mg/kg, malformations, including split palate and dysplasia of the facial bones and rear limb, were observed with a NOAEL of 6.1 mg/kg-d. A similar study in rats found delayed ossification at 2 mg/kg-d. Other studies have found gross abnormalities and reduced fetal weight at doses ranging from 1.5 to 19.7 mg/kg-d (ATSDR, 1997). Oral cadmium exposure of young mice depresses their humoral immune responses; the study did not find the same effect in adult mice (ATSDR, 1997).

More sensitive measures of effects for cadmium have identified effects at much lower doses. ATSDR has determined that:

> . . . the most sensitive indicator of development toxicity of cadmium in animals appears to be neurobehavioral development. Offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg-day prior to and during gestation had reduced exploratory locomotor activity and rotorod performance at age 2 months. . . (ATSDR, 1997).

Reduced locomotor activity and impaired balance were noted at a LOAEL of 0.04 mg/kg-d with 11 weeks of exposure occurring prior to and during gestation. The effects were also observed at 0.7 mg/kg-d with exposure occurring only during gestation. Neurobehavioral effects were observed in other developmental studies and in chronic studies of effects in adult animals. Two longer-term studies yielding similar neurobehavioral results were conducted with maternal exposures of 7.0 and 14.0 mg/kg-d (see numerous citations in Baranski et al., 1983; ATSDR 1997).

Studies of developmental toxicity in human populations have been conducted on women exposed via inhalation in the workplace. Decreased birth weight has been reported in two studies, one with statistically significant results and the other

lacking statistical significance. Inhalation studies in animals have found structural and neurobehavioral abnormalities similar to those found in the oral dosing studies (ATSDR, 1997).

Based on the mutagenicity data results (discussed below), heritable defects may result from exposure to cadmium. However, mutagenicity assays do not provide dose-response data suitable for use for the calculation of a risk value. Calcium deficiency has been shown to increase the fetotoxicity of cadmium, and lindane exposure increased developmental toxicity in animal studies (ATSDR, 1997).

5.2.2.6 Mutagenicity—

Results of bacteria and yeast assays have been mixed. Results were conflicting in chromosomal aberration studies on human lymphocytes treated both in vitro and obtained from exposed workers. Mouse and hamster germ cell studies indicate that cadmium may interfere with spindle formation resulting in aneuploidy. Positive results have also been obtained in Chinese hamster ovary and mouse lymphoma cell assays (IRIS, 1999).

5.2.2.7 Carcinogenicity—

Epidemiological studies have been conducted on population groups in high cadmium exposure areas via food and water, and organ-specific cancer rates have been examined (kidney, prostate, and urinary tract). Most studies yielded negative results. A study in Canada found that elevated rates of prostate cancer paralleled the elevated cadmium exposure of the populations studied. In animals, oral studies conducted at relatively low exposure levels (up to 4.4 mg/kg-d) have yielded negative results. One study in rats showed an increase in prostatic proliferative lesions, leukemia, and testicular tumors in rats fed cadmium in a zinc-controlled diet. Rats fed zinc-deficient diets had decreased overall incidence for tumors of the prostate, testes, and hematopoietic system thus indicating that zinc deficiency in the diet may inhibit the carcinogenic effects of cadmium ingestion. EPA has determined that data are insufficient to determine the carcinogenic status of cadmium by the oral route.

An increased risk for respiratory tract cancers has been observed in several epidemiological studies of workers exposed to cadmium-containing fumes and dusts. For this reason, cadmium is classified as a probable human carcinogen (B1) by EPA based on **inhalation** studies in humans. The airborne cancer potency is 1.8×10^{-3} per $\mu g/m^3$ (IRIS, 1999).

5.2.2.8 Special Susceptibilities—

Populations with genetically determined lower ability to induce metallothionein are less able to sequester cadmium. Populations with depleted stores of dietary components such as calcium and iron due to multiple pregnancies and/or dietary deficiencies may have increased cadmium absorption from the GI tract.

Increased calcium excretion associated with cadmium-induced renal damage may lead to increased risk of osteoporosis, especially in postmenopausal women. The relationship between cadmium toxicity and iron levels is not well established; however, in some studies it appears that iron-deficient individuals may be at greater risk. Individuals with kidney disease, diabetes, and age-related decreased kidney function may be at greater risk of cadmium-induced kidney toxicity (ATSDR, 1997).

Immunological effects may be of concern for children because it appears, based upon animal studies, that young individuals may be at greater risk than adults. In addition, the immune system is not fully developed in humans until approximately 12 years of age. Immunological effects have also been observed in multiple animal studies of adults. These pose special risks for individuals with compromised immune systems (e.g., those with AIDS).

A variety of types of developmental effects have been associated with cadmium exposure (see discussion above). These all pose special risks for infants and children, as well as women of reproductive age.

5.2.2.9 Interactive Effects—

Dietary deficiencies of calcium, protein, zinc, copper, iron, and vitamin D may cause increased susceptibility to adverse skeletal effects from cadmium exposure. Lead increased neurotoxicity and selenium decreased the clastogenic effect of cadmium on bone marrow. Exposure to chemicals that induce metallothionein (e.g., metals) reduced toxicity with parenteral cadmium exposure (ATSDR, 1997).

MIXTOX reports a number of interactive studies on cadmium and selenium compounds. The studies have yielded mixed results with reports of inhibition, potentiation, additive effects, and no effects (MIXTOX, 1992).

5.2.2.10 Critical Data Gaps—

A joint team of scientists from ATSDR, National Toxicology Program (NTP), and EPA have identified the following data gaps: immunotoxicity, neurotoxicity, and developmental toxicity in human populations, quantitative data on acute and intermediate toxicity in humans, and chronic exposure studies in humans using sensitive indicators of kidney toxicity, animal and human studies of carcinogenic effects, human genotoxicity, animal reproductive, immunotoxicity, and pharmacokinetic studies (ATSDR, 1997).

5.2.2.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	1×10^{-3} mg/kg-d
Carcinogenicity	Group B1 (probable human carcinogen).

5.2.2.12 Major Sources—

ATSDR (1997), HSDB (1993), IRIS (1999), U.S. FDA (1993).

5.2.3 Mercury

5.2.3.1 Background—

Mercury is widely distributed in the environment due to both natural and anthropogenic processes. It is released generally as elemental mercury (Hg^0) or divalent mercury (Hg^{2+}). It can be converted between these forms and may form mercury compounds by chemical processes in air, water, and soil. Biological processes in other media, primarily soil and sediment, can convert inorganic mercury into organic, mostly methylmercury.

In fish tissue, the majority of mercury is methylmercury. Generally, the amount of mercury in fish tissue increases with the age and the size of the fish. The accumulation of mercury in fish varies among species; for the most part, the fish-eating species of fish accumulate higher concentrations of mercury than do non-piscivorous fish. Mercury is found in highest concentrations in organs and muscle.

Data on mercury toxicity have been reviewed for inclusion in IRIS. Currently there are both RfDs and cancer assessments in IRIS for elemental mercury, inorganic mercury (mercuric chloride), and methylmercury (interim RfD). EPA, in response to a mandate of the Clean Air Act Amendments of 1990, has prepared a multivolume *Mercury Study Report to Congress*. This has been peer reviewed extensively including a recent review by the Science Advisory Board (SAB). (U.S. EPA, 1997d). Methylmercury has also been the subject of evaluation by numerous states. Detailed analyses have been conducted in some specific areas, including evaluation of data regarding blood and hair mercury levels, toxic effects, and biological half-life values to estimate safe consumption levels of contaminated fish (Shubat, 1991, 1993; Stern, 1993).

As discussed in previous sections, a total exposure assessment is beyond the scope of this document. Readers may wish to consult other sources to obtain information on background levels of methylmercury in the environment. Additional information on dietary sources of mercury is available in the FDA *Adult Total Diet Study*, conducted from October 1977 through September 1978, which contains information on total mercury content (not restricted to methylmercury) in a number of foods (Podrebarac, 1984). Readers are also referred to Volume III, *An Assessment of Exposure from Anthropogenic Mercury Emissions in the United States* of the *Mercury Study Report to Congress* (U.S. EPA, 1997d).

5.2.3.2 Pharmacokinetics—

Methylmercury is rapidly and nearly completely absorbed from the gastrointestinal tract; 90 to 100 percent absorption is estimated (WHO, 1990).

Methylmercury is somewhat lipophilic, allowing it to pass through lipid membranes of cells and facilitating its distribution to all tissues, and it binds readily to proteins. Methylmercury in fish binds to amino acids in fish muscle tissue.

The highest methylmercury levels in humans are generally found in the kidneys. Methylmercury in the body is considered to be relatively stable and is only slowly transformed to form other forms of mercury. Methylmercury readily crosses the placental and blood/ brain barriers. Estimates for its half-life in the human body range from 44 to 80 days (U.S. EPA, 1997d). Excretion of methylmercury is via the feces, urine, and breast milk. Methylmercury is also distributed to human hair and to the fur and feathers of wildlife; measurement of mercury in these materials has served as a useful biomonitor of contamination levels.

5.2.3.3 Acute Toxicity—

Acute high-level exposures to methylmercury may result in impaired central nervous system function, kidney damage and failure, gastrointestinal damage, cardiovascular collapse, shock, and death. The estimated lethal dose is 10 to 60 mg/kg (ATSDR, 1999).

5.2.3.4 Chronic Toxicity—

Although both elemental and methylmercury produce a variety of health effects at relatively high exposures, neurotoxicity is the effect of greatest concern. This is true whether exposure occurs to the developing embryo or fetus during pregnancy or to adults and children.

Human exposure to methylmercury has generally been through consumption of contaminated food. Two major episodes of methylmercury poisoning through fish consumption have occurred. The first occurred in the early 1950s among people, fish-consuming domestic animals such as cats, and wildlife living near Minamata City on the shores of Minamata Bay, Kyushu, Japan. The source of the methylmercury contamination was effluent from a chemical factory that used mercury as a catalyst and discharged wastes into the bay where it accumulated in the tissues of fish and shellfish that were dietary staples of this population. Average fish consumption was reported to be in excess of 300 g/d (reviewed by Harada et al., 1995); 20 times greater than is typical for recreational fishers in the United States. By comparison, about 3 to 5 percent of U.S. consumers routinely eat 100 grams of fish per day. Among women of childbearing age, 3 percent routinely eat 100 grams of fish per day.

Symptoms of Minamata disease in children and adults included: impairment of peripheral vision, disturbances in sensations ("pins and needles" feelings, numbness) usually in the hands and feet and sometimes around the mouth, incoordination of movements as in writing, impairment of speech, hearing, and walking, and mental disturbances. It sometimes took several years before individuals were aware that they were developing the signs and symptoms of methylmercury poisoning. Over the years, it became clear that nervous system damage could occur to the fetus if the mother ate fish contaminated with methylmercury during pregnancy.

In 1965, another methylmercury poisoning incident occurred in the area of Niigata, Japan. The signs and symptoms of disease in Niigata were similar to those of methylmercury poisoning in Minamata.

Methylmercury poisoning also occurred in Iraq following consumption of seed grain that had been treated with a fungicide containing methylmercury. The first outbreak occurred prior to 1960; the second occurred in the early 1970s. Imported mercury-treated seed grains that arrived after the planting season were ground into flour and baked into bread. Unlike the long-term exposures in Japan, the epidemic of methylmercury poisoning in Iraq was short in duration lasting approximately 6 months.

The signs and symptoms of disease in Iraq were predominantly in the nervous system: difficulty with peripheral vision or blindness, sensory disturbances, incoordination, impairment of walking, and slurred speech. Both children and adults were affected. Infants born to mothers who had consumed methylmercury-contaminated grain (particularly during the second trimester of pregnancy) showed nervous system damage even though the mother was only slightly affected.

Recent studies have examined populations that are exposed to lower levels of methylmercury as a consequence of routine consumption of fish and marine mammals, including studies of populations around the Great Lakes and in New Zealand (Kjellstrom et al., 1986a, 1986b), the Amazon basin (e.g., Lebel et al., 1996; Marsh et al., 1995b), the Seychelles Islands (Marsh et al., 1995a), and the Faroe Islands (Dahl et al., 1996). The last two studies are of large populations of children presumably exposed to methylmercury in utero. Very sensitive measures of developmental neurotoxicity in these populations are still being analyzed and published. A 1998 workshop discussed these studies and concluded that they have provided valuable new information on the potential health effects of methylmercury. Significant uncertainties remain, however, because of issues related to exposure, neurobehavioral end points, confounders and statistics, and study design.

The EPA interim RfD for methylmercury is based on data on neurologic changes in 81 Iraqi children who had been exposed in utero; that is, their mothers had eaten methylmercury-contaminated bread during pregnancy. The data were

collected by interviewing the mothers of the children and by clinical examination by pediatric neurologists conducted approximately 30 months after the poisoning episode. The incidence of several endpoints (including late walking, late talking, seizures, or delayed mental development and scores on clinical tests of nervous system function) were mathematically modeled to determine a mercury level in hair (measured in all the mothers in the study) that was associated with no adverse effects. Delays in motor and language development were defined by the following criteria:

- Inability to walk two steps without support by 2 years of age
- Inability to respond to simple verbal communication by age 2 years among children with good hearing
- Scores on physical examination by a neurologist who assessed cranial nerve signs, speech, involuntary movements, limb tone, strength, deep tendon reflexes, plantar responses, coordination, dexterity, primitive reflexes, sensation, posture, and ability to sit, stand, walk, and run
- Assessment of mental development or the presence of seizures based on interviews with the child's mother.

In calculating the mercury level in hair that was associated with no adverse effects in children exposed in utero, EPA used a benchmark dose (in this instance the lower bound for 10 percent risk of neurological changes) based on modeling of all effects in children. This lower bound was 11 ppm methylmercury in maternal hair. A dose-conversion equation was used to estimate a daily intake of 1.1 µg methylmercury/kg body weight-day that, when ingested by a 60-kg individual, will maintain a concentration of approximately 44 µg/L of blood or a hair concentration of 11 µg mercury/g hair (11 ppm).

A composite uncertainty factor of 10 was used to account for the following: variability in the human population (particularly the variation in biological half-life and variability in the hair-to-blood ratio for mercury), lack of data on long-term sequelae of exposure, and the lack of a two-generation reproductive study. The resulting interim RfD for methylmercury is 1×10^{-4} mg/kg-d or 0.1 µg/kg-d (IRIS, 1999).

The range of uncertainty in the interim methylmercury RfD and the factors contributing to this range were evaluated in qualitative and quantitative uncertainty analyses. The uncertainty analyses indicated that paresthesia (numbness or tingling) in the hands and feet and occasionally around the mouth in adults is not the most reliable endpoint for dose-response assessment because it is subject to the patient's recognition of the effect. Paresthesia in adults is not the basis for EPA's interim methylmercury RfD.

There are, however, uncertainties associated with the interim RfD based on developmental effects from methylmercury in children exposed in utero. There are difficulties with reliability in recording and classifying events such as late walking in children because the data were collected approximately 30 months after the child's birth. In addition, the data were collected on a population that did not necessarily follow Western cultural practices or use Western calendars in the recording of events such as first steps or first words. It should be noted, however, that the endpoints used represented substantial developmental delays; for example, a child's inability to walk two steps without support at 2 years of age, inability to talk based on use of two or three meaningful words by 2 years, or presence of generalized convulsive seizures. There is both variability and uncertainty in the pharmacologic parameters that were used in estimating the ingested mercury dose. There is also a degree of uncertainty introduced by the size of the study population (81 mother-child pairs).

The interim RfD is supported by additional studies in children exposed in utero. These include investigations among Cree Indians in Canada and New Zealanders who consume large amounts of fish. In these studies, the hair concentration of mercury was used to monitor mercury exposure over time. Conclusions by the investigators in their official reports cite developmental delays among the children born of mothers whose hair mercury concentrations during pregnancy were 6 to 18 ppm, consistent with the benchmark dose of 11 ppm. The published data on the pilot study portion of the ongoing work in the Seychelles Islands (data on children of about 5 years of age) are also consistent with EPA's benchmark dose.

A 1997 review by the Science Advisory Board determined that the RfD is scientifically sound as supported by data in published human and animal studies. The RfD is a risk assessment tool, not a risk management decision. Judgments as to a "safe" dose and exposure are decisions that involve risk management components.

Two new major prospective longitudinal studies, one in the Seychelles Islands and the other in the Faroe Islands, have recently begun to publish their findings in the literature. In November 1998, a federally sponsored workshop, Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury, concluded that the results from the Faroe and Seychelles Islands studies are credible and provide valuable new information on the potential health effects of methylmercury. Significant uncertainties remain, however, because of issues related to exposure, neurobehavorial endpoints, confounders and statistics, and design (NIEHS, 1999).

The Science Advisory Board stated that the Seychelles and Faroe Island studies have advantages over the studies in Iraq and New Zealand; they have much larger sample sizes, a larger number of developmental endpoints, potentially more sensitive developmental endpoints, and control a more extensive set of potentially confounding factors. However, the studies also have some limitations in terms of low exposures and ethnically homogeneous societies. The SAB

concluded that the interim RfD may need to be reassessed in terms of the most sensitive endpoints from these new studies. The National Academy of Sciences (NAS) conducted an independent assessment of the interim RfD. They concluded "On the basis of its evaluation, the committees' consensus is that the value of EPA's current RfD for methylmercury, 0.1 µg/kg per day, is a scientifically justifiable level for the protection of public health." However, the NAS recommended that the Iraqi study no longer be used as the scientific basis for the RfD. They recommended that the developmental neurotoxic effects of methylmercury reported in the Faroe Islands study be used for the derivation of the RfD (NAS, 2000a).

5.2.3.5 Reproductive and Developmental Toxicity—

Data are available on reproductive and developmental effects in rats, mice, guinea pigs, hamsters, and monkeys. Convincing data from a number of human studies i.e., Minamata Japan) also indicate that methylmercury causes subtle to severe neurologic effects depending on dose and individual susceptibility. EPA considers methylmercury to have sufficient human and animal data to be classified as a developmental toxicant.

Methylmercury accumulates in body tissue; consequently, maternal exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing fetus. In addition, infants may be exposed to methlymercury through breast milk. Therefore, it is advisable to reduce methylmercury exposure to women with childbearing potential to reduce overall body burden.

5.2.3.6 Mutagenicity—

Methylmercury appears to be clastogenic but not to be a point mutagen; that is, mercury causes chromosome damage but not small heritable changes in DNA.

EPA has classified methylmercury as being of high concern for potential human germ cell mutagenicity. The absence of positive results in a heritable mutagenicity assay keeps methylmercury from being included under the highest level of concern. The data on mutagenicity were not sufficient, however, to permit estimation of the amount of methylmercury that would cause a measurable mutagenic effect in a human population.

5.2.3.7 Carcinogenicity—

Experimental animal data suggest that methylmercury may be tumorigenic in animals. Chronic dietary exposures of mice to methylmercury resulted in significant increases in the incidences of kidney tumors in males but not in females. The tumors were seen only at toxic doses of methylmercury. Three human studies have been identified that examined the relationship between methylmercury exposure and cancer. There was persuasive evidence of

increased carcinogenicity attributable to methylmercury exposure in any of these studies. Interpretation of these studies was limited by poor study design and incomplete descriptions of methodology and/or results. EPA has not calculated quantitative carcinogenic risk values for methylmercury (IRIS, 1999). EPA has found methylmercury to have inadequate data in humans and limited evidence in animals and has classified it as a possible human carcinogen, Group C.

All of the carcinogenic effects were observed in the presence of profound damage to the kidneys. Tumors may be formed as a consequence of repair in the damaged organs. Evidence points to a mode of action for methylmercury carcinogenicity that operates at high doses certain to produce other types of toxicity in humans. Given the levels of exposure most likely to occur in the U.S. population, even among consumers of large amounts of fish, methylmercury is not likely to present a carcinogenic risk.

5.2.3.8 Special Susceptibilities—

The developing fetus is at greater risk from methylmercury exposure than are adults. Data on children exposed only after birth are insufficient to determine if this group has increased susceptibility to central nervous system effects of methlymercury. In addition, children are considered to be at increased risk of methylmercury exposure by virtue of their greater food consumption (mg food/kg body weight) by comparison to adult exposures. Additional risk from higher mercury ingestion rates may also result from the apparently decreased ability of children's bodies to eliminate mercury.

5.2.3.9 Interactive Effects—

Potassium dichromate andatrazine may increase the toxicity of mercury, although these effects have been noted only with metallic and inorganic mercury. Ethanol increases the toxicity of methylmercury in experimental animals. Vitamins D and E, thiol compounds, selenium, copper, and possibly zinc are antagonistic to the toxic effects of mercury (ATSDR, 1999).

5.2.3.10 Critical Data Gaps—

Additional data are needed on the exposure levels at which humans experience subtle, but persistent, adverse neurological effects. Data on immunologic effects and reproductive effects are not sufficient for evaluation of low-dose methyl-mercury toxicity for these endpoints.

5.2.3.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	1×10^{-4} mg/kg-d
Carcinogenicity	Group C (possible human carcinogen).

5.2.3.12 Major Sources—

ATSDR (1999), IRIS (1999), Shubat (1993a), Stern (1993), U.S. EPA (1997d).

5.2.4 Selenium

5.2.4.1 Background—

Selenium is an element that occurs naturally in many areas and is produced through industrial processes. It is an essential nutrient with a recommended dietary allowance (RDA) of 55 µg/d (0.055 mg) for adult men and women. The Tolerable Upper Intake Level for adults is set at 400 µg/d (0.4 mg/d) based on selenosis as the adverse effect (NAS, 2000b). ATSDR has identified daily intake at nontoxic levels of approximately 0.05 to 0.15 mg/d (ATSDR, 1996a; HSDB, 1993). This is approximately equivalent to 7×10^{-4} to 2×10^{-3} mg/kg-d in a 70-kg individual.

Selenium plays a critical role in the antioxidant enzyme glutathione peroxidase. Selenium deficiency has been associated with muscle degeneration in humans. A serious form of this, congestive cardiomyopathy (Keshan disease), has been studied in areas of China with low naturally occurring levels of selenium. Selenium has also been shown to have a protective effect against chemically induced cancers in laboratory animals (Robbins et al., 1989). Although selenium is an essential nutrient, it is toxic at high exposure levels and is mutagenic in some test systems (ATSDR, 1996a).

Definitive information concerning the chemical forms of selenium found in fish is not available (U.S. EPA, 1993a). Due to the lack of information on chemical forms, the toxicities of a variety of selenium forms are included in the discussion below. In some parts of the United States, particularly in western states, soil concentrations lead to selenium levels in plants that can cause human exposure at potentially toxic levels (ATSDR, 1996a). This exposure should be considered in evaluating the overall exposure to selenium and in developing fish consumption advisories.

5.2.4.2 Pharmacokinetics—

Selenium contained in food is generally associated with proteins as organic selenium compounds. It is easily absorbed by the body and accumulates primarily in the liver and kidneys. It accumulates to a lesser extent in the blood, lungs, heart, testes, and hair. Most of the selenium that enters the body is quicky excreted in the urine, feces, and breath (ATSDR, 1996a).

5.2.4.3 Acute Toxicity—

Signs of acute selenium poisoning include difficulty in walking; labored breathing; cyanosis of the mucous membranes; congestion of the liver; endocarditis and myocarditis; degeneration of the smooth musculature of the GI tract, gall bladder and bladder; and erosion of the long bones. Subacute selenosis (prolonged exposure at relatively high doses) causes impaired vision, ataxia, disorientation, and respiratory distress (IRIS, 1999). "Blind staggers" disease is a disease in livestock that results from acute consumption of plants high in selenium. It is characterized by impaired vision, aimless wandering behavior, reduced consumption of food and water, and paralysis (ATSDR, 1996a).

5.2.4.4 Chronic Toxicity—

IRIS provides an RfD of 0.005 mg/kg-d for selenium and selenium compounds based on a NOAEL of 0.015 mg/kg-d from a 1989 human epidemiological study that found clinical selenosis at the LOAEL of 0.023 mg/kg-d. The NOAEL was calculated from regression analysis of blood selenium levels and selenium intake. An uncertainty factor of 3 rather than 10 was used for intraspecies variability. EPA has medium confidence in the study on which the RfD was based due to some possible interactions that were not fully explored. But because there are many animal and epidemiologic studies that support the principal study, EPA has high confidence in the database and, consequently, in the RfD (IRIS, 1999).

In epidemiological studies of populations exposed to high levels of selenium in food and water, discoloration of the skin, loss of nails and hair, excessive tooth decay and discoloration, garlic odor in the breath and urine, lack of mental alertness, and listlessness were reported (IRIS, 1999). In high-selenium areas of China, peripheral anesthesia and pain in the limbs have been reported. Exaggerated tendon reflexes, convulsions, paralysis, and hemiplegia were estimated to occur at a minimum chronic exposure of 0.053 mg/kg-d. A NOAEL of 0.027 mg/kg-d was estimated (ATSDR, 1996a).

In animals, neurological dysfunction, respiratory distress, skin lesions with alopecia, necrosis and loss of hooves, emaciation, and liver toxicity as indicated by increases in serum transaminases and alkaline phosphatase have been seen (IRIS, 1999). Cows with high, naturally occurring dietary exposures were found to have irritation in the upper GI tract (ATSDR, 1996a; IRIS,1999).

Lifetime exposure of mice to sodium selenate or sodium selenite at 0.57 mg/kg-d caused amyloidosis of the lung, liver, kidney, adrenal gland, and heart. Mice appear to be more sensitive to selenium with regard to lung toxicity than rats. (ATSDR, 1996a).

Hematological effects have been observed in multiple acute and chronic animal studies. Rats subchronically exposed to wheat containing selenium at a dose of

0.56 mg/kg-d for 6 weeks had a 79 percent reduction of blood hemoglobin (ATSDR, 1996a).

Bone softening in rats has been noted with an LOAEL of 0.2 mg/kg-d with exposure over several months (less than 100 days). Other musculoskeletal effects have also been observed in livestock. Adverse effects on the liver and kidneys have been observed in multiple animal studies with LOAELs of 0.1 mg/kg-d and above. Endocrine effects have been observed in animals fed seleniferous wheat at doses of 0.4 mg/kg-d for 6 weeks. Dermal effects have been observed at doses as low as 0.016 mg/kg-d in humans with dietary exposure (ATSDR, 1996a). Depression of the immune system was observed in rats exposed subchronically to sodium selenite at 0.7 mg/kg-d. At lower doses (0.07 mg/kg-d and 0.28 mg/kg-d), mixed results were obtained, with a stimulation of some components of the immune system and depression of others (ATSDR, 1996a).

5.2.4.5 Reproductive and Developmental Toxicity—

Limited information is available on the reproductive and developmental toxicity of selenium in humans. In animals, selenium has caused growth retardation, decreased fertility, embryotoxicity, fetotoxicity, and teratogenic effects.

A multigenerational study in mice dosed with selenate at 0.39 mg/kg-d identified a significant increase in young deaths in the F1 generation and increased runts in the F1 through F3 generations. Because only one dose was used, only a LOAEL can be obtained from this study. A one-generation mouse study found a NOAEL of 0.39 mg/kg-d. An early five-generation study identified a NOAEL of 0.075 mg/kg-d and a LOAEL of 0.125 mg/kg-d with a 50 percent reduction in the number of young reared at that dose (IRIS, 1999).

Multiple studies have determined that exposure of livestock (e.g., sheep, pigs, cattle) to naturally seleniferous diets resulted in fetal malformations and interference with normal fetal development. Malformations were associated with other manifestations of toxicity. The specific selenium compounds associated with these effects have not been identified (ATSDR, 1996a). At 0.4 mg, pigs exposed from 8 weeks of age had offspring with significantly reduced birth weight and weaning weights (ATSDR, 1996a).

Chronic exposure studies in animals have identified multiple adverse effects on the reproductive ability of animals and on offspring viability. Effects include: altered menstrual cycles in monkeys exposed to 0.08 mg/kg-d for 30 days, reduced rates of conception at 0.4 mg/kg-d in pigs exposed from 8 weeks of age (other offspring effects are listed under developmental effects), abnormal length estrus cycles in rats exposed subchronically to 0.31 mg/kg-d, increased fetal resorption and decreased conception rate in livestock exposed at a LOAEL of approximately 0.5 mg/kg-d, failure to breed in a three-generation study of mice exposed at 0.57 mg/kg-d, no effects in a two-generation study of rats at 0.21

mg/kg-d, and a 50 percent reduction in the number of young successfully reared with maternal exposure to 0.35 mg/kg-d for 1 year. Male fertility also appears to be affected by selenium exposure. Decreased sperm counts have been observed in male rats exposed subchronically to 0.1 mg/kg-d and higher while abnormal sperm and decreased testicular weights were observed at 0.2 mg/kg-d (ATSDR, 1996a).

5.2.4.6 Mutagenicity—

Data on the mutagenicity of selenium and its compounds are mixed. There are many positive mutagenicity assays on selenium compounds including unscheduled DNA synthesis, increased chromosomal aberrations in human lymphocytes and in the bone marrow of rats, and an increase in sister chromatid exchanges in human whole-blood cultures. There are also assays with negative results (IRIS, 1999).

Inorganic selenium compounds appear to have genotoxic effects at relatively high doses and antigenotoxic effects at lower doses. For example, a study of mice exposed to mutagens and given doses of 0.05 to 0.125 mg/kg-d of selenium indicates that selenium may inhibit the mutagenic effects of chemical agents (ATSDR, 1996a).

5.2.4.7 Carcinogenicity—

Epidemiological studies that used the selenium concentration in crops as an indicator of dietary selenium have generally reported an inverse association between selenium levels and cancer occurrence. Animal studies have reported that selenium supplementation results in a reduced incidence of several tumor types (ATSDR, 1996; IRIS, 1999). EPA has determined that selenium is not classifiable as to its carcinogenicity in humans (Group D) because of insufficient data. EPA has classified selenium sulfide, an insoluble salt, as a probable human carcinogen (B2) based on liver and lung tumors in oral exposure studies in multiple species (IRIS, 1999).

5.2.4.8 Special Susceptibilities—

ATSDR has listed the following groups as potentially having greater susceptibility: pregnant women and their fetuses, persons exposed to high fluoride levels in drinking water (evidence equivocal), those with vitamin E deficiencies, and insulin-dependent diabetics (ATSDR, 1996a).

5.2.4.9 Interactive Effects—

Selenium alters the toxicity of many chemicals. It reduces the toxicity of mercury, cadmium, lead, silver, and copper. Most forms of selenium interact with arsenic to reduce the toxicity of both elements. Selenium also interacts with vitamins,

sulfur-containing amino acids, xenobiotics, and essential and nonessential elements (ATSDR, 1996a).

5.2.4.10 Critical Data Gaps—

ATSDR has reported the following data gaps: human epidemiological data for all relevant effects, relationship between selenium dietary exposure levels and cancer; mechanisms of genotoxicity, reproductive, immunotoxicity, neurotoxicity, especially behavioral and histopathological CNS effects, pharmacokinetic, and bioaccumulation; and bioavailability from environmental media (ATSDR, 1996a).

5.2.4.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-3} mg/kg-d
Carcinogenicity	Group D (not classifiable).

5.2.4.12 Major Sources—

ATSDR (1996a), HSDB (1993), IRIS (1999).

5.2.5 Tributyltin Oxide

5.2.5.1 Background—

Tributyltin oxide belongs to the organometallic family of tin compounds that have been used as biocides, disinfectants, and antifoulants. This compound and other tributyltin compounds have high bioconcentration factors in aquatic organisms and are acutely and chronically toxic to these organisms at low concentrations. Because of concerns over these compounds' effects on nontarget aquatic species, in 1986 EPA initiated a special review of tributyltin compounds used as antifoulants (U.S. EPA, 1986e). In 1988, the Organotin Antifouling Paint Control Act (OAPCA) was enacted, which contained interim and permanent tributyltin restrictions as well as environmental monitoring, research, and reporting requirements.

The tributyltin compounds registered for use as antifoulants are: tributyltin oxide, tributyltin adipate, tributyltin dodecenyl succinate, tributyltin sulfide, tributyltin acetate, tributyltin acrylate, tributyltin fluoride, tributyltin methacrylate, and tributyltin resinate (U.S. EPA, 1986e). This toxicological profile discusses only tributyltin oxide, since this is the only tributyltin compound with risk assessment information (an RfD) and there is more toxicological information on this compound than any other.

5.2.5.2 Pharmacokinetics—

The pharmacokinetic information available consists of data on organotin compounds as a group; there are few data specific to tributyltin oxide. Organotin

compounds appear to be absorbed in mammals, with studies in rats showing detection of tin compounds in the gastrointestinal tract, kidney, and liver, with little retention observed in the brain and blood. One study specific to tributyltin oxide found the highest levels of tin in the liver and kidneys, with levels in the brain and adipose tissue at 10 to 20 percent of the liver and kidney levels. The metabolism of organotin compounds appears to involve dealkylation, with the liver as the active site. There are no data regarding the excretion of organotin compounds (ATSDR, 1992).

5.2.5.3 Acute Toxicity—

The limited available data show tributyltin oxide to be quite toxic to animals, with oral LD_{50}s ranging between 122 and 194 mg/kg in rats (ATSDR, 1992; HSDB, 1999) and 52 to 130 mg/kg in mice (WHO, 1999).

5.2.5.4 Chronic Toxicity—

There are no studies on the effects of tributyltin oxide in humans. Animal studies have shown effects on the blood (lowered corpuscular volume and hemoglobin mass and decreased leukocytes) and liver, and immunological effects including thymus atrophy and depletion of T-lymphocytes in the spleen and lymph nodes from tributyltin exposure (ATSDR, 1992; HSDB, 1999).

IRIS provides an RfD for tributyltin oxide of 3.0×10^{-4} mg/kg-d, based on a benchmark dose (10 percent relative change as the benchmark response) of 0.03 mg/kg-d and an uncertainty factor of 100. This was based on a chronic rat feeding study in which immunotoxicity was observed. The uncertainty factor of 100 reflects the uncertainty in extrapolating from laboratory animals to humans and the uncertainty in the range of human sensitivity (IRIS, 1999; U.S. EPA, 1997g).

EPA has high confidence in the studies on which the RfD was based, medium to high confidence in the overall database, and medium to high confidence in the RfD. This is based on the fact that the principal study was a well-designed and well-conducted chronic toxicity assay.(IRIS, 1999; U.S. EPA, 1997g).

5.2.5.5 Reproductive and Developmental Toxicity—

No studies are available on the reproductive and developmental effects of tributyltin oxide in humans. In a two-generation reproductive study in rats, there were no effects on mating, pregnancy, fertility, litter size, or pup survival in either generation. Compound-related developmental effects were limited to decreased pup body weight during lactation in both generations at the high dose. The NOAEL for reproductive toxicity in this study was 4.4 mg/kg-d, the highest dose tested. The NOAEL for developmental toxicity was 0.34 mg/kg-d (U.S. EPA, 1997g). When pregnant rats were exposed to high doses of tributyltin oxide (>10 mg/kg-d), decreased numbers of live births and decreased growth and viability of

the offspring were reported. While these findings demonstrate the fetotoxic potential of tributyltin oxide, a nonspecific effect of tributyltin oxide cannot be ruled out because of overt maternal toxicity seen at the doses used (HSDB, 1993). A developmental study in mice reported dose-related decreases in fetal weights, some skeletal abnormalities, such as fused ribs and cleft palates, at all dose levels and also in the controls. Weaknesses of this study include the occurrence of developmental effects in both treated and control animals, maternal toxicity, and lack of information on the statistical evaluation of the data (ATSDR, 1992; U.S. EPA, 1997g).

5.2.5.6 Mutagenicity—

Results from in vitro studies on tributyltin oxide have been primarily negative. Tributyltin oxide was negative in a variety of studies with *Salmonella typhimurium* and Chinese hamster cells; the only positive results were with metabolic activation. In vivo studies were also mainly negative; the compound was negative in *Drosophila melanogaster* and in the micronucleus test (at cytotoxic doses) in mice. One positive result was obtained in the micronucleus test where increased micronuclei in erythrocytes were noted (ATSDR, 1992; HSDB, 1999).

5.2.5.7 Carcinogenicity—

No human studies are available. Cancer bioassays following oral exposure have been conducted in rats and mice. The study in rats noted an increased incidence of some benign tumors at the highest dose level. However, this study is inconclusive because of increased mortality at the high dose and variable background rates for the tumors observed. In the mouse study, no increase in tumor incidence was observed. EPA has classified tributyltin oxide as Group D for carcinogenicity - not classifiable as to human carcinogenicity (U.S. EPA, 1997g).

5.2.5.8 Special Susceptibilities—

There is some evidence that a child might be more sensitive to the toxic effects of tributyltin oxide. For example, preweanling rats were shown to be more sensitive than adult rats to the immunotoxic effects of tributyltin oxide. Because the RfD is based on the effects observed when weanlings were dosed for the remainder of their lives, any potential childhood sensitivity is already accounted for. Animal toxicity studies showed no evidence of gender differences in the toxic responses to tributyltin oxide (U.S. EPA, 1997g).

5.2.5.9 Interactive Effects—

Limited information is available on the interactive effects of tributyltin oxide. Sulfur-containing compounds have been shown, in vitro, to interact with tributyltin compounds to produce other compounds with lower hemolytic activity (ATSDR, 1992).

5.2.5.10 Critical Data Gaps—

No human data are available to characterize the toxicity of tributyltin oxide. A wealth of data from laboratory animals, however, is available. These data adequately characterize the noncancer toxicity from oral exposure to tributyltin oxide. EPA has high confidence in this assessment. The species studied include monkey, dog, rat, and mouse. In addition, there is a two-generation reproduction study and several developmental studies in rats and mice. The principal study and a variety of supporting studies convincingly demonstrate that the critical effect for tributyltin oxide is immunotoxicity. The potential for neurotoxicity has not been completely studied (U.S. EPA, 1997g).

5.2.5.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3.0×10^{-4} mg/kg-d
Carcinogenicity	Group D (not classifiable).

5.2.5.12 Major Sources—

ATSDR (1992a), HSDB (1999), IRIS (1999), U.S. EPA (1997g).

5.3 ORGANOCHLORINE PESTICIDES

5.3.1 Chlordane

5.3.1.1 Background—

Chlordane is an organochlorine insecticide comprised of the sum of *cis*- and *trans*-chlordane and *trans*-nonachlor and oxychlordane for purposes of health advisory development (U.S. EPA, 1997e). First introduced in 1947, it was used extensively on agricultural crops, livestock, lawns, and for termite control. Because of concern over cancer risk, human exposure, and effects on wildlife, most uses were banned in 1978, and all uses were banned by 1988. Due to its long half-life and ability to concentrate in biological materials, it is still widely distributed in fish in the United States.

5.3.1.2 Pharmacokinetics—

Chlordane is extremely lipid soluble, and lipid partitioning of chlordane and its metabolites has been documented in both humans and animals. Concen trations of chlordanes (cis- and trans-isomers and metabolites) detected in human liver samples were 17-fold higher when expressed on a fat rather than a wet weight basis. Chlordane is metabolized via oxidation, which results in a number of metabolites, including oxychlordane, that are very persistent in body fat. Reductive dehalogenation of chlordane forms free radicals, which are hypothesized to be significant in chlordane toxicity (ATSDR, 1994a).

Human studies have found chlordane in pesticide applicators, residents of homes treated for termites, and those with no known exposures other than background (e.g., food or airborne). Human milk fat contained a mean chlordane residue of approximately 188 ppm. Oxychlordane residues were detected in 68 percent of human milk samples in a low-pesticide-usage area and in 100 percent of the 50 samples tested in Hawaii. It is anticipated that all routes of exposure were involved in maternal exposure to chlordane. Fat accumulation of chlordane appears to depend on the exposure duration (ATSDR, 1994a).

Mechanisms of toxicity include: the binding of chlordane and its metabolites irreversibly to cellular macromolecules, causing cell death or disrupting normal cellular function; increasing tissue production of superoxide radicals, which accelerates lipid peroxidation and disrupts the function of membranes; possible suppression of hepatic mitochondrial energy metabolism; and alteration of neurotransmitter levels in various regions of the brain; a reduction in bone marrow stem cells prenatally; and suppression of gap junction intercellular communication (ATSDR, 1994a).

5.3.1.3 Acute Toxicity—

Chlordane is moderately to highly toxic with an estimated lethal dose to humans of 6 to 60 g (IRIS, 1999). Effects reported in humans after acute exposure include headaches, irritability, excitability, confusion, incoordination, seizures, and convulsions. There is also some evidence that acute exposures to chlordane may be associated with immunologic dysregulation, aplastic anemia in humans (U.S. EPA, 1997e).

5.3.1.4 Chronic Toxicity—

IRIS provides an RfD of 5.0×10^{-4} mg/kg-d based on a NOAEL of 0.15 mg/kg-d for hepatic necrosis in a 2-yr feeding study in mice (IRIS, 1999). The LOAEL in the principal study was 0.75 mg/kg-d. An uncertainty factor of 300 was applied to the NOAEL, 10 each for inter- and intraspecies variability and 3 for lack of any reproductive studies. The confidence in the principal study is rated medium, as is the confidence in the database.

Multiple neurological effects have been reported in humans exposed both acutely and chronically to chlordane. When adults (109 women and 97 men) who had been exposed to uncertain levels of chlordane via both air and oral routes were examined, significant ($p < 0.05$) differences were observed with a battery of neurophysiological and neuropsychological function tests (U.S. EPA, 1997e). Also, profiles of mood states (including tension, depression, anger, vigor, fatigue, and confusion) all were affected significantly ($p < 0.0005$) as compared to a referent population.

5.3.1.5 Reproductive and Developmental Toxicity—

According to the IRIS file, "there have been 11 case reports of CNS effects, blood dyscrasias and neuroblastomas in children with pre/postnatal exposure to chlordane and heptachlor" (IRIS,1999).

ATSDR reports a number of developmental effects. Prenatal and early postnatal exposure in mice may have permanent effects on the immune system, including a reduction in the number of stem cells required to form the mature immune system. Effects were observed at 4 mg/kg-d. Neurological effects include abnormal behavior and increased seizure thresholds in mice at 1 mg/kg-d prenatal and postnatal (via lactation) exposure (no NOEL was identified). Alterations in plasma corticosterone levels were observed, which may result from a change in the neuroendocrinological feedback mechanisms (ATSDR, 1994a).

Concerning cancer in children, see the discussion in Section 5.3.1.7.

5.3.1.6 Mutagenicity—

Mutagenicity assays of chlordane have yielded mixed results, with positive results generally obtained in higher organism cell assays and negative results in bacterial assays (IRIS, 1999).

5.3.1.7 Carcinogenicity—

Chlordane is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. An increased incidence of hepatocellular carcinoma was observed in both sexes in mice in two separate studies using different strains. Hepatocellular carcinomas were also observed in another study in male mice using a third strain. The oral cancer slope factor of 0.35 per mg/(kg-d) is the geometric mean of the cancer potencies calculated from five data sets (IRIS, 1999).

Five compounds structurally related to chlordane (aldrin, dieldrin, heptachlor, heptachlor epoxide, and chlorendic acid) have produced liver tumors in mice. Chlorendic acid also has produced liver tumors in rats.

Neuroblastoma and acute leukemia have also been associated with prenatal and early childhood exposure to chlordane (ATSDR, 1994a).

5.3.1.8 Special Susceptibilities—

Based on the results of animal studies showing prenatal exposure causes damage to the developing nervous and immune systems, fetuses and children may be at greater risk than adults from chlordane exposure. According to ATSDR:

> Given the generally greater sensitivity to toxicants of incompletely developed tissues, it seems possible that prenatal exposure of humans to chlordane could result in compromised immunocompetence and subtle neurological effects (ATSDR, 1994a).

Due to the interactive effects of chlordane with other chemicals via microsomal enzymes (see Section 5.3.1.9), ATSDR has cautioned that: "doses of therapeutic drugs and hormones may require adjustment in patients exposed to chlordane." The results of an acute animal study suggest that protein-deficient diets may also increase the toxic effects of chlordane (ATSDR, 1994a).

ATSDR has listed the following populations as unusually susceptible: those with liver disease or impaired liver function; infants, especially those with a hereditary predisposition to seizures; and the fetus (ATSDR, 1994a).

5.3.1.9 Interactive Effects—

Chlordane is a potent inducer of hepatic microsomal enzymes. Chlordane exposure has been associated with an increased rate of metabolism of therapeutic drugs, hormones, and many other endogenous and xenobiotic compounds. Exposure to other chemicals that induce the same enzymes may increase the toxicity of chlordane by enhancing its metabolism to its toxic intermediate. The acute toxic effects of aldrin, endrin, and methoxychlor with chlordane were greater than the additive sum of the individual toxicities (ATSDR, 1994a).

It has been suggested that increased dietary vitamins C or E or selenium may be protective against free-radical-induced toxicity (ATSDR, 1994a).

MIXTOX reported synergistic effects between chlordane and endrin in mice exposed via gavage and both potentiation and inhibition with γ-hexachloro-cyclohexane in rodents exposed via gavage. Synergism is reported with toxaphene and malathion together with chlordane in mice exposed via gavage (MIXTOX, 1992).

5.3.1.10 Critical Data Gaps—

IRIS lists the following data gaps for chlordane: chronic dog feeding study, rat reproduction study, rat teratology study, and rabbit teratology study (IRIS, 1999). Other studies that are needed include a multigeneration study, which includes a measurement of reproductive system toxicity, immunological effects—particularly with developmental exposures, pharmacokinetic studies, and studies to determine methods for reducing body burden (ATSDR, 1994a).

5.3.1.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-4} mg/kg-d
Carcinogenicity	0.35 per mg/kg-d.

5.3.1.12 Major Sources—

ATSDR (1994a), HSDB (1993), IRIS (1999), EPA (1997e).

5.3.2 DDT, DDE, DDD

5.3.2.1 Background—

DDT is an organochlorine pesticide that has not been marketed in the United States since 1972 but is ubiquitous due to its widespread use in previous decades and its relatively long half-life. DDT's close structural analogs, DDE and DDD, are metabolites of DDT and have also been formulated as pesticides in the past (Hayes, 1982). DDT is very widely distributed; it has been found in seals in

Finland and reptiles in the Everglades (HSDB, 1993). The NHANES II study (National Human Monitoring Program of the EPA) detected DDE, a metabolite of DDT, in 99 percent of the 12- to 74-yr-old study subjects (living in the Northeast, Midwest, and South). The median level was 11.8 ppb in blood serum (HSDB, 1993).

Although some use of DDT continues throughout the tropics, it remains of human health concern in the United States primarily due to its presence in water, soil, and food (Hayes, 1982). Because individuals are typically exposed to a mixture of DDE, DDT, and DDD and their degradation and metabolic products (ATSDR, 1994b), the sum of the 4,4'- and 2,4'- isomers of DDT, DDE, and DDD should be considered in the development of fish consumption limits for this group of chemicals (U.S. EPA, 1993a).

5.3.2.2 Pharmacokinetics—

DDT and its analogs are stored in fat, liver, kidney, and brain tissue; trace amounts can be found in all tissues (Hayes, 1982). DDE is stored more readily than DDT (Hayes, 1982). DDT is eliminated through first-order reduction to DDD and, to a lesser extent, to DDE. The DDD is converted to more water-soluble *bis* (p-chlorophenyl)-acetic acid, with a biological half-life of 1 year. DDE is eliminated much more slowly, with a biological half-life of 8 years. Because elimination occurs slowly, ongoing exposure may lead to an increase in the body burden over time.

5.3.2.3 Acute Toxicity—

The low effect dose for severe effects (acute pulmonary edema) in infants has been reported to be 150 mg/kg. In adults, behavioral effects were noted at 5 to 6 mg/kg and seizures at 16 mg/kg (HSDB, 1993).

Evidence from acute exposure studies of dogs indicates that DDT may sensitize the myocardium to epinephrine. This was observed for both injected epinephrine and epinephrine released by the adrenal glands during a seizure and resulted in ventricular fibrillation (Hayes, 1982). DDT may concurrently act on the CNS, in a manner similar to that of other halogenated hydrocarbons, to increase the likelihood of fibrillation (Hayes, 1982). Chronic exposure to 10 mg/kg-d did not produce increased incidence of arrhythmias in rats or rabbits (Hayes, 1982).

DDD is considered less toxic than DDT in animals. Symptoms develop more slowly and have a longer duration with DDD than with DDT exposure. Lethargy is more significant and convulsions are less common than with DDT exposure (HSDB, 1993).

5.3.2.4 Chronic Toxicity—

Extensive research has been conducted on chronic and subchronic exposure effects of DDT in animals and in humans working with DDT. These studies have primarily focused on carcinogenic effects, which are discussed in Section 5.3.2.7. Studies have also identified liver damage, and there is limited evidence that DDT may cause leukocytosis and decreased hemoglobin level (Hayes, 1982).

Immunological effects have been associated with exposure to DDT. Exposure to DDT at 2.63 mg/kg-d for 10 days resulted in immunological effects in rabbits. With 31 days of exposure at 1 mg/kg-d in rats, a decrease in the number of mast cells was observed. A relatively recent 8-week study in rabbits found decreases in germinal centers of the spleen and atrophy of the thymus at 0.18 mg/kg-d. Other effects were observed at higher doses. No studies were provided on immunological effects following chronic exposure (ATSDR, 1994b).

IRIS lists an oral RfD of 5×10^{-4} mg/kg-d for DDT based on liver effects with a NOAEL of 0.05 mg/kg-d from a 27-wk rat feeding study conducted in 1950. Uncertainty factors of 10 each for inter- and intraspecies variability were used; however, the usual factor of 10 for a less-than-lifetime study was not applied "because of the corroborating chronic study in the data base" (IRIS, 1999). The corroborating study was conducted in 1948.

5.3.2.5 Reproductive and Developmental Toxicity—

DDT causes embryotoxicity and fetotoxicity but not teratogenicity in experimental animals (ATSDR, 1994b). Studies indicate that estrogen-like effects on the developing reproductive system occur (ATSDR, 1994b). This also occurs with chronic exposure as discussed in Section 5.3.2.4. Rabbits exposed to 1 mg/kg-d early in gestation had decreased fetal brain, kidney, and body weights (ATSDR, 1994b). Prenatal exposure in mice at 1 mg/kg on 3 intermittent days resulted in abnormal gonad development and decreased fertility in offspring, which was especially evident in females (Hayes, 1982).

A three-generation rat reproduction study found increased offspring mortality at all dose levels with a LOAEL of 0.2 mg/kg-d. Three other reproduction studies found no effects at much higher dose levels (IRIS, 1999). Effects on the urogenital system were found with 8 days' prenatal exposure in mice. Behavioral effects in mice exposed prenatally for 7 days were noted at 17.5 mg/kg-d (HSDB, 1993).

Prenatal 1-day exposure of rabbits to DDT resulted in an abnormal persistence of preimplantation proteins in the yolk sac fluid. The results suggest that DDT caused a cessation of growth and development before implantation or during later uterine development. The authors suggest that damage can be repaired but may result in offspring with prenatal growth retardation in the absence of gross abnormalities (HSDB, 1993). Most dosages tested for these effects have been

relatively high. Postnatal exposure of rats for 21 days to 21 mg/kg (the only dose tested) resulted in adverse effects on lactation and growth.

In dogs, placental passage of DDT to the fetus has been demonstrated. This was confirmed in mice. Primary targets include the liver, adipose tissue, and intestine. Rabbit blastocysts (a very early stage of development) contained a significant amount of DDT shortly after administration to the mother (HSDB, 1993).

Biomagnification in human milk has been observed. In lactating women with an intake of 5×10^{-4} mg/kg-d of DDT, the milk contained 0.08 ppm. This was calculated to result in infant doses of 0.0112 mg/kg-d, which is approximately 20 times the dosage to the mothers (HSDB, 1993).

DDT is suspected of causing spontaneous abortion in humans and cattle (Hayes, 1982). The average concentration of DDE in the blood of premature babies (weighing <2,500 g) was significantly greater than those of higher birth weight infants (HSDB, 1993). The relationship between spontaneous abortion, premature delivery, and maternal exposure and body burden requires clarification.

DDT accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If a female has been exposed to DDT, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

DDT may have reproductive system toxicity. It appears to bind to uterine tissue and have estrogenic activity (Hayes, 1982). Metabolites of DDT bind to the cytoplasmic receptor for estrogen, which may result in inadvertent hormonal response (agonist) or depress normal hormonal balance (antagonist). Either may result in reproductive abnormalities (HSDB, 1993). The animal studies of the reproductive system have yielded mixed results. Chronic animal studies have identified LOELs that range over orders of magnitude. Serious adverse effects (decreased fertility and decreased litter size) have been observed at 0.35 and 0.91 mg/kg-d, respectively, in subchronic animal studies. Edema of the testes occurred at 2 mg/kg-d in a rat study. NOAELs are not available for these studies. Other studies have identified NOAELs ranging from 2.4 to 10 mg/kg-d with severe effects at 12 mg/kg-d (increased maternal and offspring death) (ATSDR, 1994b). Significant reproductive (function and lactation) abnormalities have also been observed at higher doses (83 mg/kg-d in rats and at 33.2 mg/kg-d in mice). Function abnormalities have also been observed in dogs (Hayes, 1982).

5.3.2.6 Mutagenicity—

Genotoxicity studies in human systems strongly suggest that DDT may cause chromosomal damage (ATSDR, 1994b). This is supported by in vitro and in vivo

studies in animals (ATSDR, 1994b) and in some bacterial assays (HSDB, 1993). There are multiple positive assays including human lymphocytes, human leukocytes, human fibroblasts, an oncogenic transformation, and unscheduled DNA synthesis in rats in multiple studies (ATSDR 1994b; HSDB, 1993).

5.3.2.7 Carcinogenicity—

DDE, DDT, and DDD are all considered probable human carcinogens (B2) based on animal studies, with cancer potencies of 0.24, 0.34, and 0.34 per mg/kg-d, respectively (IRIS, 1999). Liver tumors were associated with each chemical. It is noted in the IRIS file that 24 of the 25 carcinogenicity assays of DDT have yielded positive results. The occupational studies of workers exposed to DDT are of insufficient duration to assess carcinogenicity (IRIS, 1999). Elevated leukemia incidence, particularly chronic lymphocytic leukemia, was noted in two studies of workers. Lung cancer has also been implicated in one study. Bone marrow cells in experimental animals have also been affected by exposure, including an increase in chromosomal fragments in the cells (HSDB, 1993).

It is recommended that the total concentration of the 2,4'- and 4,4'-isomer of DDT and its metabolites, DDE and DDD, be evaluated as a group using the cancer potency of 0.34 per mg/kg-d (U.S. EPA, 1993a). In addition, the EPA Carcinogenicity Assessment Group has recommended that this value be used for combinations of dicofol with the above three compounds (U.S. EPA, 1993a).

5.3.2.8 Special Susceptibilities—

Based on the information obtained from a recent developmental study that found neurotoxicity and structural brain alterations at relatively low exposures (approximately 50-fold less than in adults), children may be at greater risk from DDT exposure than adults.

The results of the cardiac toxicity studies are not consistent; however, it is safest to assume that exposure to DDT or its analogs **may** pose a risk for individuals with cardiac disease at exposure levels estimated to be safe for the general population (Hayes, 1982).

Individuals exposed to DDT may metabolize some drugs more rapidly than the general population (HSDB, 1993). For example, increased phenobarbital metabolism resulting from an increased body burden of DDT (10 µg) led to a 25 percent decrease in effectiveness of the drug in experimental animals. The toxicity of chloroform was enhanced by the addition of DDT to the diet due to its capacity as a microsomal stimulator (HSDB, 1993). Alterations in the metabolism of drugs, xenobiotics, and steroid hormones may result from DDT exposure due to DDT's induction of the hepatic mixed-function oxidase system at relatively low doses (HSDB, 1993). Individuals who use medications that involve the mixed function oxidase system directly (MFO inhibitors) or through metabolic processes may be at risk for alteration of the drug's efficacy and/or timing if they are exposed

to DDT. Information is not available for this document on the specific relationships between various pharmaceuticals and DDT/DDE/DDD body burdens or intakes. This type of information merits further investigation.

ATSDR notes that persons with diseases of the nervous system or liver may be particularly susceptible to the effects of DDT (ATSDR, 1994b). Based on information discussed above concerning biomagnification in milk, nursing infants may also be at greater risk due to their increased exposure.

5.3.2.9 Interactive Effects—

As discussed in Section 5.3.2.8, DDT exposure may alter the response to drugs, xenobiotics, and endogenous steroid hormones. DDT is reported to promote some tumorigenic agents and antagonize others. The actions may be related to the induction of microsomal enzymes (ATSDR, 1994b).

5.3.2.10 Critical Data Gaps—

IRIS notes the lack of a NOAEL for reproductive effects and a relatively short duration for the critical study on which the RfD is based.

Information was not located for this document on the specific relationships between various pharmaceuticals and DDT/DDE/DDD body burdens or intakes. Information on the relationship between pre- and postnatal exposure and behavioral effects and maternal exposure and milk concentrations is also needed.

An interagency group of researchers from NTP, ATSDR, and EPA have identified the following data gaps: pharmacokinetic data; animal studies on respiratory, cardiovascular, GI, hematological, musculoskeletal, and dermal/ocular effects; the significance of subtle biochemical changes such as the induction of microsomal enzymes in the liver and the decreases in biogenic amines in the nervous system in humans; an epidemiological study in humans of estrogen-sensitive cancers including endometrial, ovarian, uterine, and breast cancer; reproductive system toxicity; developmental toxicity; a multiple assay battery for immunotoxicity; subtle neurological effects in humans; and mechanisms of neurotoxicity in the neonate (ATSDR, 1994b).

5.3.2.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-4} mg/kg-d (DDT only)
Carcinogenicity	0.34 per mg/kg-d. (sum of the 4,4' and 2,4'-isomers of DDT DDE, and DDD)

5.3.2.12 Major Sources—

ATSDR (1994b), Hayes (1982), HSDB (1993), IRIS (1999).

5.3.3 Dicofol (Kelthane)

5.3.3.1 Background—

Dicofol is an organochlorine miticide/pesticide first registered for use in 1957. Dicofol is used mainly on cotton, apples, and citrus crops; most of the use is in California and Florida (U.S. EPA, 1998a). Dicofol is considered a DDT analog based on its structure and activity (Hayes and Laws, 1991). In the past, dicofol often contained 9 to 15 percent DDT and its analogs. In 1989, EPA required that these contaminants constitute less than 0.1 percent of dicofol (HSDB, 1993).

5.3.3.2 Pharmacokinetics—

Studies with radiolabeled dicofol in rats indicated that most of the label was eliminated in the feces after oral dosing (U.S. EPA, 1998a). Intact dicofol was preferentially stored in adipose tissue. The major metabolic pathway was reductive halogenation to dichlorodicofol and subsequent oxidation to more water-soluble compounds.

5.3.3.3 Acute Toxicity—

The acute oral LD_{50} for dicofol in rats was 587 mg/kg (U.S. EPA, 1998a). A single large oral dose of dicofol to rats caused ataxia at 350 mg/kg and weight loss at 75 mg/kg. The NOAEL for neurotoxicity in this study was 15 mg/kg. An acute dietary RfD of 0.05 mg/kg-d was calculated based on this NOAEL and using an uncertainty factor of 300 (U.S. EPA, 1998a).

5.3.3.4 Chronic Toxicity—

No RfD is currently listed in the IRIS file for this chemical (IRIS, 1999). The OPP has recently derived an RfD of 0.0004 mg/kg-d for chronic dietary exposure (U.S. EPA, 1998a). The critical effect was hormonal toxicity, based on inhibition of adrenocortical trophic hormone (ACTH)-stimulated release of cortisol in dogs. The NOAEL of 0.12 mg/kg-d was divided by an uncertainty factor of 300 (10X for interspecies variation, 10X for intraspecies extrapolation, and 3X for the protection of infants and children.

5.3.3.5 Reproductive and Developmental Toxicity—

In a two-generation reproduction study in rats, the NOAEL for reproductive toxicity was 0.4 mg/kg-d based on the ovarian vacuolation in the F1 females, an effect on reproductive physiology. For offspring toxicity, the NOAEL was 2 mg/kg-d based on decreased F2 pup viability (U.S. EPA, 1998a).

In a special one-generation postnatal toxicity study in rats, the NOAEL for both offspring and parental toxicity was 1.7 mg/kg-d, based on histopathologic findings in the liver. No treatment-related effects were observed on parameters of

reproductive function or performance. The NOAEL for reproductive toxicity was >9.8 mg/kg-d (U.S. EPA, 1998a).

No developmental toxicity was seen in a study in rats. The NOAEL was 25 mg/kg-d, the highest dose tested. In a developmental toxicity study in rabbits, the NOAEL was 4 mg/kg-d, based on an increased incidence of abortions in the does at 40 mg/kg-d (U.S. EPA, 1998a).

5.3.3.6 Mutagenicity—

Dicofol was negative for mutagenicity in the Ames test and for structural chromosomal aberrations in Chinese hamster ovary cells. Dicofol did not induce a clastogenic response in the chromosomes of rat bone marrow cells after oral dosing (U.S. EPA, 1998a). Studies of dicofol in human lymphoid cells in vitro were positive with an incidence of events 13 times that of controls. It induced sister chromatid exchange with activation. Other mutagenicity studies in bacteria have yielded negative results (HSDB, 1993).

5.3.3.7 Carcinogenicity—

In 2-yr carcinogenicity studies in mice and rats, dicofol administration resulted in an increase in liver adenomas and combined liver adenomas and carcinomas in male mice (U.S. EPA, 1998a). No increase in tumor incidence was observed in female mice or in rats or in another 2-yr feeding study in either sex of rats. Dicofol has been classified as a group C carcinogen (possible human carcinogen) based on the increase in liver adenomas and combined liver adenomas and carcinomas in male mice (U.S. EPA, 1998a).

5.3.3.8 Special Susceptibilities—

Toxicity data for dicofol provide no indication of increased susceptibility of rats or rabbit fetuses following in utero exposures in the prenatal developmental toxicity studies or following postnatal exposure in the two-generation reproduction study. For this reason, the additional 10X Safety Factor for the protection of infants and children was reduced to 3X (U.S. EPA, 1998a).

5.3.3.9 Interactive Effects—

As with other organochlorine pesticides, microsomal enzyme induction occurs and may cause interactions with other chemicals. No additional data were located (U.S. EPA, 1998a).

5.3.3.10 Critical Data Gaps—

EPA is requiring a developmental neurotoxicity study in rats for dicofol (U.S. EPA, 1998a). No other data gaps were identified (U.S. EPA, 1998a).

5.3.3.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	4.0×10^{-4} mg/kg-d
Carcinogenicity	Group C (possible human carcinogen).

5.3.3.12 Major Sources—

HSDB (1993), U.S. EPA (1993e), U.S. EPA (1998a).

5.3.4 Dieldrin

5.3.4.1 Background—

Dieldrin is an organochlorine pesticide that was phased out between 1974 and 1987. Dieldrin was mainly used on soil-dwelling pests and for termite control. It continues to be detected nationwide due to its relatively long half-life. Dieldrin is also a product of aldrin metabolism, a structurally similar organochlorine pesticide which is also no longer in use (ATSDR, 1991).

5.3.4.2 Pharmacokinetics—

Dieldrin is absorbed from the GI tract and transported via the hepatic portal vein and the lymphatic system. It is found shortly after exposure in the liver, blood, stomach, and duodenum. Dieldrin is lipophilic and is ultimately stored primarily in fat and tissues with lipid components (e.g., brain) (ATSDR, 1991).

In dosing studies with volunteers at 0.0001 to 0.003 mg/kg-d over 2 years, the time to achieve equilibrium was approximately 15 months. A dynamic equilibrium was theorized with the average ratio of the concentration in adipose tissue to blood of 156. Cessation of dosing led to decreases in blood levels following first-order kinetics with a half-life ranging from 141 to 592 days and an average of 369 days (ATSDR, 1991).

The metabolism of dieldrin is described in detail in ATSDR (1991). Sex and species differences have been reported in the metabolism and tissue distribution of dieldrin based on chronic exposure studies and toxicokinetic studies in animals. Males appear to metabolize and excrete dieldrin more rapidly than females (ATSDR, 1991).

A correlation between exposure and dieldrin levels in human breast milk has been established. Placental transfer of dieldrin has been observed in women, with higher concentrations measured in fetal blood than in maternal blood (ATSDR, 1991).

5.3.4.3 Acute Toxicity—

Acute effects include possible hematological effects in humans (pancytopenia and thrombocytopenia, immunohemolytic anemia) (ATSDR, 1991). An estimated human lethal dose is 65 mg/kg (HSDB, 1993).

5.3.4.4 Chronic Toxicity—

IRIS provides an RfD of 5×10^{-5} mg/kg-d based on a NOAEL of 0.005 mg/kg-d from a 1969 2-year rat feeding study that found liver lesions (focal proliferation and hyperplasia). Uncertainty factors of 10 each for inter- and intraspecies variability were applied (IRIS, 1999). Liver toxicity has been observed in multiple animal studies and in human acute exposure episodes. Adaptive changes (e.g., liver enlargement) have been observed at 0.00035 mg/kg-d in a subchronic rat study.

Although the critical effect in the IRIS study was liver lesions, it was noted that, at the next highest dose (0.05 mg/kg-d), "all animals became irritable and exhibited tremors and occasional convulsions" (IRIS, 1999). There was no listing of additional neurobehavioral studies in the IRIS file. As an organochlorine pesticide, it is expected that dieldrin is a CNS toxicant. This is supported by acute toxicity effects of dieldrin and the neurotoxicity studies listed below.

Other effects associated with dieldrin exposure include: arterial degeneration in rats with a chronic exposure to 0.016 mg/kg-d, hematological disorders in experimental animals at 0.25 and 1 mg/kg-d, musculoskeletal pathology at 0.015 mg/kg-d in a chronic rat study, kidney degeneration and other changes at 0.125 mg/kg-d in chronic animal studies in multiple species, hypertension in humans (exposure level unknown), and multiple deficits in immune system function in multiple studies (ATSDR, 1991). Increased susceptibility to tumor cells was observed in a subchronic mouse study (dose not specified in material reviewed) (HSDB, 1993).

Neurological effects of dieldrin have been observed in experimental animals and in humans exposed acutely and chronically. Wheat mixed with aldrin and lindane was consumed for 6 to 12 months by a small human population. Effects were attributed to aldrin (converted to dieldrin via metabolism) because the wheat had been mixed with lindane in previous years without adverse effect. A variety of CNS disorders were observed, and abnormal EEGs were noted. Some symptoms (myoclonic jerks, memory loss, irritability) continued for at least 1 year after cessation of exposure. A child is believed to have developed mild mental retardation as a result of exposure. Quantitative exposure information was not available in the data reviewed (ATSDR, 1991).

Neurotoxicity has been observed in humans with chronic inhalation and dermal exposures (ATSDR, 1991). Chronic exposure of pesticide applicators to dieldrin led to idiopathic epilepsy, which ceased when exposure was terminated (HSDB,

1993). Dermal and inhalation exposure were the likely routes of exposure. No exposure quantitation was available.

A 1967 study of human exposure effects over 18 months at levels up to 0.003 mg/kg-d identified no effects on the CNS (as measured by EEG), peripheral nerve activity, or muscle activity (ATSDR, 1991).

Animal studies have identified neurological effects including behavioral disorders and learning deficits at doses of 0.1 to 0.25 mg/kg-d in subchronic and chronic studies. Higher doses produced more dramatic effects (e.g., convulsions, tremors). Cerebral edema and degeneration were found with chronic exposure of rats to 0.016 mg/kg-d (ATSDR, 1991). Neural lesions (cerebral, cerebellar, brainstem, and vascular) were observed in chronically exposed rats at 0.004 mg/kg-d (HSDB, 1993).

5.3.4.5 Reproductive and Developmental Toxicity—

IRIS provides limited information regarding the developmental toxicity of dieldrin. A NOAEL of 6 mg/kg-d was obtained from a mouse teratology study with exposure occurring from the 7th to 16th day of gestation. Fetotoxicity (decreased numbers of caudal ossification centers and an increased incidence of extra ribs) was observed with an LOAEL of 6 mg/kg-d. This study was not considered in development of the IRIS file because 41 percent of the maternal fatalities occurred at the LOAEL dose (IRIS, 1999).

A variety of effects in multiple organ systems have been observed in experimental animals exposed prenatally to dieldrin. Skeletal anomalies and malformations (e.g., cleft palate, webbed foot, open eyes, extra ribs) were identified at relatively large doses (LEL of 3 mg/kg-d) (ATSDR, 1991).

Abnormalities of the CNS, eye, and ear were noted with a TD L_o (similar to a LOAEL) of 30.6 mg/kg prenatal exposure, and craniofacial abnormalities were observed at a single prenatal dose of 15 mg/kg-d (HSDB, 1993). Liver damage has been observed in experimental animals at dosages as low as 0.016 mg/kg-d (ATSDR, 1991). Note that liver lesions are the basis for the chronic toxicity RfD derived from a study of adult animals, as reported in IRIS (IRIS, 1999). A multigeneration study in mice found histological changes in liver, kidney, lungs, and brain tissues in the first and second generation offspring at an LOAEL of 3 ppm (0.075 mg/kg-d) (HSDB, 1993).

Multiple studies have reported increased postnatal mortality following prenatal exposure to dieldrin. Studies in dogs, rats, and mice have found LELs of 0.125 to 0.65 mg/kg-d associated with high mortality in offspring in the absence of increased maternal mortality. Studies designed to evaluate the underlying causes of mortality suggest that cardiac glycogen depletion, leading to cardiac failure, may be causal (ATSDR, 1991).

Neural lesions in prenatally exposed rats were found at an LOAEL of 0.004 mg/kg-d. Effects included cerebral edema, internal and external hydrocephalus, and focal neuronal degeneration. Postnatal exposure of rats from day 5 of gestation to 70 days of age resulted in increased learning ability at 3.5×10^{-4} mg/kg-d (the only dose tested). ATSDR has cautioned that "interpretation of the results is difficult because the significance of improved performance in behavioral paradigms is unknown, and the study is limited because only one dose of dieldrin was tested" (ATSDR, 1991). In a rat multigeneration study, a TD L_o of 0.014 mg/kg-d with behavioral effects was observed (HSDB, 1993).

Dieldrin is known to accumulate in human milk. In one study of 102 samples in the United States, 91.2 percent of the samples contained measurable levels of dieldrin, with a mean concentration of 0.062 ppm lipid basis. Another U.S. study found 80 percent of the 1,436 samples were positive with a range of 0.16 to 0.44 ppm milk fat (HSDB, 1993). This indicates that lactation may provide a significant dietary source in infants with mothers who have been exposed to dieldrin. As discussed above, studies in humans also determined that dieldrin can pass through the placenta and is found in fetal blood.

Neurotoxicity appears to be a relatively sensitive endpoint for developmental toxicity. The association of neurotoxic effects with dieldrin exposure is supported by the observation of neurological effects in human populations exposed to dieldrin. The study noted in the paragraph above that identified neural lesions associated with prenatal exposure provided an LOAEL of 0.004 mg/kg-d provides the most sensitive developmental toxicity measure of those reviewed. If the LOAEL from this study were used to calculate an estimated exposure limit for developmental effects, the standard uncertainty factors would typically take into consideration inter- and intraspecies variability and the use of an LOAEL rather than a NOAEL.

As with the other organochlorines, it is anticipated that dieldrin can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If a female has been exposed to dieldrin, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

Dieldrin causes reproductive system disorders in animals and one study suggests that it may cause adverse effects in humans. In a study evaluating the blood and placental levels of organochlorines associated with premature labor or spontaneous abortions in women, positive results were obtained for aldrin. Most exposed subjects had multiple chemical exposures; consequently, interpretation of study results is difficult (ATSDR, 1991). See also notes regarding estrogenic activity in Section 5.3.4.7.

Studies of reproductive effects in animals indicate that exposure to dieldrin may cause a number of adverse effects. Dieldrin exposure causes changes in the levels of serum luteinizing hormone (LH) in females and gonadotropin in males. Dieldrin interferes with the binding of dihydrotestosterone to male sex hormone receptors (HSDB, 1993). These three hormones are critical to normal reproductive function. A mouse study found decreased fertility with exposure to 1.3 mg/kg-d in females and 0.5 mg/kg-d in males. Another study found no effects at much higher exposure levels. Adverse reproductive effects in dogs exposed at LOAEL of 0.15 mg/kg-d for 14 months prior to mating included increased stillbirth rates, delayed estrus, reduced libido, and a lack of mammary function and development. Maternal behavior was studied in mice exposed for 4 weeks prior to delivery until weaning at 1.95 mg/kg-d. Exposed maternal animals violently shook the pups, ultimately killing them; others neglected their litters (ATSDR, 1991).

5.3.4.6 Mutagenicity—

There is limited information on the mutagenicity of dieldrin. Positive in vivo studies have found an increased incidence in the number of abnormal metaphases in dividing spermatocytes and in univalents. Dominant lethal assays (in vivo) have yielded mixed results. In vitro assays have also yielded mixed results. Positive results have been obtained in cultured human lung cells and mouse bone marrow cells (both found increases in chromosome aberrations) and sister chromatid exchange (SCE) assays.

Dieldrin may not act directly on DNA; however, it may act by depressing transfer RNA activity, increasing unscheduled DNA synthesis, and inhibiting metabolic cooperation and gap junctional intercellular communication, according to mechanistic studies. The inhibition of gap junctional communication may be responsible for carcinogenic activity through depressing the cells' ability to control excess proliferation. This inhibition has been correlated with strains and species in which dieldrin has been shown to be carcinogenic. This type of activity is considered promotion rather than initiation of tumors (ATSDR, 1991).

5.3.4.7 Carcinogenicity—

Dieldrin is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer slope factor is 16 per mg/kg-d. Liver carcinoma was identified in the animal studies. The geometric mean of 13 data sets (with a range of a factor of 8) was used to develop the cancer potency (IRIS, 1999).

A variety of tumor types have been observed in animal studies including pulmonary, lymphoid, thyroid, and adrenal (ATSDR, 1991). ATSDR has concluded that dieldrin is probably a tumor promotor, based on genotoxicity and mechanistic studies reviewed (ATSDR, 1991). Dieldrin has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive

cells (Soto et al., 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis et al., 1993). In addition to potential carcinogenic effects, dieldrin may also cause disruption of the endocrine system due to its estrogenic activity (Soto et al., 1994).

5.3.4.8 Special Susceptibilities—

ATSDR has identified the following populations as unusually susceptible: very young children with immature hepatic detoxification systems, persons with impaired liver function, and persons with impaired immune function (ATSDR, 1991). Based on the toxicity data reviewed above, individuals with the following diseases or disorders may also be at increased risk: hypertension, hematological disorders, musculoskeletal diseases, neurological diseases, and kidney disease.

The data also indicate that prenatal exposure may generate risks to children at relatively low levels of exposure. Postnatal exposure, especially via lactation, may also be a significant concern.

5.3.4.9 Interactive Effects—

In cows, dieldrin exposure increased the toxicity of diazinon; greater depression in blood cholinesterase activity occurred, leading to severe clinical signs (HSDB, 1993).

MIXTOX has reported inhibition between dieldrin and hexachlorobenzene in rats exposed orally via food. Studies have also reported additive effects (MIXTOX, 1992).

5.3.4.10 Critical Data Gaps—

A joint team of scientists from EPA, NTP, and ATSDR have identified the following study data gaps: mechanism of animal carcinogenicity, genotoxicity in vivo and in vitro, reproductive system toxicity, developmental toxicity, especially mechanisms of postnatal mortality and teratogenesis, immunotoxicity, neurotoxicity focusing on sensitive endpoints, and pharmacokinetics (ATSDR, 1991).

5.3.4.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-5} mg/kg-d
Carcinogenicity	16 per mg/kg-d.

5.3.4.12 Major Sources—

ATSDR (1991), HSDB (1993), IRIS (1999).

5.3.5 Endosulfan I, II

5.3.5.1 Background—

Endosulfan is an organochlorine pesticide comprised of stereoisomers designated I and II, which have similar toxicities (U.S. EPA, 1993a). Endosulfan I and II are referred to collectively as endosulfan; discussions refer to both isomers unless otherwise noted. Endosulfan has been in use since 1954.

5.3.5.2 Pharmacokinetics—

Endosulfan is absorbed through the GI tract and is distributed throughout the body. Endosulfan is metabolized to lipophilic compounds and both the parent and metabolites are found initially primarily in the kidney and liver and fatty tissue, with distribution to other organs occurring over time. Endosulfan can induce microsomal enzyme activity and is a nonspecific inducer of drug metabolism. In sheep, approximately 1 percent of a single dose was recovered in milk. Females may accumulate endosulfan more readily than males according to animal studies. This may be causal in the higher toxicity seen in females (see Acute Toxicity below) (ATSDR, 1993a).

5.3.5.3 Acute Toxicity—

Acute accidental or intentional ingestion of large amounts of endosulfan has resulted in death in humans. However, available data are insufficient to estimate a lethal dose of endosulfan in humans. Mice appear to be quite sensitive to endosulfan's lethal effects with an LD_{50} of 7 mg/kg. In rats, exposed males and females appear to have different sensitivities to the lethal effects of endosulfan (e.g. oral LD_{50} values were 10-23 mg/kg in females and 40-125 mg/kg in males). Insufficient data were available to determine whether differences in sensitivity to lethal effects exist between males and females of species other than the rat. Acute toxicity in humans and animals involve a large number of organ systems (respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal). The most prominent sign of acute overexposure to endosulfan in both humans and animals is central nervous system stimulation (hyperactivity, tremors, decreased respiration, convulsions) (ATSDR, 1993a)."

5.3.5.4 Chronic Toxicity—

IRIS provides an RfD of 6×10^{-3} mg/kg-d (IRIS 1999). The principal study on which this RfD is based was a 2-yr feeding study in rats. Reduced body weight gain in males and females, increased incidence of marked progressive glomerulonephrosis, and blood vessel aneurysms in males were observed. The LOAEL for systemic toxicity was 2.9 mg/kg-day in males and 3.8 mg/kg-d in females. The NOAEL for systemic toxicity was 0.6 mg/kg-d in males and 0.7 mg/kg-d in females. The NOAEL of 0.6 mg/kg-d was divided by an uncertainty factor of 100; 10 for intraspecies variability and 10 for interspecies extrapolation.

5.3.5.5 Reproductive and Developmental Toxicity—

In a two-generation reproduction study in rats, no evidence of reproductive toxicity was found at the highest dose tested of 6 mg/kg-d. The NOAEL for offspring toxicity was 1 mg/kg-d based on increased pituitary and uterine weights at the next higher dose of 6 mg/kg-d. A number of adverse effects were noted in a developmental study in rats (increased incidence of misaligned sternebrae, extra ribs, poor ossification). However, the study had a number of deficiencies and the US EPA recommended that it be repeated. In a study in rabbits, no developmental effects were noted at the highest dose tested of 1.8 mg/kg-d (IRIS, 1994).

5.3.5.6 Mutagenicity—

Results of mutagenicity assays of endosulfan are mixed, with multiple positive and negative studies (ATSDR, 1993a; HSDB, 1993; IRIS, 1999). Endosulfan has resulted in an increase in the percentage of aberrant colonies and the frequency of gene convertants and revertants in yeast and was genetically effective without activation. Longer duration of exposure increased effects (HSDB, 1993). In vivo assays have found chromosomal aberrations and gene mutations in mice (ATSDR, 1993a). However, some of these data may be suspect because some formulations contained epichlorohydrin, a known genotoxic chemical, as a stabilizer (ATSDR, 1993).

5.3.5.7 Carcinogenicity—

ATSDR has concluded that the available animal study data were negative or inconclusive (ATSDR, 1993b). EPA has classified endosulfan in Group E (evidence of noncarcinogenicity for humans) (U.S. EPA, 1999c).

5.3.5.8 Special Susceptibilities—

The limited toxicity data available for endosulfan suggest that several subgroups of the population may be more susceptible to endosulfan exposure than the general population. These subgroups include those with liver, kidney, immunological, or blood diseases; compromised immune systems such as AIDS patients, infants, and elderly people; hematologic disorders; seizure disorders; and low protein diets (see below) (ATSDR, 1993a).

> There is evidence from animal studies indicating that unborn and neonates may be more susceptible to the toxic effects of endosulfan because hepatic detoxification systems are immature and therefore unable to metabolize xenobiotic substances efficiently (ATSDR, 1993a).

5.3.5.9 Interactive Effects—

Human anecdotal information suggests that endosulfan may act synergistically with alcohol (ATSDR, 1993a). In rats, moderate protein deprivation doubled the toxicity of endosulfan (ATSDR, 1993a).

Pentobarbital and endosulfan have demonstrated an interactive effect that is probably related to microsomal enzyme activity. Endosulfan induces the mixed function oxidase system (ATSDR, 1993a). Vitamin A inhibited the endosulfan-induced activity of the mixed function oxidase system (ATSDR, 1993a).

5.3.5.10 Critical Data Gaps—

The increased susceptibility of female rats to endosulfan should be studied to determine the underlying cause and to evaluate whether the effect occurs with chronic species other than the rat.

Additional data are needed on the teratogenic and neurobehavioral effects during development resulting from endosulfan exposure. Current data do not provide a consistent picture nor do they explain underlying mechanisms of toxicity.

A joint team of scientists from ATSDR, NTP, and EPA have identified the following data gaps: acute oral exposure studies, mechanisms of anemia-inducing effects, reproductive system toxicity and related performance, developmental toxicity studies, mechanisms of immunotoxicity, sensitive neurological function and histological studies for long-term exposures, epidemiological studies, pharmacokinetics of intermediate and chronic duration exposures, and studies evaluating mechanisms underlying the differences in male and female toxicity. No ongoing studies were identified for endosulfan (ATSDR, 1993a).

5.3.5.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	6×10^{-3} mg/kg-d
Carcinogenicity	Group E (no evidence of carcinogenicity).

5.3.5.12 Major Sources—

ATSDR (1993a), HSDB (1993), IRIS (1999), U.S. EPA (1993g).

5.3.6 Endrin

5.3.6.1 Background—

Endrin is an organochlorine pesticide whose registration was canceled in 1984 (U.S. EPA, 1993a).

5.3.6.2 Pharmacokinetics—

Endrin, like the other organochlorine pesticides, is lipophilic. It bioaccumulates and is distributed in fat, the liver, the brain, and kidneys and is rapidly metabolized in mammals via oxidation of the methylene bridge. Metabolic products are probably more toxic than endrin and the toxic entity has been hypothesized to be 12-ketoendrin. In humans, this compound is excreted directly in urine and feces (ATSDR, 1990).

5.3.6.3 Acute Toxicity—

The primary target of endrin is the central nervous system (ATSDR, 1990).

5.3.6.4 Chronic Toxicity—

IRIS provides an RfD of 3×10^{-4} mg/kg-d based on a NOAEL of 0.025 mg/kg-d from a 1969 chronic exposure dog study that identified mild histological effects in the liver and occasional convulsions in study subjects exposed at the LOAEL of 0.05 mg/kg-d. Uncertainty factors of 10 each for inter- and intraspecies variability were applied (IRIS, 1999).

OPP tox one-liners list a 1959 2-year dog feeding study with a LOAEL of 0.015 mg/kg-d based on hypersensitivity in the neck and shoulder area. Increased erythropoiesis was noted at 0.125 mg/kg-d (U.S. EPA, 1993k). The LOAEL of 0.015 is within 1 order of magnitude of the LOAEL identified in the critical IRIS study.

5.3.6.5 Reproductive and Developmental Toxicity—

No developmental effects were listed in the IRIS file for endrin (IRIS, 1999). ATSDR listed a number of prenatal exposure studies that identified structural abnormalities and neurotoxicity associated with endrin exposure. Structural abnormalities have been observed in mice and hamsters exposed to endrin. These include fused ribs and cleft palate at 5 mg/kg-d for 3 prenatal days and webbed foot and open eye effects in hamster fetuses prenatally exposed for 1 day. Meningeocephaloceles in hamsters were caused by a single prenatal exposure "above" 1.5 mg/kg and fused ribs "above" 5 mg/kg in hamsters. In mice, a single prenatal exposure to 2.5 mg/kg caused an increase in open eyes. Exencephaly and fused ribs were seen with one exposure at 9 mg/kg endrin. A rat study reported no developmental effects with exposure to 0.45 mg/kg-d (it was not clear if behavioral effects were evaluated) (ATSDR, 1990). The variation in effects is probably due in part to the different prenatal periods during which exposure occurred (see ATSDR, 1990). Reproductive outcome was adversely affected in hamsters exposed to 1.5 mg/kg-d with decreased survival of pups (16 percent mortality) (ATSDR, 1990).

Nervous system effects are a significant concern with organochlorine exposure.

In hamsters, abnormally increased pup activity in hamsters was observed with 1.5 mg/kg prenatal exposures for 9 days. The NOAEL for these behavioral effects was 0.075 mg/kg-d (ATSDR, 1990). In rats, increased activity was seen with prenatal exposure to 0.3 mg/kg-d (ATSDR, 1990). Abnormally increased activity has been observed for other organochlorine pesticides (see DDT) and has been associated with probable altered learning ability and permanent structural changes to the brain.

As noted in the pharmacokinetics section above, endrin can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

5.3.6.6 Mutagenicity—

In vitro assays of endrin suggest that it is not genotoxic. There were no in vivo assay results located (ATSDR, 1990).

5.3.6.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of endrin. EPA has classified endrin as a Group D carcinogen (not classifiable as to human carcinogenicity). Some studies have yielded positive results and some studies that reported negative results were considered to be inadequate (IRIS, 1999). Tumors have been noted in the adrenal glands, pituitary glands, liver, mammary gland, uterus, and thyroid in various studies and multiple species (IRIS, 1999). Endrin is structurally related to a number of chemicals that are carcinogenic in test animals, including chlordane, aldrin, dieldrin, heptachlor, and chlorendic acid (IRIS, 1999). Because endrin has been classified as a Group D carcinogen, no cancer potency has been listed by EPA.

5.3.6.8 Special Susceptibilities—

ATSDR has reported that children may be more sensitive to acute endrin exposure than adults, based on effects observed in children during a poisoning incident. Children appeared more susceptible to neurotoxic effects and have exhibited convulsions. This is supported by results observed in experimental animals where young rats were more susceptible than adults (ATSDR, 1990).

In addition, the skeletal and behavioral abnormalities associated with endrin exposure in experimental animals indicate that prenatal exposure may generate special risks.

Based on animal studies, females may be more susceptible than males to endrin-induced toxicity (ATSDR, 1990).

5.3.6.9 Interactive Effects—

Dietary pretreatment with endrin potentiates the hepatotoxicity of carbon tetrachloride. MIXTOX has reported synergism between endrin and chlordane in mice with gavage exposure (MIXTOX, 1992).

5.3.6.10 Critical Data Gaps—

A joint team of researchers from ATSDR, NTP, and EPA have identified the following data gaps: human responses to acute, intermediate (14 to 365 days), and chronic exposures; subchronic reproductive tests in various species; immunotoxicity studies of animals and humans; human dosimetry studies; pharmacokinetic studies; and studies of interspecies differences in metabolism and toxicity (ATSDR, 1990).

5.3.6.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3×10^{-4} mg/kg-d
Carcinogenicity	Group D (not classifiable).

5.3.6.12 Major Sources—

ATSDR (1990), IRIS (1999), U.S. EPA (1993k).

5.3.7 Heptachlor Epoxide

5.3.7.1 Background—

Heptachlor epoxide is a breakdown product of the organochlorine pesticides heptachlor and chlordane and is a contaminant of both products. It is more toxic than either parent compound (ATSDR, 1993b). Although most uses of heptachlor were suspended in 1978 and chlordane was removed from the market in 1988 (U.S. EPA, 1993h), heptachlor epoxide continues to be a widespread contaminant due to its relatively long half-life.

5.3.7.2 Pharmacokinetics—

Based upon animal and limited human data, heptachlor epoxide is absorbed through the GI tract and is found primarily in the liver, bone marrow, brain, and fat, although it is distributed widely to other tissues as well. It is stored primarily in fat. Fetal blood levels were approximately four times those measured in women. Levels in human milk range from zero to 0.46 ppm (ATSDR, 1993b).

Heptachlor epoxide has a very long half-life, particularly in adipose tissue. Human tissue levels have correlated well to age, with 97 percent of North Texas residents tested (ages 41 to 60) having measurable levels. Based on the Texas study, heptachlor epoxide tissue levels have not decreased appreciably since the 1960s (ATSDR, 1993b).

5.3.7.3 Acute Toxicity—

The LD_{50}s for heptachlor range from 40 to 162 mg/kg in rodents (ATSDR, 1993b).

5.3.7.4 Chronic Toxicity—

IRIS provides an RfD of 1.3×10^{-5} mg/kg-d based on an LOAEL of 0.0125 mg/kg-d from a 60-week dog feeding study reported in 1958. The critical effect was increased liver-to-body-weight ratios in both males and females at the lowest dose tested. Uncertainty factors of 10 each were applied for inter- and intraspecies variability and the use of an LOAEL rather than a NOAEL (IRIS, 1999). No additional uncertainty factors were applied for the use of a less-than-lifetime study. The principal study is of low quality and there is low confidence in the RfD (IRIS, 1999).

Animal studies have identified the following effects associated with heptachlor (and subsequently heptachlor epoxide via metabolism) or heptachlor epoxide directly: elevated bilirubin and white blood cell count, increased serum creatinine phosphokinase levels suggestive of muscle damage, muscle spasms secondary to CNS stimulation, adrenal gland pathology, and neurological disorders (ATSDR, 1993b). Significant changes in EEG patterns were found in female adult rats exposed to 1 and 5 mg/kg-d for three generations (ATSDR, 1993b).

5.3.7.5 Reproductive and Developmental Toxicity—

A human study conducted in Hawaii was not considered adequate due to many study design deficiencies (ATSDR, 1993b). In another epidemiological study of women who had premature deliveries, significantly higher levels of heptachlor epoxide and other organochlorine pesticides were detected in sera (ATSDR, 1993b).

A 1973 two-generation dog reproductive study identified a NOAEL of 0.025 mg/kg-d with an LOAEL of 0.075 mg/kg-d with liver lesions in pups. Other studies with higher LELs based on a lethality endpoint are listed in the IRIS file. They were not used in this evaluation due to insufficient information. The IRIS file notes data gaps as rat and rabbit teratology studies (IRIS, 1999).

Exposure of adult rats to 6 mg/kg-d caused lens cataracts in 22 percent of the adults, 6 to 8 percent of the F1 generation offspring, and 6 percent of the F2 generation offspring. A rat study with exposure to 0.25 mg/kg-d occurring 60 days

prior to mating and during gestation resulted in severely reduced pup survival (15 percent) at 21 days postpartum (ATSDR, 1993b).

As noted in Section 5.3.7.2, heptachlor can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

A study of reproductive system toxicity with males and females dosed at 0.25 mg/kg-d prior to and during gestation found a significantly decreased pregnancy rate among exposed animals. Based on specific fertility tests, it was determined that males were most likely affected and that sperm were probably killed (ATSDR, 1993b). Another reproductive system toxicity study with doses at and above 0.075 mg/kg-d resulted in the failure of animals to reproduce. There were serious deficiencies in this study (ATSDR, 1993b).

5.3.7.6 Mutagenicity—

Mixed results have been obtained in mutagenicity assays of heptachlor epoxide.

5.3.7.7 Carcinogenicity—

Heptachlor epoxide is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer slope factor is 9.1 per mg/kg-d. This value is based on the geometric mean of several studies that identified liver carcinomas (IRIS, 1999). Five structurally related compounds have produced tumors in mice and rats: chlordane, aldrin, dieldrin, heptachlor, and chlorendic acid (IRIS, 1999).

Statistically significant increases in adenomas and carcinomas of the thyroid were found in female rats. Some researchers discounted the results due to the low incidence and known variability in the control population (ATSDR, 1993b).

Heptachlor (and consequently heptachlor epoxide) exposures have been associated with cerebral gliosarcoma in children exposed prenatally. Multiple chromosomal abnormalities were also identified in the tumor cells. It was not determined whether the effects were caused by environmental or familial factors (ATSDR, 1993b).

5.3.7.8 Special Susceptibilities—

Based on the toxicity data reviewed above, individuals with diseases or disorders of the following systems may be at greater risk than the general population: liver, hematopoietic, musculoskeletal, neurological, and adrenal gland. ATSDR has

noted that preadolescent children may be more susceptible due to their greater rate of glutathionine turnover (ATSDR, 1993b). In addition, children exposed prenatally may be at higher risk, based on the results of developmental toxicity studies.

5.3.7.9 Interactive Effects—

Heptachlor induces the mixed function oxidase system. No specific interactive effects have been noted.

5.3.7.10 Critical Data Gaps—

The IRIS file notes data gaps as rat and rabbit teratology studies (IRIS, 1999). A joint team of scientists from EPA, NTP, and ATSDR have identified the following data gaps: a model to describe the relationship between tissue and blood levels and exposure in humans, chronic oral exposure effects in humans, epidemiological and in vivo animal genotoxicity studies, developmental and reproductive toxicity studies and neurotoxicity and immunotoxicity studies in animals, and pharmacokinetic studies (ATSDR, 1993b).

5.3.7.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	1.3×10^{-5} mg/kg-d
Carcinogenicity	9.1 per mg/kg-d.

5.3.7.12 Major Sources—

ATSDR (1993b), IRIS (1999).

5.3.8 Hexachlorobenzene

5.3.8.1 Background—

Hexachlorobenzene was used as a fungicide on seeds of onions, sorghum, wheat, and other grains until 1984. It was also used in pyrotechnics and as a chemical intermediate but is no longer used commercially in the United States (ATSDR, 1996b).

5.3.8.2 Pharmacokinetics—

Hexachlorobenzene is persistent in the body, accumulating preferentially in fat and tissues with a high lipid content, because of its lipophilic nature. It is found in human breast milk (ATSDR, 1996b), which may be a significant route of exposure for young children. Hexachlorobenzene is also readily transferred through the placenta from the mother to the fetus in animal experiments. Hexachlorobenzene is very slowly converted by microsomal enzymes in the liver

to its major metabolites, pentachlorophenol, pentachlorothiphenol, and pentachlorobenzene, which are mainly excreted in the urine.

5.3.8.3 Acute Exposure—

Acute exposure studies in animals indicate a relatively low acute toxicity with LD_{50}s between 1,700 and 4,000 mg/kg (ATSDR, 1996b). Exposure to hexachlorobenzene does not appear to cause the acute neurological effects observed with the organochlorines that have been used as insecticides (e.g., DDT). Based on animal studies, the following systems are adversely affected following acute exposure: liver, kidney, hematological, endocrine, and dermal (ATSDR, 1996b).

5.3.8.4 Chronic Toxicity—

Hexachlorobenzene exposure of a large number of people in Turkey occurred between 1955 and 1959 due to consumption of contaminated grain. No precise exposure estimates are available for children or adults in this episode; it is likely that exposures occurred over a continuum, with some individuals consuming much higher levels than others. Researchers have estimated relatively low exposure levels occurred over several years as a result of consumption (50 to 200 mg/d). These exposure levels are approximately 0.7 to 2.9 mg/kg-d for a 70-kg individual. It should be emphasized that the exposure estimates are unverified (ATSDR, 1996b).

The following effects have been associated with hexachlorobenzene exposure in individuals exposed chronically via contaminated bread (Turkey): shortening of the digits due to osteoporosis, painless arthritis, decreased uroporphyrin synthase levels, muscle weakness, rigidity and sensory shading, thyroid enlargement, and histopathological changes in the liver often accompanied by skin lesions (ATSDR, 1996b). These effects were also observed in numerous animal studies (See discussion under Section 5.3.8.5 also.)

The hepatic system appears to be the most sensitive systemic endpoint for hexachlorobenzene exposure, IRIS provides an RfD value of 8×10^{-4} mg/kg-d based on a NOAEL of 0.08 mg/kg-d in a lifetime rat study. An uncertainty factor of 100 was applied; 10 for interspecies and 10 for intraspecies variability. Numerous other studies identified NOAELs in the same numerical range, so the confidence in the database is rated as high. The IRIS file notes that the sensitive endpoint of porphyria, which is an effect noted in exposed human populations, was not evaluated in the critical animal study, so the confidence in the RfD is rated as medium (IRIS, 1999).

5.3.8.5 Reproductive and Developmental Toxicity—

Lactational exposure to hexachlorobenzene is of significant concern, based on the rapid transfer of the chemical through breast milk and effects observed in children of exposed mothers in a contamination incident in Turkey. In a study of nursing infants, blood levels of hexachlorobenzene were two to five times that of their mothers; tissue levels were higher as well. A study of monkeys found that the concentration in milk was 17 times higher than that in maternal serum (ATSDR, 1996b). Young children (under 1 year) of lactating mothers who were exposed via contaminated bread had an extremely high mortality rate. Skin lesions, weakness, and convulsions were reported in these infants. Although adults were also adversely affected, children appeared to be at higher risk. The maternal exposure was roughly estimated to be 0.7 to 2.9 mg/kg-d (ATSDR, 1996b).

Among slightly older children (average age of 7), exposure via food resulted in the development of small or atrophied hands and fingers, short stature, pinched faces, osteoporosis in the hands, and other arthritic changes. Exposure was estimated to be approximately 0.7 to 2.9 mg/kg-d (ATSDR, 1996b).

It is known that hexachlorobenzene can cross the human placenta; however, no data were available on effects resulting from prenatal exposure in humans. Very limited information is available on experimental animals. Cleft palate and kidney abnormalities were observed in one study in a single litter and fetus at 100 mg/kg-d (ATSDR, 1996b). In another study, the survivability of prenatally exposed rats was significantly reduced at 2 mg/kg-d (estimated from ppm with conversion factor of 0.05 mg/kg per 1 ppm diet for rats). Death was attributed to maternal body burden and cumulative lactational exposure (ATSDR, 1996b). Alterations in immune function levels were reported in pre- and postnatally exposed rats at 4 mg/kg (ATSDR, 1996b).

As noted above, hexachlorobenzene accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If a female has been exposed to hexachlorobenzene, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

5.3.8.6 Mutagenicity—

The results of mutagenicity studies on hexachlorobenzene are mixed (IRIS, 1999). Hexachlorobenzene was negative in dominant lethal studies (in vivo) at doses from 60 to 221 mg/kg (ATSDR, 1996b).

5.3.8.7 Carcinogenicity—

Carcinogenic assays of hexachlorobenzene in animals have identified an increased incidence of multiple tumor types including hepatomas, hemangioendotheliomas, liver, and thyroid tumors in multiple species. EPA developed a cancer potency of 1.6 mg/kg-d based on liver carcinoma in female rats exposed via diet. In support of this value, cancer potencies were calculated for 14 different data sets; the results were within 1 order of magnitude. Hexachlorobenzene is classified as a probable human carcinogen (B2) based on the results of animal studies (IRIS, 1999).

Follow-up studies of exposure victims in Turkey have not identified cancers in the 25- and 20- to 30-year exposure cohorts; however, ATSDR suggests that the enlarged thyroids noted in members of these groups have not been sufficiently investigated (ATSDR, 1996b). It should also be noted that most cancers have multiple-decade latency periods and often occur in the later part of life. Consequently, it will not be possible to assess the carcinogenic impact of exposures in Turkey for some time.

5.3.8.8 Special Susceptibilities—

ATSDR has concluded that young children are susceptible to hexachlorobenzene exposure based on human poisoning episodes. Exposure led to permanent debilitating effects. Both human and animal data suggest that the risk of exposure to nursing infants may be greater than the risk to their mothers (ATSDR, 1996b).

Based on the toxicity data reviewed above, individuals with liver disease may be at greater risk than the general population.

5.3.8.9 Interactive Effects—

Hexachlorobenzene induces microsomal enzymes. Pentachlorophenol increases the porphyrinogenic effects of hexachlorobenzene. Hexachlorobenzene potentiated the thymic atrophy and body weight loss caused by 2,3,7,8-TCDD. A 50 percent food deprivation increased liver hypertrophy and microsomal enzyme induction by hexachlorobenzene (ATSDR, 1996b).

5.3.8.10 Critical Data Gaps—

A joint team of scientists from EPA, NTP, and ATSDR have identified the study following data gaps: human carcinogenicity, in vivo and in vitro genotoxicity, animal reproductive toxicity, animal developmental toxicity, immunotoxicity studies in humans, and pharmacokinetics (ATSDR, 1996b). Information is needed to develop a model that can be used to estimate the relationship between maternal intake, human milk concentration, and adverse effects in infants.

5.3.8.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	8×10^{-4} mg/kg-d
Carcinogenicity	1.6 per mg/kg-d.

5.3.8.12 Major Sources—

ATSDR (1996b), IRIS (1999).

5.3.9 Lindane (γ-hexachlorocyclohexane)

5.3.9.1 Background—

Lindane is an organochlorine pesticide that is comprised of isomers of hexachlorocyclohexane, with the γ isomer constituting the major (>99 percent) component. There appears to be some difference in toxicity of the various hexachlorocyclohexane isomers (U.S. EPA, 1993a). The following data assume that lindane can be defined as the γ isomer. Lindane is used primarily for controlling wood-inhabiting beetles and as a seed treatment. Lindane is also used as a prescription pharmaceutical to control head lice and mites (scabies) in humans.

5.3.9.2 Pharmacokinetics—

Lindane is readily absorbed by the GI tract following oral exposure. Distribution is primarily to the adipose tissue but also to the brain, kidney, muscle, spleen, adrenal glands, heart, lungs, blood, and other organs. It is excreted primarily through urine as chlorophenols. The epoxide metabolite may be responsible for carcinogenic and mutagenic effects (ATSDR, 1994c).

Male exposure to lindane through the environment results in accumulation in testes and semen in addition to the tissues listed above (ATSDR, 1994c). See also a discussion in Section 5.3.9.5 of the accumulation of lindane by pregnant women.

5.3.9.3 Acute Toxicity—

The estimated human lethal dose is 125 mg/kg (HSDB, 1993). Occupational and accidental exposures in humans have resulted in headaches, vertigo, abnormal EEG patterns, seizures, and convulsions. Death has occurred primarily in children.

5.3.9.4 Chronic Toxicity—

IRIS provides an RfD of 3×10^{-4} mg/kg-d based on a NOAEL of 0.33 mg/kg-d from a subchronic rat study that found liver and kidney toxicity at higher doses. Uncertainty factors of 10 each for inter- and intraspecies variability and the use

of a less-than-lifetime study were applied (IRIS, 1999). The confidence in the principal study, database, and RfD are rated as medium. A recently completed 2-year study is under evaluation and may provide additional information regarding toxicity (U.S. EPA, 1993i). Liver damage has been observed in many animal studies and appears to be the most sensitive effect (U.S. EPA, 1993i). Immune system effects have been observed in humans exposed via inhalation and in orally dosed animals. A 5-week study in rabbits found immunosuppression at 1 mg/kg-d (ATSDR, 1994c).

Most observed effects in humans exposed accidentally to lindane are neurological. Behavioral effects have also been noted in many studies on experimental animals, and at relatively high levels seizures were reported. More subtle behavioral effects were noted at an LOAEL of 2.5 mg/kg-d with 40 days of exposure in rats. No NOAEL was reported (ATSDR, 1994c).

5.3.9.5 Reproductive and Developmental Toxicity—

Two developmental toxicity studies in rats and rabbits both identified a NOAEL of 10 mg/kg (no effects were described for higher doses). A three-generation rat study found no adverse reproductive effects at 5 mg/kg-d, the highest dose tested (U.S. EPA, 1993i). A recent mouse study found increased resorptions at 5 mg/kg-d. Studies in rats and mice have found increased incidence of extra ribs at 5 to 20 mg/kg-d (ATSDR, 1994c). There are multiple studies showing pre- and postimplantation fetotoxicity and skeletal abnormalities resulting from prenatal exposure at higher doses (HSDB, 1993).

Lindane accumulates in the fatty tissue of pregnant (and nonpregnant) women where it can be transferred to the fetus through the placenta and to infants through breast milk. Human milk concentrations are approximately five to seven times greater than maternal blood levels. Concentrations in maternal blood are proportional to the length of time over which exposure occurred, with older women having higher blood levels. During pregnancy, the lindane concentration in blood from fetal tissue, uterine muscle, placenta, and amniotic fluid was higher than levels in maternal adipose tissue, and blood serum levels increased during delivery (ATSDR, 1994c). There is little information on the effects of exposure during lactation. One study (dose unspecified) in rats indicated that exposure during gestation and lactation did not cause developmental effects; however, this is not consistent with other studies that found effects associated with gestational exposure.

Based on what is known regarding the transfer of lindane into human milk, nursing infants must be considered at some risk if their mothers have been exposed to significant amounts of lindane (lindane is a lipid-seeking chemical). Additional information is needed to characterize the relationship between maternal intake, body burden (blood or adipose levels), milk concentrations, and adverse effects.

Multiple studies have reported that lindane exposure (as measured by body tissue level of lindane) is associated with premature labor and spontaneous abortions. The causal relationship has not been established for this action (ATSDR, 1994c); however, the reproductive system effects discussed in Section 5.3.9.4 (biochemical changes in uterine, cervical, and vaginal tissues and antiestrogenic effects) may be involved.

As noted above, lindane accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Two recent reproductive studies in rats found adverse effects on the male reproductive system. In a 7-wk study, decreased sperm counts were noted at 50 mg/kg-d and, in a 180-d study, seminiferous tubular degeneration was noted at 6 mg/kg-d with a NOAEL of 3 mg/kg-d. An older study had identified the same effects at 64.6 mg/kg-d in a 3-mo study. Experimental data indicate that the female reproductive system may also be altered by lindane exposure. A study of rats found uterine, cervical, and vaginal biochemical changes at 20 mg/kg-d in a 30-d study. Antiestrogenic effects were found at 20 mg/kg-d in female rats in a 15-wk study with a NOAEL of 5 mg/kg-d. This action was also found in two other recent studies (ATSDR, 1994c).

5.3.9.6 Mutagenicity—

In animals, ingestion of technical-grade hexachlorocyclohexane-induced dominant lethal mutations in mice. Studies found that lindane binds to mouse liver DNA at a low rate. Based on a review of genotoxicity studies, ATSDR concluded that lindane "has some genotoxic potential, but the evidence for this is not conclusive" (ATSDR, 1994c).

5.3.9.7 Carcinogenicity—

Lindane has been classified as Group B2/C (probable/possible human carcinogen) (U.S. EPA, 1999c) and a cancer potency of 1.3 per mg/kg-d has been listed (HEAST, 1997). Lindane's related isomers, alpha and beta hexachlorocyclohexane, are classified as probable human carcinogens and have cancer potencies similar to that of lindane. In addition to tumors identified in experimental animals, human study data indicate that this chemical may cause aplastic anemia (U.S. EPA, 1993a).

5.3.9.8 Special Susceptibilities—

ATSDR has recommended that pregnant and/or lactating women should not be exposed to lindane. The potential for premature labor and spontaneous abortion is noted (ATSDR, 1994c). People with epilepsy, cerebrovascular accidents, or head injuries who have lower thresholds for convulsions may be at greater risk of lindane-induced CNS toxicity and seizures. Also, individuals with protein-deficient diets, liver or kidney disease, or immunodeficiencies may be at greater risk from lindane exposure than the general population (ATSDR, 1994c).

Children may also be at greater risk from lindane exposure because of the immaturity of their immune and nervous systems. ATSDR has cautioned that:

> Infants and children are especially susceptible to immuno-suppression because their immune systems do not reach maturity until 10 to 12 years of age (ATSDR, 1994c).

5.3.9.9 Interactive Effects—

High- and low-protein diets and vitamin A and C deficiencies increased the toxicity of lindane in experimental animals. Vitamin A supplements decreased toxicity. Cadmium inhibited the metabolism of lindane. Combined cadmium and lindane exposure caused significant embryotoxic and teratogenic effects in rats at dosages that caused no effects when administered alone. Exposure to the α, β, and δ hexachlorocyclohexane isomers may reduce the neurotoxic effects of lindane (ATSDR, 1994c).

MIXTOX has reported mixed results for studies of lindane and chlordane, lindane and hexachlorobenzene, lindane and toxaphene, and lindane and mirex interactions, including inhibition, no effect, and potentiation for these combinations in rodents exposed via gavage (MIXTOX, 1992).

5.3.9.10 Critical Data Gaps—

As discussed above, effects on both the male and female reproductive systems have been evaluated in short-term studies. Evaluation of these effects in a longer-term study and identification of the underlying mechanisms of toxicity would provide information needed for a more complete evaluation of toxicity and dose-response dynamics. Additional information is also needed, as noted in Section 5.3.9.5, on the potential for exposure via lactation and on mechanisms and dose-response for premature labor and spontaneous abortion.

ATSDR has identified data gaps that include chronic duration oral studies; in vivo genotoxicity tests; reproductive, developmental immunotoxicity, and neurotoxicity studies; human studies correlating exposure levels with body burdens of lindane and with specific effects; and pharmacokinetic studies (ATSDR, 1994c).

5.3.9.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3×10^{-4} mg/kg-d
Carcinogenicity	1.3 per mg/kg-d.

5.3.9.12 Major Sources—

ATSDR (1994c), HSDB (1993), IRIS (1999).

5.3.10 Mirex

5.3.10.1 Background—

Mirex was used as both an organochlorine pesticide and fire retardant from the late 1950s until 1975 (U.S. EPA, 1993a). A major use of mirex was for the control of ants, particularly fire ants in the southern United States. Mirex has the potential to concentrate many thousandfold in food chains (Hayes and Laws, 1991).

5.3.10.2 Pharmacokinetics—

Mirex is a lipophilic compound and is readily taken up in fat tissue. The highest residues were found in fat and the liver. Based on a study in cows, it is also found in milk. At 0.01- and 1-ppm dietary exposure for 32 weeks, cows' milk levels were 0.01 to 0.08 ppm (U.S. EPA, 1993m).

No clear data on half-life in humans were found; however, studies in primates found that 90 percent of the original dose was retained in fat after 106 days. The researchers predicted that mirex had an extremely long half-life in monkeys. Based on this, mirex would be expected to have a very long half-life in humans.

5.3.10.3 Acute Toxicity—

Acute hepatic effects have been observed in experimental animals. These may result from the following cytological effects: disaggregated ribosomes, glycogen depletion, formation of liposomes, and proliferation of smooth endoplasmic reticulum (U.S. EPA, 1993m).

5.3.10.4 Chronic Toxicity—

IRIS lists a chronic exposure RfD of 2×10^{-4} mg/kg-d for mirex based on a NOAEL of 0.07 mg/kg-d from a chronic (2-year) dietary rat study. Effects noted in the study at higher doses were: splenic fibrosis, nephropathy, renal medullary hyperplasia, multiple types of liver damage, and cystic follicles of the thyroid. The RfD is based on the latter two critical effects. Uncertainty factors of 10 each were applied for inter- and intraspecies variability and a factor of 3 was applied for lack of a complete database (multigenerational data on reproductive effects and cardiovascular toxicity data). The IRIS file also indicates that effects on the testes

(testicular degeneration, hypocellularity, and depressed spermatogenesis), which were noted in other studies, may not have been detected in the critical study because of age-related degenerative changes in the study animals (IRIS, 1999).

5.3.10.5 Reproductive and Developmental Toxicity—

Studies in animals suggest that both male and female reproductive systems are adversely affected by mirex. Acute exposure of male rats to 6 mg/kg-d mirex daily for 10 days decreased their fertility significantly. Although residues of mirex were found in the testes of the 6-mg/kg-d dose-group males, this did not affect reproduction parameters in subsequent mating trials. The authors attributed the observed decrease in the incidence of pregnancy in females mated with males in this dose group to a subclinical toxic effect as suggested by reduction in body weight gain in the dosed males (ATSDR, 1995a).

In a 28-day dietary study, decreased sperm count was noted in male rats at dosages as low as 0.025 mg/kg-d; testicular degeneration was observed at dosage levels of 2.5 and 3.7 mg/kg-d. However, mirex fed to rats at 1.3 to 3.1 mg/kg-d for two generations resulted in no decrease in fertility. In contrast, females given 1.8 to 2.8 mg/kg-d for two generations produced a decreased number of litters. Administration of 0.25 mg/kg-d to male and female rats for 91 days prior to mating and then through lactation resulted in decreased mating and litter size (ATSDR, 1995a).

Exposure of maternal rats and mice during gestation resulted in increases in resorptions and stillbirths and decreases in postnatal viability at doses as low as 1.25 mg/kg-d when administered from gestation days 4 through 22. Examination of fetuses at the end of gestation showed increases in the incidence of edematous fetuses and fetuses with cardiac arrhythmia; the incidence was slightly increased at doses as low as 0.1 mg/kg-d. Additional effects were reported in a few studies and included enlarged cerebral ventricles; undescended testes; cleft palate; short tail; decreased skeletal ossification, fetal weight, and liver and kidney weights; and liver and thyroid lesions. Cataracts were also observed in offspring in several studies from pre- and postnatal exposures (ATSDR, 1995a).

5.3.10.6 Mutagenicity—

Most genotoxicity tests reported in the tox one-liners are bacterial assays and are negative (U.S. EPA, 1993m). A dominant lethal mutagenicity test in rats (in vivo) found a decreased incidence of pregnancy at 6 mg/kg-d with a NOEL of 3 mg/kg-d. Exposure took place over 10 days prior to mating. However, parameters indicative of dominant lethality were unaffected by treatment (ATSDR, 1995a)

5.3.10.7 Carcinogenicity—

A marked increased incidence in neoplastic nodules in the liver of both male and female rats was observed in a 2-year feeding study with mirex (NTP, 1990). This effect was noted at doses of 0.7 mg/kg-d and above in males and at 3.8 mg/kg-d and above in females. In addition, increased tumors of the adrenal gland in male rats and mononuclear cell leukemias in female rats were observed. EPA's Office of Pesticide Programs has classified mirex as Group B2 (probable human carcinogen) (HEAST, 1997). In addition, NTP considers mirex as "reasonably anticipated to be a human carcinogen" based on sufficient evidence of carcinogenicity in experimental animals (NTP, 2000).

5.3.10.8 Special Susceptibilities—

Juveniles may be more susceptible than adults based on the results of animal studies. At 60 ppm (approximately 3 mg/kg-d), adult mice exposed for 15 days experienced only weight loss; this level was lethal for young mice (Hayes and Laws, 1991).

Based on a review of the toxicity data above, individuals with diseases or disorders of the following organ systems may be at higher risk than the general population: kidney, liver, spleen, thyroid, parathyroid, cardiovascular, and male reproductive. Due to the developmental toxicity observed in experimental animals, prenatal exposure and lactation exposure may pose a risk to children. The possibility exists that newborn children may also develop cataracts if exposed to mirex shortly after birth (ATSDR, 1995a).

5.3.10.9 Interactive Effects—

Mirex induces the mixed function oxidase system. No specific interactive effects have been noted.

MIXTOX reports mixed results for interactions between lindane and mirex and for Aroclor 1254 and mirex. Other studies of Aroclor and mirex have not found interactive results (MIXTOX, 1992).

5.3.10.10 Critical Data Gaps—

Additional information is needed on the developmental effects of mirex to identify a NOAEL for sensitive developmental toxicity endpoints so that a well-founded exposure limit for developmental effects can be determined. In a related area, the mutagenicity data indicate a potential mutagenic effect based on in vivo studies. A better understanding of the relationship between the results of these types of studies and mutagenic effects in the human population is needed. The chronic exposure toxicity studies do not provide consistent results. Additional clarification of the NOAELs for sensitive endpoints in this area is needed.

5.3.10.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	2×10^{-4} mg/kg-d
Carcinogenicity	Group B2 (probable human carcinogen).

5.3.10.12 Major Sources—

ATSDR (1995a), Hayes and Laws (1991), IRIS (1999), U.S. EPA (1993m).

5.3.11 Toxaphene

5.3.11.1 Background—

Toxaphene is an organochlorine pesticide that is comprised of a mixture of at least 670 chlorinated camphenes. Toxaphene was probably the most heavily used pesticide in the United States during the 1970s after DDT was banned. It was banned for most uses in 1982; all uses were banned in 1990. However, due to its relatively long half-life, it persists in the environment. The soil half-life is approximately 1 to 14 years (HSDB, 1993).

5.3.11.2 Pharmacokinetics—

The components of toxaphene are metabolized in mammals via dechlorination, dehydrodechlorination, and oxidation, primarily through the action of the mixed function oxidase system and other hepatic microsomal enzymes. Conjugation may occur but is not a major route of metabolism. Each component of toxaphene has its own rate of biotransformation, making the characterization of toxaphene pharmacokinetics complex. Some components of toxaphene are highly lipophilic and poorly metabolized; these components may accumulate in body fat (ATSDR, 1996c).

5.3.11.3 Acute Toxicity—

Acute high-level exposures to toxaphene and toxaphene-contaminated food have resulted in death in adults and children with an estimated minimum lethal dose of 2 to 7 g, which is equivalent to 29 to 100 mg/kg for an adult male. LD_{50} values in rats were 80 mg/kg for females and 90 mg/kg for males. Transient liver and kidney effects, and periods of memory loss have been observed in humans after single large oral exposures. In animals, the most sensitive organ is the liver. Toxicity to the central nervous system, kidney, and adrenal glands have also been observed (ATSDR, 1996c).

5.3.11.4 Chronic Toxicity—

IRIS does not provide a discussion of chronic effects of exposure to toxaphene or an RfD (IRIS, 1999). An RfD of 2.5×10^{-4} mg/kg-d is listed in the Office of

Pesticide Program's Reference Dose Tracking Report (U.S. EPA, 1997c) and has been agreed upon by the Office of Pesticide Programs and the Office of Water.

Chronic exposure to toxaphene may result in damage to the following organ systems: liver, kidney, adrenal, immunological, and neurological. Chronic exposure to toxaphene may cause hormonal alterations. A study on chronic exposures found increased levels of hepatic metabolism of the hormones estradiol and estrone and a decrease in their uterotropic action. Some adverse effects of toxaphene that do not occur with a single exposure may result from repeated exposures. Exposures at 0.06 mg/kg-d over 5 weeks caused adrenal hormone reductions, whereas a single dose of 16 mg/kg did not cause effects.

5.3.11.5 Reproductive and Developmental Toxicity—

Women exposed to toxaphene by entering a field that had recently been sprayed with the chemical exhibited a higher incidence of chromosomal aberrations in cultured lymphocytes than did unexposed women. Dermal and inhalation were the probable routes of exposure; however, the exposure was not quantified (ATSDR, 1996c). Animal study results suggest that toxaphene does not interfere with fertility in experimental animals at the doses tested (up to 25 mg/kg-d) (ATSDR, 1996c).

Adverse developmental effects, including immunosuppressive and behavioral effects, were noted in experimental animals at levels below those required to induce maternal toxicity. Immunosuppression (reduction in macrophage levels, cell-mediated immunity, and humoral immunity) was observed in test animals exposed during gestation and nursing as were alterations in kidney and liver enzymes and delayed bone development. Other adverse effects noted in offspring of maternally exposed individuals included histological changes in the liver, thyroid, and kidney (ATSDR, 1996c).

Toxaphene is known to be rapidly conveyed into breast milk after maternal exposure to the chemical. The half-life of toxaphene in milk has been estimated at 9 days.

As noted above, toxaphene accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. Therefore, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden.

Depending on the timing and extent of an individual's prior exposure to toxaphene, the outcome of pregnancy may be affected even if exposure during pregnancy is reduced.

5.3.11.6 Mutagenicity—

Changes in human genetic material have been noted in workers exposed to toxaphene (HSDB, 1993). There are also numerous positive mutagenicity assays of toxaphene: the Ames test, sister chromatid exchange, chromosomal aberrations in toxaphene-exposed humans, and forward mutation assays. The implications of this for human germ cells are not known. One assay designed to assess the effects of dominant lethal effects on implantations in mice yielded negative results. Some data suggest that the polar fraction of toxaphene may be more mutagenic than the nonpolar fraction (ATSDR, 1996c; HSDB, 1993).

5.3.11.7 Carcinogenicity—

Toxaphene is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals (IRIS, 1999). No conclusive human epidemiological studies are available for toxaphene (ATSDR, 1996c). Oral administration of toxaphene resulted in an increased incidence of hepatocellular carcinomas and neoplastic nodules in mice, and thyroid tumors in rats (IRIS, 1999). The cancer potency is 1.1 per mg/kg-d, based on liver tumors in experimental animals (IRIS, 1999).

Toxaphene has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells (Soto et al., 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis et al., 1993). In addition to potential carcinogenic effects, toxaphene may also cause disruption of the endocrine system due to its estrogenic activity (Soto et al., 1994).

5.3.11.8 Special Susceptibilities—

A protein-deficient diet may increase the toxicity of toxaphene approximately threefold based on an LD_{50} study in rats (ATSDR, 1996c). Individuals with latent or clinical neurological diseases, such as epilepsy or behavioral disorders, may be at higher risk for toxaphene toxicity. In addition, children may be especially susceptible to toxaphene-induced neurotoxicity based on early reports of acute ingestion toxicity (ATSDR, 1996c).

Other individuals who may be at higher risk are those with diseases of the renal, nervous, cardiac, adrenal, and respiratory systems. Individuals using certain medications are also at potential risk due to the induction of hepatic microsomal enzymes by toxaphene (discussed further in the following section).

5.3.11.9 Interactive Effects—

Metabolism of some drugs and alcohol may be affected by toxaphene's induction of hepatic microsomal enzymes. This was observed in a man using warfarin as an anticoagulant while he used toxaphene as an insecticide. The effectiveness of the drug was reduced because toxaphene's induction of microsomal enzymes increased the drug's metabolism (ATSDR, 1996c).

Based on acute studies in animals and anecdotal reports of acute exposure in humans, exposure to chemicals that increase microsomal mixed-function oxidase systems (e.g., lindane) are likely to reduce the acute toxicity of other chemicals detoxified by the same system (e.g., toxaphene) because the system is functioning at a higher than normal level. Toxaphene, in turn, may reduce the acute toxicity of chemicals that require this system for detoxification (ATSDR, 1996c).

5.3.11.10 Critical Data Gaps—

The following data gaps have been identified for toxaphene: mammalian germ cell genotoxicity, studies that investigate sensitive developmental toxicity endpoints including behavioral effects, epidemiological and animal studies of immunotoxicity, long-term neurotoxicity studies in animals using sensitive functional and neuropathological tests and behavioral effects on prenatally exposed animals, epidemiological studies evaluating multiple organ systems, and pharmacokinetic studies (ATSDR, 1996c).

5.3.11.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	2.5×10^{-4} mg/kg-d
Carcinogenicity	1.1 per mg/kg-d.

5.3.11.12 Major Sources—

ATSDR (1996c), HSDB (1993), IRIS (1999).

5.4 ORGANOPHOSPHATE PESTICIDES

Please note that these analytes are currently undergoing reassessment by the EPA under the provisions of the Food Quality Protection Act of 1996. This reassessment may result in changes in the RfD values. Contact EPA for the most current information.

5.4.1 Chlorpyrifos

5.4.1.1 Background—

Chlorpyrifos is an organophosphate insecticide first registered in 1965 and used throughout the United States. Chlorpyrifos is used to control foliar and soil insects for a wide variety of crops. While most use is agricultural, significant amounts of chlorpyrifos are used in urban settings for termite control and commercial landscape maintenance and pest control. Chlorpyrifos formulations (e.g., Dursban) are also used by the general public for home, lawn, and garden insect control.

5.4.1.2 Pharmacokinetics—

Chlorpyrifos accumulates in fat and has a longer half-life in fatty tissues than in other tissues. It has been detected in cows' milk (HSDB, 1993) and would be expected to occur in human milk of exposed mothers. This is of concern because organophosphates may have a higher toxicity for immature individuals than adults (e.g., malathion was more toxic to juveniles in three species tested) (U.S. EPA, 1992f). Chlorpyrifos is rapidly metabolized and excreted based on studies in animals (Hayes and Laws, 1991).

5.4.1.3 Acute Toxicity—

Effects commonly associated with acute high-level exposure to chlorpyrifos include the following: headache, dizziness, weakness, incoordination, muscle twitching, tremor, nausea, abdominal cramps, diarrhea, sweating, blurred or dark vision, confusion, tightness in the chest, wheezing, productive cough, pulmonary edema, slow heartbeat, salivation, tearing, toxic psychosis with manic or bizarre behavior, influenza-like illness with weakness, anorexia, malaise, incontinence, unconsciousness, and convulsions (HSDB, 1999).

5.4.1.4 Chronic Toxicity—

IRIS provides an oral RfD of 0.003 mg/kg-d based on a NOAEL in a 20-day study reported in 1972 that found cholinesterase inhibition in adult male humans after 9 days of exposure. There were four subjects per dosed group. An uncertainty factor of 10 was used to calculate the RfD (IRIS, 1999). There are limitations in the use of this study for a chronic toxicity RfD. Although effects were observed at levels lower than the NOAEL, they were discounted due to an inability to

achieve statistical significance; however, it is very difficult to achieve statistical significance with four subjects. No uncertainty factor was applied for the acute nature of the study. Most important, EPA is reviewing its methods for evaluating cholinesterase inhibitors. Cholinesterase inhibition alone is not necessarily considered an adverse effect in the absence of other effects. The value listed on IRIS was confirmed in 1993 by an Office of Pesticide Programs RfD Peer-Review Committee (U.S. EPA, 1993c).

Other chronic exposure effects have been observed in study animals. In a 1991 two-generation rat study, adrenal lesions were reported at 1 and 5 mg/kg-d. In a subchronic study at higher doses, the same effects were observed along with increased brain and heart weight (U.S. EPA, 1992f).

There are significant uncertainties regarding an appropriate threshold for effects of chlorpyrifos exposure. These include the very limited data on the recently identified adrenal and cardiac effects of chlorpyrifos and the utility of a cholinesterase endpoint. The IRIS value was used to calculate fish consumption limits shown in Section 4 for chronic toxicity. Future improvements in the database may result in alteration in this recommended value.

5.4.1.5 Reproductive and Developmental Toxicity—

Chlorpyrifos has been evaluated for developmental toxicity in mice, rats, and rabbits (U.S. EPA, 2000b). Most studies only show effects at doses that cause maternal toxicity due to cholinesterase inhibition (i.e., $\geq$ 5 mg/kg-d). However, in a study where observations were carried out to postnatal day 66, delayed alterations in brain development were noted in offspring of rats receiving 1.0 mg/kg-d. Decreases in measurements of the parietal cortex were observed in females. In addition, several studies show that neonates and young animals are more susceptible to chlorpyrifos-induced cholinesterase inhibition than adults (U.S. EPA, 2000b). For these reasons, a Population Adjusted Dose has been calculated to provide extra protection for infants, children, and women of childbearing age.

5.4.1.6 Mutagenicity—

Chlorpyrifos was not mutagenic in bacteria or mammalian cells. Slight genetic alterations in yeast and DNA damage in bacteria have been observed. Chlorpyrifos did not induce chromosome aberrations in vitro, was not clastogenic in the mouse micronucleus test in vivo, and failed to induce unscheduled DNA synthesis in isolated rat hepatocytes (U.S. EPA, 2000b).

5.4.1.7 Carcinogenicity—

Chlorpyrifos did not increase cancer incidence in 2-yr feeding studies in mice and rats (U.S. EPA, 1992f). EPA has classified chlorpyrifos as Group E (evidence of noncarcinogenicity for humans) (U.S. EPA, 1999c).

5.4.1.8 Special Susceptibilities—

There is a recognized human population that may be at high risk with respect to organophosphate exposure. Approximately 3 percent of the human population has an abnormally low plasma cholinesterase level resulting from genetic causes. These people are particularly vulnerable to cholinesterase-inhibiting pesticides. Others at greater risk include persons with advanced liver disease, malnutrition, chronic alcoholism, and dermatomyositis because they exhibit chronically low plasma cholinesterase activities. Red blood cell (RBC) acetylcholinesterase is reduced in certain conditions such as hemolytic anemias; people with these conditions may be at greater risk than the general population from exposure to organophosphates (U.S. EPA, 1999).

5.4.1.9 Interactive Effects—

No data were located. However, it is possible that coexposure to compounds with a similar mechanism of action (i.e., organophosphate and carbamate pesticides) may result in additive or synergistic effects.

5.4.1.10 Critical Data Gaps—

Data are needed on potential noncholinesterase effects of chronic exposure and on the mechanism of toxicity that underlies the alterations in brain development observed in the offspring of chlorpyrifos-treated rats. Additionally, toxicokinetic data are needed to explain the differential extent of cholinesterase inhibition between adult and young animals.

5.4.1.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3×10^{-4} mg/kg-d (3×10^{-5} mg/kg-d for infants, children, and women ages 13-50)
Carcinogenicity	Group E (evidence of noncarcinogenicity for humans).

5.4.1.12 Major Sources—

HSDB (1993), IRIS (1999), U.S. EPA (1992f, 2000b).

5.4.2 Diazinon

5.4.2.1 Background—

Diazinon is an organophosphorus insecticide that has been used widely since its introduction in 1952. Most use is agricultural, although diazinon formulations are also used commercially and by the general public for home, lawn, and garden insect control.

5.4.2.2 Pharmacokinetics—

Diazinon is converted in the liver into its active form diazoxon. Both diazinon and diazoxon are rapidly deactivated by esterases in the blood and liver. Animal studies indicate that diazinon and its metabolites are cleared from all tissues in the body within 12 days after single exposures (ATSDR, 1996d). Human milk may contain trace amounts of diazinon based on the results of exposure in cows (HSDB, 1993).

5.4.2.3 Acute Toxicity—

Diazinon is highly toxic. The estimated adult oral fatal dose is approximately 25 g (HSDB, 1993). Toxic effects are seen in the central and peripheral nervous system due to inhibition of cholinesterase.

5.4.2.4 Chronic Toxicity—

There is currently no IRIS file for diazinon. However, OPP provides an RfD of 7×10^{-4} mg/kg-d based on a NOAEL of 0.025 mg/kg-d observed for plasma cholinesterase inhibition in a human study. The uncertainty factor was 30:10 for intraspecies variability and 3 for the protection of infants and children (U.S. EPA, 1998b).

Very little dose-response data are available on chronic systemic toxicity other than cholinesterase effects. Hematocrit depression was observed in a rat chronic feeding study at 50 mg/kg-d. Gastrointestinal disturbances were noted at 5 mg/kg-d with a NOEL of 0.05 mg/kg-d in a chronic monkey study (U.S. EPA, 1993d). If an alternative to cholinesterase inhibition is required, the monkey study can be used with standard uncertainty factors that take into consideration inter- and intraspecies variability.

5.4.2.5 Reproductive and Developmental Toxicity—

The reproductive/teratogenic studies listed in the tox one-liners report no adverse effects at the highest doses tested (U.S. EPA, 1993d).

HSDB reported multiple studies indicating diazinon is teratogenic; however, the relevance of these studies is questionable since they were not conducted using standard protocols and administration of diazinon was by parenteral routes. In a prenatal exposure study (dose not specified), multiple doses of diazinon resulted in a higher incidence of urinary malformations, hydronephrosis, and hydroureter. Diazinon was teratogenic in rats administered a single dose on day 11 of gestation. Decreased fetal body weight was the most sensitive indicator. No dose was specified in the database (HSDB, 1993). In chicks, diazinon exposure led to abnormal vertebral column development including a tortuous and shortened structure with abnormal vertebral bodies. In the neck region, the vertebral bodies had fused neural arches and lacked most intervertebral joints. More severe

effects on other elements of the skeleton were observed at higher doses (HSDB, 1993; Hayes, 1982). The dose (1 mg/egg) is not easily convertible to a mammalian dose.

Behavioral effects were observed in mice exposed prenatally at 0.18 and 9 mg/kg-d throughout gestation. The high-dose group showed decreased growth, several behavioral effects, and structural pathology of the forebrain. The low-dose group did not have brain pathology or growth abnormalities; however, they showed small but measurable defects in behavior and a delay in reaching maturity (ATSDR, 1996d)

5.4.2.6 Mutagenicity—

Most mutagenicity assays were negative; one positive sister chromatid exchange assay was noted (U.S. EPA, 1993d). A study on the effect of diazinon on mitosis in human lymphocytes reported chromosomal aberrations in 74 percent of the cells at 0.5 mg/mL (HSDB, 1993).

5.4.2.7 Carcinogenicity—

No evidence of carcinogenicity was observed in several long-term feeding studies with diazinon in rodents (ATSDR, 1996d). EPA has classified diazinon as "not likely" to be a human carcinogen (U.S. EPA, 1999c).

5.4.2.8 Special Susceptibilities—

There is a recognized human population that may be at high risk with respect to organophosphate exposure. Approximately 3 percent of the human population has an abnormally low plasma cholinesterase level resulting from genetic causes. These people are particularly vulnerable to cholinesterase-inhibiting pesticides. Others at greater risk include persons with advanced liver disease, malnutrition, chronic alcoholism, and dermatomyositis because they exhibit chronically low plasma cholinesterase activities. Red blood cell (RBC) acetylcholinesterase is reduced in certain conditions such as hemolytic anemias; people with these conditions may be at greater risk than the general population from exposure to organophosphates (U.S. EPA, 1999).

5.4.2.9 Interactive Effects—

MIXTOX has reported antagonistic effects between diazinon and toxaphene with exposure in rats via gavage (MIXTOX, 1992).

5.4.2.10 Critical Data Gaps—

OPP lists the following data gaps: reproduction study in rats, chronic feeding oncogenicity study in rats, and chronic feeding study in dogs (U.S. EPA, 1992d). A multigeneration reproductive study that evaluated developmental effects at low

doses and defined a NOAEL would be useful in establishing an appropriate RfD.

5.4.2.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	7×10^{-4} mg/kg-d based on cholinesterase inhibition
Carcinogenicity	"Not likely" to be a human carcinogen.

5.4.2.12 Major Sources—

ATSDR (1996d), Hayes (1982), HSDB (1993), U.S. EPA (1993d).

5.4.3 Disulfoton (Disyston)

5.4.3.1 Background—

Disulfoton is an organophosphate pesticide used on a wide variety of crops; major uses are on corn, wheat, potatoes, and cotton. It is also used on fruit and nut trees and ornamental plants.

5.4.3.2 Pharmacokinetics—

Disulfoton is readily absorbed after ingestion. Metabolism of disulfoton involves sequential oxidation of the thioether sulfur and/or oxidative desulfuration in addition to hydrolytic cleavage. The major metabolites are the sulfoxide acid sulfone analogs of the compound. These are toxic metabolites that are degraded rapidly to water-soluble nontoxic metabolites. Their estimated half-life is 30 to 32 hours (U.S. EPA, 1993f). Disulfoton is rapidly absorbed through the mucous membrane of the digestive system and conveyed by the blood to body tissues. The kidneys are the main route of elimination of the metabolites (HSDB, 1993).

5.4.3.3 Acute Toxicity—

The acute oral LD_{50} in animals ranges from 2 to 27.5 mg/kg (U.S. EPA, 1993f). Disulfoton is highly toxic to all mammals by all routes of exposure (HSDB, 1993).

5.4.3.4 Chronic Toxicity—

IRIS provides an RfD of 4.0×10^{-5} mg/kg-d based on an LOAEL of 0.04 mg/kg-d from a 2-year rat study that demonstrated cholinesterase inhibition and optic nerve degeneration (IRIS, 1999). An uncertainty factor of 100 was used to account for the interspecies differences and the spectrum of sensitivity in the human population, plus a 10-fold factor to account for the lack of a no-effect level.

Numerous other effects of disulfoton have been reported at doses within 1 order of magnitude of the LOAEL identified in the critical study. Toxicity, as reflected in changes in absolute and relative organ weights, has been observed at 0.1 mg/kg-d (the lowest dose tested) for the following systems: spleen, liver, pituitary, brain,

seminal vesicles, and kidneys (IRIS, 1999). In addition, at 0.65 mg/kg-d, rats exhibited atrophy of the pancreas, chronic inflammation and hyperplasia in the stomach, and skeletal muscle atrophy (U.S. EPA, 1993h).

5.4.3.5 Reproductive and Developmental Toxicity—

In a rat teratogenicity study, incomplete ossification of the parietals and sternebrae were noted at 1 mg/kg-d with a NOEL of 0.3 mg/kg-d in rats. In a 1966 three-generation reproduction study in rats, male offspring had juvenile hypoplasia in the testes, females had mild nephropathy in the kidneys, and both had preliminary stages of liver damage at 0.5 mg/kg-d. No NOAEL was obtained, and no data were provided on a number of critical parameters, including weight, growth rate, and number of stillborn animals. Insufficient histologic data and incomplete necropsy reports were identified by EPA reviewers (IRIS, 1999, U.S. EPA, 1993f).

A more recent two-generation rat study identified a NOAEL of 0.04 mg/kg-d with an LOAEL of 0.12 mg/kg-d based on decreased litter sizes, pup survival, and pup weights (U.S. EPA, 1993f).

5.4.3.6 Mutagenicity—

Disulfoton was not mutagenic in most assays; however, it was positive for unscheduled DNA synthesis without activation in human fibroblasts, in a reverse mutation assay in *Salmonella* (U.S. EPA, 1993f), and in other in vitro assays (HSDB, 1993).

5.4.3.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of disulfoton. Disulfoton has been classified as Group E (evidence of noncarcinogenicity for humans (U.S. EPA, 1999c)

5.4.3.8 Special Susceptibilities—

Based on the organ toxicities observed in animal studies, individuals with diseases or disorders of the following systems may be at greater risk from exposure to disulfoton: pancreas, stomach, spleen, liver, pituitary, brain, seminal vesicles, kidneys, musculoskeletal, and ocular. In addition, children who were exposed prenatally to disulfoton may be at risk, depending on the level of exposure.

5.4.3.9 Interactive Effects—

No data were located.

5.4.3.10 Critical Data Gaps—

The IRIS file notes that additional rat reproduction studies and studies to evaluate the ocular effects of disulfoton are needed (IRIS, 1999). HSDB notes that, because of data gaps, a full risk assessment cannot be completed. Major relevant data gaps noted under the Federal Insecticide Fungicide, and Rodenticide Act (FIFRA) heading in HSDB include chronic toxicity, oncogenicity, and mutagenicity data; animal metabolism; subchronic toxicity; and human dietary and nondietary exposures (some data gaps may have been filled, cited in HSDB, 1993). As noted above, additional studies are needed to identify the NOEL for sensitive measures of the testicular, liver, and kidney toxicity identified in the multigeneration study.

5.4.3.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	4×10^{-5} mg/kg-d
Carcinogenicity	Group E (evidence of noncarcinogenicity for humans).

5.4.3.12 Major Sources—

HSDB (1993), IRIS (1999), U.S. EPA (1993f).

5.4.4 Ethion

5.4.4.1 Background—

Ethion is an organophosphate pesticide used primarily on citrus crops (U.S. EPA, 1993a).

5.4.4.2 Pharmacokinetics—

Absorption of ethion is rapid by the oral route. Ethion is desulfurated by P-450 enzymes in the liver to its active form, ethion monooxon, which causes toxicity because of its potent inhibition of neural cholinesterase. Ethion and its oxon form are detoxified by the action of esterases in the blood and liver, producing diethyl phosphate and other metabolites that have not been characterized. Ethion and its metabolites were cleared from the body within 7 days after single dose experiments in animals (ATSDR, 1998a).

5.4.4.3 Acute Toxicity—

Effects commonly associated with acute high-level exposure to ethion include the following: headache, dizziness, weakness, incoordination, muscle twitching, tremor, nausea, abdominal cramps, diarrhea, sweating, blurred or dark vision, confusion, tightness in the chest, wheezing, productive cough, pulmonary edema,

slow heartbeat, salivation, tearing, toxic psychosis with manic or bizarre behavior, influenza-like illness with weakness, anorexia, malaise, incontinence, unconsciousness, and convulsions (HSDB, 1999).

5.4.4.4 Chronic Toxicity—

IRIS provides an RfD of 5×10^{-4} mg/kg-d based on two principal studies. A study of 10 men reported a NOAEL of 0.05 mg/kg-d for plasma cholinesterase inhibition. A second study in dogs reported a NOAEL of 0.06 and 0.07 mg/kg-day for males and females, respectively, for plasma and brain cholinesterase inhibition Uncertainty factors of 10 each were applied for intraspecies sensitivity and because of concern for the significant effect on brain cholinesterase observed at the next highest dose (0.71 mg/kg-d) in the dog study (IRIS, 1999, U.S. EPA, 1999d).

5.4.4.5 Reproductive and Developmental Toxicity—

In a rat developmental toxicity study, both the maternal and developmental toxicity NOAELs were 0.6 mg/kg-d. Both the maternal and developmental toxicity LOAELs were 2.5 mg/kg-d based on signs of hyperactivity in the parents. In a rabbit developmental toxicity study, the NOAEL and LOAEL for maternal toxicity were 2.4 and 9.6 mg/kg-d, respectively, based on weight loss, reduced food consumption, and orange colored urine. The NOAEL for developmental toxicity was 9.6 mg/kg-d, the highest dose tested (U.S. EPA, 1999d).

In a three-generation reproductive study in rats, the reproductive NOAEL was 1.25 mg/kg-d, the highest dose tested. The systemic toxicity NOAEL was 0.2 mg/kg-d and the LOAEL was 1.25 mg/kg-d based on decrease in serum cholinesterase activity in F_1 and F_2 female rats (U.S. EPA, 1999d).

5.4.4.6 Mutagenicity—

Ethion has shown no evidence of genotoxicity in several in vitro tests. Ethion was negative in tests for point mutations, DNA repair, recombination, sister chromatid exchange, and unscheduled DNA synthesis (ATSDR, 1998a). No in vivo tests of ethion genotoxicity were located.

5.4.4.7 Carcinogenicity—

In 2-yr feeding studies with ethion in rodents, no evidence of carcinogenicity was observed in rats (up to 2 mg/kg-d) or mice (up to 1.2 mg/kg-d) (ATSDR, 1998a). On this basis, ethion is classified as a Group E chemical, evidence of non-carcinogenicity for humans (U.S. EPA, 1999d).

5.4.4.8 Special Susceptibilities—

In the case of ethion, EPA's Office of Pesticide Programs considered that a 10X safety factor was not necessary for the protection of infants and children. This recommendation was based on the following weight of evidence: no evidence of enhanced susceptibility in fetuses in developmental studies in rats and rabbits, no enhanced susceptibility in pups in a two-generation reproductive study in rats, no evidence of developmental neurotoxicity, and completeness of the toxicology database to assess susceptibility to infants and children (U.S. EPA, 1999).

5.4.4.9 Interactive Effects—

Potentiation between ethion and malathion has been observed. In rats, the potentiation was approximately 2.9-fold. In dogs, there was very slight, if any, potentiation (U.S. EPA, 1993l).

5.4.4.10 Critical Data Gaps—

IRIS lists a chronic dog feeding study as a data gap (IRIS, 1999).

5.4.4.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-4} mg/kg-d
Carcinogenicity	Group E (evidence of noncarcinogenicity for humans).

5.4.4.12 Major Sources—

ATSDR (1998a), IRIS (1999), U.S. EPA (1999d).

5.4.5 Terbufos

5.4.5.1 Background—

Terbufos is an organophosphorus insecticide/nematicide applied to the soil to control insects in a variety of crops.

5.4.5.2 Pharmacokinetics—

After a single oral dose of terbufos in rats, 83 percent was eliminated in urine as metabolites and 3.5 percent in the feces over the following 7 days. No unusual distribution of terbufos or its metabolites was noted in tissues (U.S. EPA, 1995).

5.4.5.3 Acute Toxicity—

Terbufos has a high acute toxicity to humans. Animal studies yielded the following results: an oral LD_{50} in rats of 1.3 to 1.6 mg/kg (surveillance index) and an oral LD_{50} in mice of 1.3 to 6.6 mg/kg (U.S. EPA, 1992e).

5.4.5.4 Chronic Toxicity—

Limited information is available on terbufos toxicity, and the focus of most toxicity evaluations is on its cholinesterase inhibition properties. There is currently no IRIS file for terbufos. The OPP lists an RfD of 2×10^{-5} mg/kg-d based on a NOAEL of 0.005 mg/kg-d for plasma cholinesterase inhibition in a 28-day study in dogs (U.S. EPA, 1997h). An uncertainty factor of 300 (10 for interspecies variation, 10 for intraspecies variation, and 3 for protection of infants and children) was applied to the NOAEL.

Quantitative chronic toxicity information on cholinesterase inhibition is available. In rats, a 1974 lifetime oral study found a LOAEL of 0.0125 mg/kg-d (the lowest dose tested); a 1987 1-year oral study found a NOAEL of 0.025 mg/kg-d. In dogs, a 1972 6-month oral study found a NOAEL of 0.0025 mg/kg; a 1986 1-year study found a LOAEL of 0.015 mg/kg-d (the lowest dose tested); a 1987 28-d dog study identified a NOAEL of 0.00125 mg/kg-d (U.S. EPA, 1992e).

Quantitative data on chronic effects that are not directly related to cholinesterase inhibition are limited because of the lack of "no effect levels" from many studies and the need for specific information on some effects. Chronic exposure effects include: corneal cloudiness and opacity, eye rupture, alopecia, disturbances in balance, and exophthalmia noted in multiple studies and multiple species at 0.0125 mg/kg-d and above (U.S. EPA, 1992e). Increased liver weight and increased liver extramedullary hematopoiesis at 0.025 mg/kg-d and above, and mesenteric and mandibular lymph node hyperplasia at 0.05 mg/kg-d and above were noted in a subchronic (3-mo) rat study (animals were not examined for this lesion at lower exposure levels) (U.S. EPA, 1992e).

5.4.5.5 Reproductive and Developmental Toxicity—

Data currently available on developmental toxicity are limited because the endpoints identified were gross measures of toxicity (death) and the underlying causes of toxicity were not identified. The studies are not based on sensitive measures of developmental toxicity. Results from two developmental studies and one multigeneration study are available: a 1984 rat study found a NOAEL of 0.1 mg/kg-d with increased fetal resorptions at 0.2 mg/kg-d; a 1988 rabbit study identified a NOAEL of 0.25 mg/kg-d with fetal resorptions at 0.5 mg/kg-d. A 1973 multigeneration reproductive study found a NOAEL of 0.0125 mg/kg-d in rats, based on an increase in the percentage of deaths in offspring (U.S. EPA, 1992e).

5.4.5.6 Mutagenicity—

Terbufos was negative in most assays. It was positive in an in vivo dominant-lethal assay in rats; at 0.4 mg/kg, the numbers of viable implants was reduced (U.S. EPA, 1992e).

5.4.5.7 Carcinogenicity—

EPA has classified terbufos as Group E, evidence of noncarcinogenicity for humans (U.S. EPA, 1999c).

5.4.5.8 Special Susceptibilities—

There is a recognized human population that may be at high risk with respect to organophosphate exposure. Approximately 3 percent of the human population has an abnormally low plasma cholinesterase level resulting from genetic causes. These people are particularly vulnerable to cholinesterase-inhibiting pesticides. Others at greater risk include persons with advanced liver disease, malnutrition, chronic alcoholism, and dermatomyositis because they exhibit chronically low plasma cholinesterase activities. Red blood cell (RBC) acetylcholinesterase is reduced in certain conditions such as hemolytic anemias; people with these conditions may be at greater risk than the general population from exposure to organophosphates (U.S. EPA, 1999).

5.4.5.9 Interactive Effects—

No data were located.

5.4.5.10 Critical Data Gaps—

There are inconsistencies in the toxicity database for terbufos based on a comparison of acute study results and the results obtained in some chronic feeding studies, developmental studies, and the LD_{50}s. Some longer-term studies reported no effects at exposure levels above the LD_{50}s (U.S. EPA, 1992e).

The animal and human studies available on terbufos do not provide a complete and consistent basis for calculation of an alternative exposure limit. The identification of mesenteric and mandibular lymph node hyperplasia is problematic due to its potential oncogenic implications. A NOAEL for these effects was not identified and effects were not screened in low-dose groups. Other effects, which are not directly related to cholinesterase inhibition, were also noted with terbufos exposure, including optic damage at 0.0125 mg/kg-d in multiple species and studies. In addition, there is uncertainty regarding a safe exposure level to prevent adverse developmental effects, as discussed above. These results warrant further evaluation and may be considered, by some, to justify an additional modifying factor to deal with data gaps and uncertainties in the database.

5.4.5.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	2×10^{-5} mg/kg-d.
Carcinogenicity	Group E (evidence of noncarcinogenicity for humans).

5.4.5.12 Major Sources—

HSDB (1993), U.S. EPA (1992e).

5.5 CHLOROPHENOXY HERBICIDES

5.5.1 Oxyfluorfen

5.5.1.1 Background—

Oxyfluorfen is a recently introduced diphenyl ether pesticide in the chlorophenoxy class. Limited data were located on this chemical.

5.5.1.2 Pharmacokinetics—

No data were located.

5.5.1.3 Acute Toxicity—

The acute oral LD_{50} in rats is greater than 5,000 mg/kg (Hayes and Laws, 1991).

5.5.1.4 Chronic Toxicity—

IRIS provides an RfD of 3×10^{-3} mg/kg-d based on a NOAEL of 0.3 mg/kg-d from a 1977 20-month mouse feeding study that identified nonneoplastic lesions in the liver and increased absolute liver weight. Uncertainty factors of 10 each for inter- and intraspecies sensitivity were applied (IRIS, 1999).

5.5.1.5 Reproductive and Developmental Toxicity—

A three-generation rat study provided a NOAEL of 0.5 mg/kg-d and an LOAEL of 5 mg/kg-d. A rat teratology study identified a NOAEL of 100 mg/kg-d. A rabbit study found fused sternebrae at 30 mg/kg-d and a NOEL of 10 mg/kg-d (IRIS, 1999, U.S. EPA, 1993j). A rabbit teratology study data gap is noted in the IRIS file (IRIS, 1999).

5.5.1.6 Mutagenicity—

Results of mutagenicity assays on oxyfluorfen are mixed (U.S. EPA, 1993j).

5.5.1.7 Carcinogenicity—

Oxyfluorfen has been classified as a possible human carcinogen (C) based on liver tumors identified in experimental animals. A cancer slope factor of 0.0732 mg/kg-d has been derived (EPA 1998c).

5.5.1.8 Interactive Effects—

No data were located.

5.5.1.9 Critical Data Gaps—

The IRIS file notes a rabbit teratology study as a data gap (IRIS, 1999).

5.5.1.10 Summary of EPA Health Benchmarks—

Chronic Toxicity	3×10^{-3} mg/kg-d
Carcinogenicity	7.32×10^{-2} mg/kg-d.

5.5.1.11 Major Sources—

IRIS (1999), U.S. EPA (1993j).

5.6 POLYCYCLIC AROMATIC HYDROCARBONS (PAHs)

5.6.1 Background

Polycyclic aromatic hydrocarbons (PAHs) are a group of organic chemicals that have a fused ring structure of two or more benzene rings. PAHs are also commonly referred to as polynuclear aromatic hydrocarbons (PNAs). They are formed during the incomplete combustion of organic materials. Industrial activities that produce PAHs include coal coking; production of carbon blacks, creosote, and coal tar; petroleum refining; synfuel production from coal; and the use of Soderberg electrodes in aluminum smelters and ferrosilicum and iron works. Domestic activities that produce PAHs include cigarette smoking, home heating with wood or fossil fuels, waste incineration, broiling and smoking foods, and use of internal combustion engines. PAHs are ubiquitous in the environment and usually occur as mixtures. PAHs with two to five benzene rings are generally of greatest concern for environmental and human health effects (U.S. EPA, 1999a). ATSDR (1995b) has identified the following PAHs as the most important with regard to human exposure:

- Acenaphthene
- Acenaphthylene
- Anthracene
- Benz[*a*]anthracene
- Benzo[*a*]pyrene
- Benzo[*e*]pyrene
- Benzo[*b*]fluoranthene
- Benzo[*k*]fluoranthene
- Benzo[*j*]fluoranthene
- Benzo[*g,h,i*]perylene
- Chrysene
- Dibenz[*a,h*]anthracene
- Fluoranthene
- Fluorene
- Indeno[*1,2,3-cd*]pyrene
- Phenanthrene
- Pyrene.

Although these and many other PAHs are present in the environment, benzo[*a*]pyrene is the chemical with most of the available health effects data.

5.6.2 Pharmacokinetics

PAHs may be absorbed through the lungs, the stomach, or the skin. The extent of absorption varies in both humans and animals with the individual compound and is influenced by vehicle. For instance, oral absorption increases with more lipophilic PAHs or in the presence of oils in the intestinal tract. After inhalation, oral, or dermal exposure of animals, the highest levels of PAHs were found in

highly perfused tissues, such as the lung, liver, gastrointestinal tract, and kidney. Animal studies also show that PAHs cross the placenta. PAHs are rapidly metabolized and excreted in humans and animals. The elimination half-life for benzo[*a*]pyrene in rodents is 20 to 30 hours (ATSDR, 1995b).

PAHs have been shown (ATSDR, 1995b) to be metabolized to reactive intermediates by enzyme systems commonly found in the lung, intestines, and liver. These intermediates then covalently bind to cellular macromolecules, leading to mutation and tumor development.

5.6.3 Acute Toxicity

Few data are available describing the acute toxicity of PAHs after inhalation exposure in humans or animals. Limited information is available on the effects of acute oral and dermal exposure in animals. However, benzo[*a*]pyrene is fatal to mice following oral exposure to 120 mg/kg-d, and the liver and the skin have been identified as target organs in animals after oral or dermal exposure, respectively (ATSDR, 1998b).

5.6.4 Chronic Toxicity

Few controlled epidemiological studies have been reported in humans on the effects of exposure to PAHs or to PAH-containing mixtures. However, available information describing chronic-duration dermal exposure of humans to PAHs indicates that PAHs have a high chronic exposure toxicity characterized by chronic dermatitis and hyperkeratosis (ATSDR, 1995b).

Chronic studies in animals exposed to PAHs by ingestion, intratracheal installation, or skin-painting have identified adverse effects on the cardiovascular, respiratory, gastrointestinal, immune, and central nervous systems and on the blood, liver, and skin (ATSDR, 1995b).

IRIS provides an RfD of 3×10^{-1} for anthracene based on a NOAEL of 1,000 mg/kg-d in a subchronic study in mice. Uncertainty factors of 10 each for inter- and intraspecies variability were applied, with an additional uncertainty factor of 30 for use of a subchronic study and the lack of reproductive/developmental data and adequate toxicity data in a second species. Confidence in the RfD is rated low (IRIS, 1999).

An RfD of 4×10^{-2} mg/kg-d was calculated for fluoranthene based on a subchronic study in mice, a NOAEL of 125 mg/kg-d, and critical effects on the liver, blood, and kidneys. The same uncertainty factors were applied as for anthracene, with confidence also rated as low (IRIS, 1999).

IRIS provides the same RfD for fluorene as for fluoranthene; a subchronic study in mice was also used with the same NOAEL, uncertainty factors, and confidence rating. For fluorene, the critical effect was on the blood (IRIS, 1999).

For pyrene, an RfD of 3 x 10^{-2} mg/kg-d was calculated. It was also based on a subchronic study in mice, with a NOAEL of 75 mg/kg-d and kidney effects noted. The same uncertainty factors and confidence rating were used (IRIS, 1999).

5.6.5 Reproductive and Developmental Toxicity

No information is available regarding the reproductive or developmental toxicity of PAHs in humans. Animal data describing reproductive and developmental effects of benzo[*a*]pyrene administered orally or parenterally and indicate that PAHs have the potential to induce adverse reproductive and developmental effects such as sterility, resorptions, and malformations (ATSDR, 1995b).

5.6.6 Mutagenicity

Benzo[*a*]pyrene has been thoroughly studied in genetic toxicology test systems (ATSDR, 1995b). It induces genetic damage in prokaryotes, eukaryotes, and mammalian cells in vitro and produces a wide range of genotoxic effects, including gene mutations in somatic cells, chromosome damage in germinal and somatic cells, DNA adduct formation, unscheduled DNA synthesis, sister chromatid exchange, and neoplastic cell transformation. The genotoxic effects of the other PAHs have been investigated using both in vivo and in vitro assays. All but three of the PAHs (acenaphthene, acenaphthylene, and fluorene) were reported to be mutagenic in at least one in vitro assay with the bacterium *S. typhimurium*.

5.6.7 Carcinogenicity

Evidence indicates that mixtures of PAHs are carcinogenic in humans. This evidence comes primarily from occupational studies of workers exposed to mixtures containing PAHs as a result of their involvement in such processes as coke production, roofing, oil refining, or coal gasification (ATSDR, 1995b). Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lung and skin following inhalation and dermal exposure, respectively. In animals, individual PAHs have been shown to be carcinogenic by the inhalation route (benzo[*a*]pyrene) and the oral route (e.g., benz[*a*]anthracene, benzo[*a*]pyrene, and dibenz[*a,h*]anthracene). Dermal exposure of animals to benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz[*a,h*]anthracene, or indeno[*1,2,3-cd*]pyrene has been shown to be tumorigenic in mice.

EPA has performed weight-of-evidence evaluations of several PAHs. The carcinogenicity classifications are listed below (IRIS, 1999):

- Acenaphthylene — D (not classifiable as to human carcinogenicity)
- Anthracene — D
- Benz[*a*]anthracene — B2 (probable human carcinogen)
- Benzo[*a*]pyrene — B2
- Benzo[*b*]fluoranthene — B2

- Benzo[*k*]fluoranthene B2
- Benzo[*g,h,i*]perylene D
- Chrysene B2
- Dibenz[*a,h*]anthracene B2
- Fluoranthene D
- Fluorene D
- Indeno[*1,2,3-cd*]pyrene B2
- Phenanthrene D
- Pyrene D

EPA and others have developed a relative potency estimate approach for PAHs (Nisbet and LaGoy, 1992; U.S. EPA, 1993n). Using this approach, the cancer potency of the other carcinogenic PAHs can be estimated based on their relative potency to benzo[*a*]pyrene. Table 5-2 lists the toxicity equivalence factors (based on carcinogenicity) calculated by Nisbet and LaGoy (1992) for PAHs discussed above.

U.S. EPA (1993n) has derived relative potency estimates based on mouse skin carcinogenesis. These are shown in Table 5-3.

Table 5-2. Toxicity Equivalent Factors for Various PAHs

Compound	Toxicity Equivalency Factor (TEF)
Dibenz[*a,h*]anthracene	5
Benzo[*a*]pyrene	1
Benz[*a*]anthracene	0
Benzo[*b*]fluoranthene	0.1
Benzo[*k*]fluoranthene	0.1
Indeno[*1,2,3-cd*]pyrene	0.1
Anthracene	0.01
Benzo[*g,h,i*]perylene	0.01
Chrysene	0.01
Acenaphthene	0.001
Acenaphthylene	0.001
Fluoranthene	0.001
Fluorene	0.001
Phenathrene	0.001
Pyrene	0.001

Source: Nisbet and LaGoy (1992).

Table 5-3. Relative Potency Estimates for Various PAHs

Compound	Relative Potency[a]
Benzo[*a*]pyrene	1.0
Benz[*a*]anthracene	0.145
Benzo[*b*]fluoranthene	0.167
Benzo[*k*]fluoranthene	0.020
Chrysene	0.0044
Dibenz[*a,h*]anthracene	1.11
Indeno[*1,2,3-cd*]pyrene	0.055[b]

Source: U.S. EPA, 1993n.

[a] Model was $P(d)=1-\exp[-a(1+bd)^2]$ for all but indeno[1,2,3-c,d]pyrene.

[b] Simple mean of relative potencies (0.021 and 0.089); the latter derived using the one-hit model.

5.6.8 Special Susceptibilities

People with nutritional deficiencies, genetic diseases that influence the efficiency of DNA repair, and immunodeficiency due to age or disease may be unusually susceptible to the effect of PAHs. In addition, people who smoke, people with a history of excessive sun exposure, people with liver and skin diseases, and women, especially of reproductive age, may be at increased risk. Individuals with hepatic-metabolizing enzymes that can be induced by PAHs may be unusually susceptible to the toxic effects of PAH exposure by virtue of producing more toxic metabolites. Fetuses may be susceptible to the effects of toxic PAH metabolites produced by maternal exposure, because of increased permeability of the embryonic and fetal blood-brain barrier and the immaturity of the enzymatic systems that are responsible for elimination (ATSDR, 1995c).

5.6.9 Interactive Effects

Humans are usually exposed to PAHs in complex mixtures rather than to individual PAHs. Interactions may occur among chemicals in a mixture prior to exposure or may occur after exposure as a result of differing effects of the mixture components on the body. Synergistic and/or antagonistic interactions with regard to the development of health effects, particularly carcinogenesis, may occur. The interaction between noncarcinogenic and carcinogenic PAHs have been examined extensively in animals. Weakly carcinogenic or noncarcinogenic PAHs, including benzo[*e*]pyrene, benzo[*g,h,i*]perylene, fluoranthene, or pyrene exhibit co-carcinogenic potential and tumor-initiating and promoting activity when applied with benzo[*a*]pyrene to the skin of mice. In contrast, benzo[*a*]fluoranthene,

benzo[*k*]fluoranthene, chrysene, and a mixture of anthracene, phenathracene, and pyrene have been shown to significantly inhibit benzo[*a*]pyrene-induced sarcoma after injection in mice. Several experiments have indicated that mixtures of several PAHs are less potent with respect to carcinogenicity than the individual PAHs that constitute the mixture (ATSDR, 1995c).

The majority of human exposure to PAHs occurs in the presence of particles or other environmental pollutants that may influence the toxicity of the PAHs. For instance, inhalation exposure to PAHs in the presence of particulate matter greatly increases respiratory tract tumors in laboratory animals, due to the fact that the particles are cleared more slowly from the lungs, thus allowing the particle-bound PAHs to remain in the respiratory tract for longer periods of time. Similarly, concomitant exposure to asbestos increases bronchopulmonary cancers. Exposure to solvents or other environmental compounds that increase metabolism of the PAHs may increase or decrease toxicity, depending on whether the individual PAH must be transformed to toxic intermediates in order to exert its adverse effect (ATSDR, 1995c).

5.6.10 Critical Data Gaps

A joint team of researchers from ATSDR, NTP, and EPA have identified the following data gaps: human responses to acute, intermediate (14 to 365 days), and chronic exposure, subchronic reproductive tests in various species, developmental toxicity studies in two species, immunotoxicity studies of animals and humans, and neurotoxicity studies in humans and animals (ATSDR, 1995c).

5.6.11 Summary of EPA Health Benchmarks

Chronic Toxicity (anthracene)	3×10^{-1} mg/kg-d
(fluoranthene)	4×10^{-2} mg/kg-d
(fluorene)	4×10^{-2} mg/kg-d
(pyrene)	3×10^{-2} mg/kg-d
Carcinogenicity (benzo[*a*]pyrene)	7.3 per mg/kg-d.

5.6.12 Major Sources

ATSDR (1998b), IRIS (1997c), U.S. EPA (1999a, 1993n).

5.7 POLYCHLORINATED BIPHENYLS (PCBs)

5.7.1 Background

Polychlorinated biphenyls (PCBs) are a mixture of chlorinated biphenyl chemicals comprised of various chlorine substitution patterns. There are 209 possible PCB congeners. Mixtures of PCBs were marketed in the United States under the trade name Aroclor, with a numeric designation that indicated their chlorine content. Although production and use of PCBs were banned in 1979, this chemical group is extremely persistent in the environment and bioaccumulates through the food chain. However, environmental mixtures of PCBs differ from the commercial mixtures because of partitioning, transformation, and bioaccumulation. There is evidence that some of the more toxic PCB congeners preferentially accumulate in higher organisms (Aulerich et al., 1986). Consequently, the aggregate toxicity of a PCB mixture may increase as it moves up the food chain (U.S. EPA, 1993a).

PCB exposure is associated with a wide array of adverse health effects in experimental animals, but the effects of PCB exposure in humans are less clear. Many effects have only recently been investigated (e.g., endocrine effects), and the implications of newer studies are not fully known. The health effects of PCBs are still under active evaluation and currently there is not sufficient information on the specific congeners to develop congener-specific quantitative estimates of health risk (ATSDR, 1998c; U.S. EPA, 1993a). Aroclor mixtures, rather than environmental mixtures or bioconcentrated PCB mixtures, have been used in laboratory animal studies to determine toxicity. The preferable studies would be those that utilize human dose-response data from populations who have consumed PCBs via fish or who have been exposed to PCBs in occupational settings. Because sufficient human data are lacking, animal data were used to develop RfDs and CSFs for PCBs. The Office of Water recommends that total PCBs, calculated as the sum of the concentrations of the congeners or homologue groups, be reported. Aroclor analysis is not recommended, except for screening studies, because environmental PCB mixtures cannot be characterized by any commercial Aroclor mixture (Cogliano, 1998). The first volume in this document series, *Sampling and Analysis*, contains a detailed discussion of analysis of this group of chemicals (U.S. EPA, 1993a).

5.7.2 Pharmacokinetics

PCBs are absorbed through the GI tract and distributed throughout the body. Studies of individual chlorobiphenyl congeners indicate, in general, that PCBs are readily absorbed, with an oral absorption efficiency of 75 percent to greater than 90 percent (ATSDR, 1998b). Because of their lipophilic nature, PCBs, especially the more highly chlorinated congeners (tetra- through hexachlorobiphenyl), tend to accumulate in lipid-rich tissues. Greater relative amounts of PCBs are usually found in the liver, adipose tissue, skin, and breast milk. It has been shown that absorption of tetra- and higher chlorinated congeners from breast milk by nursing

infants ranges from 90 to 100 percent of the dose (ATSDR, 1998b). Offspring can also be exposed to PCBs through placental transfer. PCBs have also been measured in other body fluids including plasma, follicular fluid, and sperm fluid.

The retention of PCBs in fatty tissues is linked to the degree of chlorination and also to the position of the chlorine atoms in the biphenyl ring. In general, higher chlorinated PCBs persist for longer periods of time. Pharmacokinetics modeling of PCB disposition indicates that PCB movement in the body is a dynamic process, with exchanges between various tissues that depend on fluctuating exposure levels to specific congeners. The result is elimination of congeners that are more easily metabolized and retention of those that resist metabolism (ATSDR, 1998c). In occupationally exposed individuals, lower chlorinated congeners had half-lives between 1 and 6 years, whereas higher chlorinated PCBs had half-lives ranging from 8 to 24 years (ATSDR, 1998b).

PCBs induce mixed function oxidases, and different congeners induce specific forms (isozymes) of the cytochrome P-450 system. Although the mechanisms of PCB toxicity have been investigated in many studies, a clear definition of the mechanisms for most congeners has not been identified. The congeners appear to act by a variety of mechanisms (ATSDR, 1998b). Some PCB congeners are similar to dioxins and bind to a cytosolic protein, the Ah receptor, which regulates the synthesis of a variety of proteins. The toxicity of these congeners is similar to dioxins. The toxicity of other PCB congeners seems to be unrelated to the Ah receptor. Ultimately, the toxicity of a PCB mixture depends on the toxicity of the individual congeners, their interactions, and interactions with other chemical contaminants such as pesticides and dioxins. For example, both synergistic and antagonistic interactions have been reported with mixtures containing PCBs and dioxins (Van den Berg et al., 1998).

5.7.3 Acute Toxicity

Acute high-level exposures of laboratory animals to PCBs have resulted in liver and kidney damage, neurological effects, developmental effects,endocrine effects, hematological effects, and death. LD_{50} values for various Aroclor mixtures range from about 1,000 mg/kg to more than 4,000 mg/kg. No human deaths have been associated with acute exposure to PCBs (ATSDR, 1998b).

5.7.4 Chronic Toxicity

In animal studies, numerous effects have been documented, including hepatic, gastrointestinal, hematological, dermal, body weight changes, endocrine, immunological, neurological, and reproductive effects (ATSDR, 1998b). Most of the studies have involved oral exposure. Despite the variety of adverse effects observed in animals exposed to PCBs, overt adverse effects in humans have been difficult to document. This has been attributed to the fact that, in most cases, the dosages tested in animals were considerably higher than those found in occupational exposures and to the difficulties with interpreting epidemiological

studies (James et al.,1993; Kimbrough, 1995). These include multiple confounding factors, uncertain exposure estimates, and statistical limitations. Skin rashes and a persistent and severe form of acne (chloracne) have been reported following exposures to PCBs. Occupational and accidental exposures have indicated that PCBs may affect many organs including the gastrointestinal, respiratory, immune, central nervous, and cardiovascular systems.

EPA has derived an RfD of 2×10^{-5} mg/kg-d for Aroclor 1254 (IRIS, 1999). The RfD was based on a LOAEL of 0.005 mg/kg-d for ocular and immunological effects in monkeys. The study reported ocular exudate and inflamed Meibomian glands, distorted growth of finger and toenails, and decreased antibody response (IgM and IgG) to injected sheep red blood cells at the lowest dose tested. Uncertainty factors of 10 for sensitive individuals, 3 for extrapolation from monkeys to humans, 3 for extrapolation from a subchronic exposure to a chronic RfD, and 3 for use of a minimal LOAEL were applied, resulting in a total uncertainty factor of 300. An uncertainty factory of 3 (rather than 10) for extrapolation from subchronic to chronic exposure was used, because the duration of the critical study continued for approximately 25 percent of the lifespan of monkeys, and the immunologic and clinical changes observed did not appear to be dependent upon duration.

EPA has medium confidence in the study used as the basis for the RfD for Aroclor 1254, in the database, and in the RfD. EPA based this rating on the fact that the database consisted of a large number of laboratory animal and human studies; however, there were some inconsistencies in the effect levels for reproductive toxicity and the results of an unpublished study were considered (IRIS, 1999).

5.7.5 Developmental Toxicity

PCB mixtures have been shown to cause adverse developmental effects in experimental animals (ATSDR, 1998c). Some human studies have also suggested that PCB exposure may cause adverse effects in children and in developing fetuses while other studies have not shown effects (U.S. EPA, 1999a). Reported effects include lower IQ scores (Jacobson and Jacobson, 1996), low birth weight (Rylander et al., 1998), and lower behavior assessment scores (Lonky et al., 1996). However, study limitations, including lack of control for confounding variables, and deficiencies in the general areas of exposure assessment, selection of exposed and control subjects, and the comparability of exposed and control samples. Different findings from different studies provide inconclusive evidence that PCBs cause developmental effects in humans (ATSDR, 1998b).

The RfD for Aroclor 1016 is based on reduced birth weights observed in monkeys in a 22-month study (discussed below under longer-term developmental studies). This study established a NOAEL of 0.007 mg/kg-d. Applying an uncertainty factor of 100 (3 for sensitive individuals [infants exposed transplacentally], 3 for interspecies extrapolation, 3 for database limitations [male reproductive effects

are not directly addressed and two-generation reproductive studies are not available], and 3 for extrapolation from subchronic to chronic) to the NOAEL yields an RfD of 7×10^{-5} mg/kg-d (IRIS, 1999). However, since the RfD for Aroclor 1254 is more conservative (2×10^{-5} mg/kg-d) and protects against adult toxicity concerns as well as the risk to the fetus and children, this RfD will be used to calculate the consumption limits for all populations (adults, women of reproductive age, and children).

EPA has medium confidence in the study, in the database, and in the RfD for Aroclor 1016. EPA based this rating on the fact that the critical study was well conducted in a sensitive animal species and the database for PCBs in general is extensive; however, since mixtures of PCBs found in the environment do not match the pattern of congeners found in Aroclor 1016, EPA felt that only a medium confidence ranking could be given. For those particular environmental applications where it is known that Aroclor 1016 is the only form of PCB contamination, EPA stated that the RfD could be considered to have a high confidence rating (IRIS, 1999).

A study was conducted of pregnancy outcomes in women who had consumed PCB-contaminated fish from Lake Michigan over an average of 16 years (exposure both prior to and during pregnancy). Consumption of contaminated fish and levels of total PCBs in cord serum correlated with lower birth weight, smaller head circumference, and shorter gestational age. Fish consumption, however, was correlated with delayed neuromuscular maturity, and, at 7 months, the children had subnormal visual recognition memory. Children from this cohort were examined at age 4 and 11 years. At age 4, cord serum PCB levels were associated with impaired short-term memory. Activity level was inversely related to 4-year serum PCB level and also to maternal milk PCB level. At age 11, prenatal exposure to PCBs was associated with lower full-scale and verbal IQ scores after controlling for potential confounding variables, such as socioeconomic status. The results from this series of studies were confounded by possible maternal exposure to other chemicals and by the fact that the exposed group, on average, drank more alcohol and caffeine, prior to and during pregnancy, weighed more, and took more cold medications during pregnancy, than the nonexposed group (Fein et al., 1984a, 1984b).

Other relevant studies generally found no significant differences between control groups and exposed groups concerning stillbirths, multiple births, preterm births, congenital anomalies, and low birth weight.

Information on chronic developmental toxicity is available from studies in Rhesus monkeys (ATSDR, 1998b). Exposure periods ranged from 12 to 72 months. Inflammation of tarsal glands, nail lesions, and gum recession were noted in offspring of monkeys exposed to Aroclor 1254. Adverse neurobehavioral effects were reported following exposure to Aroclor 1016 and Aroclor 1248. Other observed effects included reduction in birth weight and increased infant death for Aroclor 1248.

Exposure via lactation is a significant concern for neonates because PCBs concentrate in milk fat. Animal studies indicate that lactational exposure, in some cases, can be more significant than transplacental transfer. In monkeys, signs of intoxication have been observed in offspring exposed to PCBs in maternal milk (ATSDR, 1998b).

In summary, the results from some studies in humans suggest that exposure to PCBs may cause developmental effects. However, limitations of these studies diminished the validity of the results. Animal studies indicate that PCBs can cause some developmental effects following prenatal or postnatal exposure.

5.7.6 Mutagenicity

The majority of mutagenicity assays of PCBs have been negative (IRIS, 1999). However, an increase in the percentage of chromosomal aberrations in peripheral lymphocytes and an increase in the sister chromatid exchange rate were reported in a study of workers manufacturing PCBs for 10 to 25 years. Although workers and controls were matched for smoking and drinking, concurrent exposure to other known human genotoxic chemicals occurred (ATSDR, 1998b). Another study found an increased incidence of chromatid exchanges in lymphocytes from workers exposed to PCBs in an electric power substation fire compared to unexposed controls. It is possibile that toxic chlorinated dioxins and/or furans generated during the fire may have been responsible for the effects.

The weight of evidence from the in vitro and in vivo genotoxicity studies suggests that PCBs are not likely to be genotoxic to humans. However, exposure to PCBs may enhance the genotoxic activity of other chemicals (ATSDR, 1998b).

5.7.7 Carcinogenicity

PCBs are classified by EPA as Group B2; probable human carcinogens . This is based on studies that have found liver tumors in rats exposed to Aroclors 1260, 1254, 1242, and 1016. Evaluation of the animal data indicate that PCBs with 54 percent chlorine content induces a higher yield of liver tumors in rats than other PCB mixtures.

Human epidemiological studies of PCBs have not yielded conclusive results (Silberhorn et al.,1990). There is some suggestive evidence that xenoestrogens, including PCBs, may play a role in breast cancer induction (ATSDR, 1998c). Some studies have indicated an excess risk of several cancers, including: liver, biliary tract, gallbladder, gastrointestinal tract, pancreas, melanoma, and non-Hodgkin's lymphoma (IRIS, 1999, ATSDR, 1998c). As with all epidemiological studies, it is very difficult to obtain unequivocal results because of the long latency period required for cancer induction and the multiple confounders arising from concurrent exposures, lifestyle differences, and other factors. The currently available human evidence is considered inadequate but suggestive that PCBs may cause cancer in humans (IRIS, 1999).

The Agency's recent peer-reviewed reassessment published in a final report, *PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures* (U.S. EPA, 1996c), adopts an innovative approach that distinguishes among PCB mixtures by using information on environmental processes. It considers all cancer studies (which used commercial mixtures only) to develop a range of cancer slope factors, then uses information on environmental processes to provide guidance on choosing an appropriate slope factor for representative classes of environmental mixtures and different pathways. Depending on the specific application, either central estimates or upper bound estimates can be appropriate. Central estimates describe a typical individual's risk, while upper bounds provide greater assurance that the true risk is not likely to be underestimated. Central estimates are used for comparing or ranking environmental hazards, while upper bounds provide information about the precision of the comparison or ranking. In this reassessment, the use of the upper bound values was found to increase cancer potency estimates by only two- or threefold over those using central tendency. Upper bounds are useful for estimating risks or setting exposure-related standards to protect public health and are used by EPA in quantitative cancer risk assessment. Thus, the cancer potency of PCB mixtures is determined using a tiered approach based on environmental exposure routes with upper-bound slope factors ranging from 0.07 to 2 per mg/kg-d for average lifetime exposures to PCBs. It is noteworthy that bioaccumulated PCBs appear to be more toxic than commercial PCBs and appear to be more persistent in the body (IRIS, 1999). In addition, there is evidence that early-life exposures may result in an increased risk (U.S. EPA, 1996c). Therefore, the highest cancer slope factor is recommended for the following conditions: food chain exposure; sediment and soil ingestion; inhalation of dust or aerosols; dermal exposure (if an absorption factor has been applied); presence of dioxin-like, tumor- promoting, or persistent congeners; and early-life exposure.

Alternatively, if site-specific congener concentrations are available, the risk assessment can be supplemented by determining the dioxin-like toxicity (U.S. EPA, 1996c; Cogliano, 1998). Cogliano (1998) presents data showing the typical composition of several commercial Aroclor mixtures (Table 5-4). Aroclors 1016, 1242, 1254, and 1260 contained concentrations of dioxin-like concentrations ranging from 0.14 ppm to 46.4 ppm TEQs. Therefore, separate risk assessments should be conducted for the dioxin-like and nondioxin-like PCB congeners if the congener analysis indicates elevated concentrations of dioxin-like congeners relative to the typical commercial mixtures (IRIS, 1999; U.S. EPA, 1996c).

Table 5-4. Reported Concentrations (ppm) of Dioxin-Like Congeners in Commercial Aroclor Mixtures

	Aroclors			
Congener	**1016**	**1242**	**1254**	**1260**
PCB-77 (3,3',4,4'-tetraCB)	66	3340	918	31
PCB-126 (3,3,4,4',5-pentaCB)	0.95	44	134.3	0.0
PCB-169 (3,3,4,4',5,5[1]-hexaCB)	0.0	0.0	1.52	0.0
PCDFs	0.05	2.2	0.13	5.5
TEQ from PCBs	0.14	8.1	46.4	7.1
TEQ from PCDFs	0.002	0.1	0.01	0.08

Source: Cogliano, 1998.
CB = Chlorinated biphenyls

In a recent study conducted by the Delaware Department of Natural Resources and Environmental Control (Greene, 1999), dioxin-like PCBs, nondioxin-like PCBs, and dioxins/furans accounted for about 64.4, 26.9, and 5.6 percent of the total cancer risk, respectively, from ingesting fish caught from the Chesapeake and Delaware Canal. Data from this study are shown in Table 5-5 to illustrate the potential importance of the dioxin-like PCB congeners. The DDNREC noted that, had cancer risk been calculated according to the traditional method (i.e., not including a separate assessment for dioxin-like PCBs), the cancer risk estimate for PCBs would have been lower by a factor of 2.9. However, PCBs contributed about 93 percent of the total dioxin risk based on 2,3,7,8-TCDD TEQs. Therefore, failure to evaluate the dioxin-like PCB congeners could result in underestimating cancer risk.

Table 5-5. PCB and Dioxin Concentrations (ppb) in Channel Catfish

Parameter	**Median**	**Mean**	**Maximum**
Total PCBs	1,104.8	1,173	1,665.3
Nondioxin-like PCBs	943.8	1,024.9	1,474.7
Dioxin-like PCBs TEQs	0.0302	0.0303	0.0509
Dioxin/furan TEQs	0.0026	0.0024	0.0043
Total TEQs	0.0328	0.0327	0.0552

Source: Greene, 1999.

5.7.8 Special Susceptibilities

There is evidence that embryos, fetuses, and neonates are more susceptible to PCBs due to their underdeveloped enzymatic systems, which may lead to increased PCB accumulation in the body. Breast-fed infants may have an increased risk because of bioconcentration of PCBs in breast milk and high intake rates relative to body weights. In addition, there is evidence that a steroid present in human milk inhibits glucuronyl transferase activity, which could, in turn, inhibit glucuronidation and excretion of PCB metabolities. Other individuals with potentially greater risk include those with liver and blood diseases or those with syndromes associated with impairment to the metabolic systems that help eliminate PCBs from the body.

5.7.9 Interactive Effects

PCBs induce microsomal enzymes; therefore, the effects of exposure to PCBs or other compounds depends on the role of oxidative metabolism. For example, preexposure to PCBs may enhance the liver toxicity of some chemicals (trichloroethylene, mirex, kepone, carbon tetrachloride, tetrachloroethylene) but decrease the liver toxicity of 1,1-dichloroethylene. Other interactive effects include increased metabolism and excretion of pentobarbital, increased genotoxicity of numerous carcinogens, increased duodenal ulcerogenic activity of acrylonitrile, and increased kidney toxicity of trichloroethylene (ATSDR, 1998b).

5.7.10 Critical Data Gaps

The following studies could help fill in some of the key data gaps for PCBs: congener-specific PCB levels in human tissues; epidemiological studies of populations living near PCB-contaminated sites and occupational settings where exposure to PCBs still occurs; reproductive studies in humans and animals, including fertility studies in males of a sensitive species; developmental and neurodevelopmental studies, immunotoxicity studies in humans and animals; neurotoxicity studies in humans with high PCB body burdens and in animals; chronic studies to determine the most sensitive animal target organ and species; and comparative toxicity of Aroclors and bioaccumulated PCBs (ATSDR, 1998b).

5.7.11 Summary of EPA Health Benchmarks

Chronic Toxicity	2×10^{-5} mg/kg-d based on Aroclor 1254
Carcinogenicity	2.0 per mg/kg-d based on mixed PCBs.

5.7.12 Major Sources

ATSDR (1998b), Cogliano (1998), HSDB (1993), IRIS (1999), James et al. (1993), Kimbrough (1995), Silberhorn et al. (1990), U.S. EPA (1996c).

5.8 DIOXINS

5.8.1 Background

Dioxins are a group of synthetic organic chemicals that contain 210 structurally related individual chlorinated dibenzo-p-dioxins (CDDs) and chlorinated dibenzofurans (CDFs). Dioxin is a generic term that is used, in this case, to refer to the aggregate of all CDDs and CDFs. It is recommended that the 17 2,3,7,8-substituted tetra- through octa-chlorinated dibenzo-*p*-dioxins and dibenzofurans be considered together as a simplifying and interim approach until further guidance is available on this chemical group. In addition, 12 PCB congeners have been identified that exhibit dioxin-like activity (U.S. EPA, 1996c, Van den Berg et al., 1998). The reader may consult guidance on the use of a toxicity equivalency approach to refine the toxicity estimate and fish consumption limit calculations (Barnes and Bellin, 1989; U.S. EPA, 1991c; U.S. EPA, 1996c).

Dioxin has been undergoing extensive review within EPA for several years. Consequently, only a brief summary, is provided below. Currently, the EPA's dioxin reassessment document, which includes two reports entitled *Estimating Exposure to Dioxin-like Compounds* (three volumes) (U.S. EPA, 1994a) and *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds* (three volumes) (U.S. EPA, 1994b) is undergoing final review. The dioxin reassessment document is scheduled for final external peer review during the third quarter of fiscal year 2000. Following peer review, the document will be sent to the EPA Science Advisory Board for final review. The final dioxin reassessment document is scheduled for release by the end of the calendar year 2000.

5.8.2 Pharmacokinetics—

Dioxins are absorbed through the gastrointestinal tract, respiratory tract, and skin and distributed throughout the body. Absorption is congener-specific with decreased absorption of hepta- and octa-congeners compared to dioxins with fewer chlorines. Because of their lipophilic nature, dioxins tend to accumulate in fat and the liver. Dioxins are slowly metabolized by oxidation or reductive dechlorination and conjugation and the major routes of excretion are the bile and feces. Reported half-lives in the body range from 5 to 15 years. Small amounts may be eliminated in the urine. The current evidence indicates that metabolities are less toxic than the parent compounds (ATSDR, 1998c, U.S. EPA 1994a).

The predominant forms retained in the tissues are the 2,3,7,8-substituted congeners. Tissue deposition depends on the route of exposure, congeners present, dose, and age. Based on a study of a human volunteer, about 87 percent of a single dose of dioxins dissolved in corn oil was absorbed and about 90 percent of the absorbed dose was distributed to fatty tissue (ATSDR, 1998c).

The half-lives for various dioxin congeners in humans have been reported to range from 2.9 to 26.9 years. Some studies have suggested longer half-lives in individuals with higher body fat (ATSDR, 1998c).

Dioxins induce mixed function oxidases and hepatic aryl hydrocarbon hydroxylase (AHH). Dioxins bind to a cytosolic protein, the Ah receptor, which regulates the synthesis of a variety of proteins. The Ah receptor has been found in many human tissues, including the lung, liver, placenta, and lymphocytes. Although evidence indicates that the Ah receptor is involved in many biological response to dioxins, the diversity of biological effects observed cannot be accounted for by characteristics of this receptor alone (ATSDR, 1998c, U.S. EPA, 1994a).

5.8.3 Acute Toxicity

LD_{50} values for dioxins vary over several orders of magnitude, depending on the congener, species, and strain of animal tested. The most toxic congener is 2,3,7,8-TCDD with LD_{50} values ranging from 22 μg/kg to 340 μg/kg in various strains of laboratory rats. Guinea pigs are the most sensitive species tested (LD_{50}s from 0.6 to 2.1 μg/kg) and hamsters are the most resistant (LD_{50}s from 1,157 to 5,051 μg/kg). In all studies, the animals died from a pronounced wasting syndrome characterized by weight loss and depletion of body fat that lasted 1 to 6 weeks. By contrast, laboratory animals have survived acute doses of 1 to 4 g/kg of 2,7-DCDD and OCDD. Single exposures to dioxins have also affected the heart, liver, kidneys, blood, stomach, and endocrine systems of laboratory animals. No human deaths have been directly associated with exposure to dioxins. (ATSDR, 1998c).

5.8.4 Chronic Toxicity

In animal studies, numerous effects have been documented, including hepatic, gastrointestinal, hematological, dermal, body weight changes, endocrine, immunological, neurological, reproductive, and developmental effects. Most of the studies have involved oral exposure. Despite the variety of adverse effects observed in animals exposed to dioxins, adverse health effects in humans have generally been limited to highly exposed populations in industrial factories or following chemical accidents and contamination episodes. The adverse human health effect most commonly associated with high-level exposure to dioxin-like agents is the skin disease chloracne, a particularly severe and prolonged acne-like skin disorder. Adverse human health effects were also noted following consumption of heated rice oil contaminated with PCBs and CDFs. Conclusive evidence of other adverse human health effects at lower dioxin exposure levels is generally lacking because of incomplete exposure data, concomitant exposure to other compounds, and/or small numbers of study participants. Some epidemiological studies have suggested that dioxins may cause immuno-suppression, respiratory effects, cardiovascular effects, and liver effects in humans (ATSDR, 1998c, U.S. EPA, 1994a).

5.8.5 Reproductive and Developmental Toxicity

Dioxins have been shown to cause adverse developmental effects in fish, birds, and mammals at low exposure levels. Several studies in humans have suggested that dioxin exposure may cause adverse effects in children and in the developing fetus. These include effects on the skin, nails, and meibomian glands; psychomotor delay; and growth retardation. However, study limitations, including lack of control for confounding variables, and deficiencies in the general areas of exposure make it difficult to interpret these results. Overall, the human data are inconclusive; however, the animal data suggest that developmental toxicity is a concern (ATSDR, 1998c, U.S. EPA, 1994a).

In mammals, learning behavior and development of the reproductive system appear to be among the most sensitive effects following prenatal exposure. In general, the embryo or fetus is more sensitive than the adult to dioxin-induced mortality across all species (ATSDR, 1998c, U.S. EPA, 1994a).

5.8.6 Mutagenicity

The majority of mutagenicity assays of dioxins have been negative. An increased incidence of chromosomal aberrations was found in fetal tissue but not maternal tissue in a group of women exposed to dioxins following an industrial accident in Italy; however, cases treated for chloracne did not have an increased incidence of chromosomal aberrations. Animal studies also are inconclusive. The available data do not provide strong evidence that dioxins are genotoxic (ATSDR. 1998c, U.S. EPA, 1994a).

5.8.7 Carcinogenicity

Dioxins are classified by EPA as Group B2 (sufficient evidence in animals, insufficient evidence in humans) when considered alone and Group B1 (sufficient evidence in animals, limited evidence in humans) when considered in association with chlorophenols and phenoxyherbicides. This is based on studies that have found multiple-site sarcomas and carcinomas in rats and mice exposed to various dioxin mixtures and congeners. Epidemiological studies suggest an increased incidence of cancer mortality (all types of cancers combined) and of some specific cancers (soft-tissue sarcoma, non-Hodgkin's lymphoma, respiratory tract cancer, and gastrointestinal cancers). In addition, there is evidence that 2,3,7,8-TCDD acts as a tumor promoter. As with all epidemiological studies, it is very difficult to obtain clear unequivocal results because of the long latency period required for cancer induction and the multiple confounders arising from concurrent exposures, lifestyle differences, and other factors. The currently available evidence suggests that dioxins may cause cancer in humans (ATSDR, 1998c, U.S. EPA, 1994a). EPA has derived a cancer slope factor of 1.56×10^{5} $(mg/kg\text{-}d)^{-1}$ for 2,3,7,8-TCDD (HEAST, 1997).

5.8.8 Special Susceptibilities

There is evidence that children are more susceptible than adults to the dermal toxicity of dioxins. Animal data suggest that the developing reproductive, immune, and nervous systems of the fetus are particularly sensitive to dioxin toxicity (ATSDR, 1998c).

5.8.9 Interactive Effects

Environmental exposure to dioxins includes various mixtures of CDDs, CDFs, and some PCBs. These mixtures of dioxin-like chemicals cause multiple effects that vary according to species susceptibility, congeners present, and interactions. Risk assessment of these complex mixtures is based on the assumption that effects are additive and there is some experimental evidence to support this. However, there also is evidence that some interactions may result in inhibition and others result in potentiation. Cotreatment of mice with various commercial PCB mixtures (Aroclors) and 2,3,7,8-TCDD has resulted in inhibiting some of the Ah receptor mediated responses. An increased incidence of cleft palate was reported when mice were treated with both 2,3,7,8-TCDD and hexachlorobiphenyl compared to treatment with 2,3,7,8-TCDD alone. Both synergistic and antagonistic responses have been observed following co-exposure of 2,3,7,8-TCDD with other chemicals as well (ATSDR, 1998c).

5.8.10 Critical Data Gaps

The following data gaps have been identified for dioxins: inhalation and dermal toxicity studies; toxicity studies of dioxin compounds other than 2,3,7,8-TCDD; continued medical surveillance of individuals with known past high exposures to dioxins; mechanistic studies; immune function tests in human cohorts; neurological tests in ongoing prospective studies of humans; congener-specific human toxicokinetic studies to better assess human dosimetry; and further studies to identify potential biomarkers for exposure and effects. Another critical data gap is the need to gather exposure data and conduct modeling for the purpose of linking human exposure to sources (ATSDR, 1998c).

5.8.11 Summary of EPA Health Benchmarks

Chronic Toxicity	Not available
Carcinogenicity	$1.56 \times 10^{+5}$ per mg/kg-d.

5.8.12 Major Sources

U.S. EPA (1994a), ATSDR (1998c), Heast (1997), Van den Berg et.al. (1998).