TOXICOLOGICAL PROFILE FOR HEPTACHLOR/HEPTACHLOR EPOXIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for heptachlor/heptachlor epoxide was released on April 1989. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, on October 17, 1990, and on October 17, 1991. A revised list of 275 substances was published on October 28, 1992.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper, M.D., M.P.H.
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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about heptachlor and heptachlor epoxide and to emphasize the human health effects that may result from exposure to them. The Environmental Protection Agency (EPA) has identified 1,300 hazardous waste sites as the most serious in the nation. These sites comprise the "National Priorities List: (NPL): Those sites which are targeted for long-term federal cleanup activities. Heptachlor and heptachlor epoxide have been found in at least 129 and 87 of these sites, respectively. However, we do not know how many of the 1,300 NPL sites have been evaluated for heptachlor and heptachlor epoxide. As EPA evaluates more sites, the number of sites at which heptachlor and heptachlor epoxide are found may change. This information is important for you to know because heptachlor and heptachlor epoxide may cause harmful health effects and because these sites are potential or actual sources of human exposure to heptachlor and heptachlor epoxide.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical when you come into contact with it. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to hazardous chemicals such as heptachlor and heptachlor epoxide, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such. as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT ARE HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Heptachlor is a synthetic chemical that was used in the past for killing insects in homes, buildings, and on food crops. It has not been used for these purposes since 1988. There are no natural sources of heptachlor or heptachlor epoxide. Trade names for heptachlor include Heptagran, Heptamul, Heptagranox, Heptamak, Basaklor, Drinox, Soleptax, Gold Crest H-60, Termide, and Velsicol 104. Heptachlor is both a breakdown product and a component of the pesticide chlordane (approximately 10% by weight). Pure heptachlor is a white powder. Technical-grade heptachlor is a tan powder and has a lower level of purity than pure heptachlor. Technical-grade heptachlor was the form of heptachlor used most often as a pesticide. Heptachlor smells somewhat like camphor. Heptachlor does not burn easily and does not explode. It does not dissolve easily in water.

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Heptachlor epoxide is a breakdown product of heptachlor. It was not manufactured and was not used as an insecticide like heptachlor. Like pure heptachlor, heptachlor epoxide is a white powder that does not explode easily. Heptachlor epoxide is made by bacteria in the environment. Animals and people also make heptachlor epoxide when heptachlor enters their bodies. This profile describes these two chemicals together because about 20% of heptachlor is changed within hours into heptachlor epoxide in the environment and in your body.

You might find heptachlor or heptachlor epoxide in the soil or air of homes treated for termites, dissolved in surface water or groundwater, or in the air near hazardous waste sites. You might also find heptachlor or its by-product, heptachlor epoxide, in plants and animals near hazardous waste sites. Heptachlor can no longer be used to kill insects on crops or in homes and buildings. However, heptachlor is still approved by EPA for killing fire ants in power transformers. More information on the chemical and physical properties of heptachlor and heptachlor epoxide is found in Chapter 3. More information on the production and use of heptachlor is found in Chapter 4.

1.2 WHAT HAPPENS TO HEPTACHLOR AND HEPTACHLOR EPOXIDE WHEN THEY ENTER THE ENVIRONMENT?

From 1953 to 1974, heptachlor entered the soil and surface water when farmers used it to kill insects in seed grains and on crops. It also entered the air and soil when professional insect exterminators and homeowners used it to kill termites. Today heptachlor is no longer used by homeowners to kill termites or other insects. However, exterminators can still use existing stocks of heptachlor to kill fire ants in power transformers. Heptachlor and heptachlor epoxide can enter the air, soil, groundwater, and surface water from leaks at hazardous waste sites or landfills. Heptachlor sticks to soil very strongly and evaporates slowly into the air. Heptachlor does not dissolve easily in water. Heptachlor epoxide dissolves more easily in water than heptachlor does and evaporates slowly from water. Like heptachlor, heptachlor epoxide sticks to soil. Both heptachlor and heptachlor epoxide can travel long distances in the wind from places where they are released, such as treated fields or manufacturing sites. In soil and water, heptachlor is changed by bacteria into the more harmful substance, heptachlor epoxide, or into other less harmful substances. Heptachlor in the soil can be taken up by plant roots. Heptachlor in the air can be deposited on plant leaves and enter the plant from contaminated soil. Animals that eat plants containing heptachlor can also absorb it. Animals can also change heptachlor to heptachlor epoxide in their bodies. Heptachlor epoxide breaks down very slowly in the environment. It can stay in soil and water for many years. Both heptachlor and heptachlor epoxide build up in fish and in cattle. People store heptachlor epoxide in their fatty tissue. Some studies show that heptachlor epoxide can still be measured in fatty tissue 3 years after a person is exposed.

Most of the breakdown products of heptachlor are thought to be less harmful than heptachlor itself. However, in laboratory animals, heptachlor epoxide is more harmful than heptachlor. For more information on heptachlor and heptachlor epoxide in the environment, see Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Exposure to heptachlor and heptachlor epoxide most commonly. occurs when you eat contaminated food. Contaminated foods might include fish, shellfish (e.g., clams), dairy products, meat, and poultry. Children and toddlers drink large amounts of milk and may have greater exposure if the milk is contaminated with heptachlor or heptachlor epoxide. Infants can be exposed to these compounds from consumption of contaminated maternal or cow's milk. Exposure can also occur when you drink water, breathe air, or touch contaminated soil at hazardous waste sites that contain heptachlor or heptachlor epoxide. People whose homes have been treated with heptachlor to kill termites can be exposed by breathing heptachlor in the air. After heptachlor is changed to heptachlor epoxide in the soil, it can get into the air. People who breathe this air will be exposed to heptachlor epoxide. Workers who use heptachlor to kill fire ants are also exposed if they breathe in the heptachlor or get it on their skin.

Background levels are levels found in the environment that cannot be traced to a specific source. Information on background levels of heptachlor and heptachlor epoxide in the air was not found. In a survey conducted more than 4 years ago, the background levels of heptachlor in drinking water and gr,oundwater in the United States ranged from 20 to 800 parts of heptachlor in one trillion parts of water (ppt). Heptachlor was found in less than 2% of U.S. groundwater. samples that are known to be contaminated from pesticide application. The average level of heptachlor in the contaminated groundwater samples was 800 ppt. No information was found for-levels of heptachlor epoxide in groundwater or drinking water. Current information on background levels of heptachlor and heptachlor epoxide in groundwater or drinking water was not found. Heptachlor epoxide has been found in surface water (river, lakes) at levels between 0.1 and 10 parts of heptachlor epoxide in one billion parts of water (ppb, 1 ppb is 1 thousand times more than 1 ppt). Heptachlor and heptachlor epoxide stick to sediment and soil. The sediment in stream beds usually contains a lot of the heptachlor that enters the water. Heptachlor has been found in less than 1% of U.S. soil samples that are known to be contaminated. The average level of heptachlor detected in contaminated soil samples was 4 ppb. Heptachlor epoxide was not found in any of the contaminated soil samples. Contaminated fish and shellfish have been found to contain 2-750 ppb heptachlor and 0.1-480 ppb heptachlor epoxide. Heptachlor epoxide has been found in human milk samples at levels ranging from 0.13 to 128 ppb. The Food and Drug Administration (FDA) estimated that for

1982-1984, the daily intake of heptachlor and heptachlor epoxide from food was 2.7 ppt for infants (up to 12 months of age), 6.1 ppt for toddlers (1-3 years of age), and 1.5±2.8 ppt for adults. See Chapter 5 for more information on how you might be exposed to heptachlor and heptachlor epoxide.

1.4 HOW CAN HEPTACHLOR AND HEPTACHLOR EPOXIDE ENTER AND LEAVE MY BODY?

When you breathe air containing heptachlor or heptachlor epoxide, both can enter your bloodstream through your lungs. It is not known how fast these compounds enter and remain in the bloodstream. Both heptachlor and heptachlor epoxide can also enter your body through your stomach after eating food or drinking water or milk containing them. Most of the heptachlor that is swallowed passes through your stomach into your blood. It can also enter your body through your skin, although it is not known how fast this happens and the exact amount has not been measured. Heptachlor and heptachlor epoxide can pass directly from a mother's blood to an unborn baby through the placenta.

Near a hazardous waste site, heptachlor and heptachlor epoxide can enter your body if you breathe contaminated air, drink contaminated water, or touch contaminated soil. Exposure around hazardous waste sites can also occur by eating plants or animals that have been contaminated with heptachlor or heptachlor epoxide. Sometimes small children eat soil. If the soil is contaminated with heptachlor or heptachlor epoxide, they will be exposed in this way. Heptachlor epoxide can enter an infant's body in mother's milk after the mother has been exposed to heptachlor or heptachlor epoxide. Heptachlor can enter the bodies of people who make it in factories if they breathe it in or get it on their skin.

Once inside your body, heptachlor is changed to heptachlor epoxide and other related chemicals. Heptachlor epoxide is more harmful than heptachlor. The other breakdown products are generally less harmful. Most of the heptachlor, heptachlor epoxide, and other breakdown products leave your body in the feces within a few days after exposure. Some breakdown products can also leave in the urine. Some heptachlor and heptachlor epoxide are stored in your body fat for long periods after exposure has occurred. Heptachlor can go from fat to other tissues in the body. Effects can thus be seen immediately as well as at a later time. The heptachlor and heptachlor epoxide that have been stored in fat leave your body much more slowly. Chapter 2 contains more information on how heptachlor and heptachlor epoxide can enter and leave the body.

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1.5 HOW CAN HEPTACHLOR AND HEPTACHLOR EPOXIDE AFFECT MY HEALTH?

People can begin to smell heptachlor or heptachlor epoxide at around 0.3 milligrams in a cubic meter of air (0.3 mg/m^3). No reliable studies in humans were found that show whether harmful health effects occur as a result of breathing heptachlor or heptachlor epoxide. Also, no reliable human studies were found that show whether harmful effects occur from eating contaminated foods, drinking contaminated liquids, or from the chemicals passing through the skin. Blood tests suggest that these chemicals may cause mild liver changes. A few human cases show that breathing pesticide mixtures containing heptachlor may affect the nervous system causing dizziness, fainting, or convulsions. We do not know if the health effects were from heptachlor or other chemicals in the mixture. Studies of people who made or used pesticides that included heptachlor found no serious health effects. An accurate measure of how much heptachlor the workers were exposed to could not be determined. Heptachlor can cross the placental barrier and has also been detected in breast milk. However, it is not known if it affects the ability of men or women to reproduce.

We do not know if animals would have harmful effects after breathing in air that contains heptachlor or heptachlor epoxide for short or long periods. Studies have shown a number of harmful health effects when animals were fed heptachlor or heptachlor epoxide. These effects were more harmful when the exposure levels were high or when exposure lasted many weeks. When rats were fed high levels of heptachlor or heptachlor epoxide one time, half of them died. At these high levels, tremors and convulsions were seen. Some changes in the kidneys were also seen after rats were fed a very large amount of heptachlor one time. When mice were fed lower levels of heptachlor for several weeks, they had damage to their liver and adrenal glands. When exposures were low or when the exposure period was short, the changes in the liver disappeared. We do not know whether these effects also occur in people exposed to heptachlor or heptachlor epoxide in the same way. However, heptachlor kills insects by causing damage to their nervous systems. The effect of the substance on insects is in agreement with the tremors and convulsions seen in both animals and humans exposed to pesticides containing heptachfor Therefore, human exposure to large amounts of heptachlor could probably affect the nervous system, at least in the short term.

Animals that ate food containing heptachlor before and/or during pregnancy, had smaller litters. Some of the offspring of these animals had damage to their eyes known as cataracts, and some of the offspring did not live very long after birth. Some animals that ate heptachlor for several weeks were unable to have offspring. We do not know whether these effects would also occur in people exposed to heptachlor in the same way.

Animals fed heptachlor throughout their lifetime had more liver tumors than animals that ate food without heptachlor. The International Agency for Research on Cancer has determined that heptachlor and heptachlor epoxide are not classifiable as to their carcinogenicity to humans.

The levels of heptachlor or heptachlor epoxide that cause death in animals when placed one time on their skin are much higher than the levels that cause death after being eaten one time. Chapter 2 contains more information on the adverse health effects of heptachlor and heptachlor epoxide.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Laboratory tests can detect heptachlor and heptachlor epoxide in blood, fat, breast milk, and body tissues after exposure to high levels. These tests are not commonly available at your doctor's office. Most often, the test for heptachlor epoxide is used because heptachlor is quickly changed into heptachlor epoxide in your body. Blood samples are used most often because they are easy to collect. These tests are specific for heptachlor and heptachlor epoxide. However, heptachlor is both a breakdown product and a component of chlordane, another pesticide. So if heptachlor and heptachlor epoxide are measured in the blood, the actual exposure could have been to chlordane.

A few days after exposure, blood levels of heptachlor and heptachlor epoxide decrease and can no longer be measured. Therefore, blood tests for these chemicals must be done within a short period after exposure. Levels in fat can be measured for a much longer period after exposure. If heptachlor or heptachlor epoxide is found in your fat, it is not possible to tell when you were exposed to these chemicals or if harmful health effects will occur. See Chapters 2 and 6 for more information on detecting these chemicals in the environment or in human tissues.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has developed regulatory standards and guidelines to protect people from the harmful health effects of heptachlor and heptachlor epoxide. EPA has banned the sale of all heptachlor products and has restricted the use of heptachlor. EPA allows companies to use heptachlor only to kill fire ants in power transformers. However, people who bought heptachlor before it was banned can still use it for killing termites.

EPA concludes that the maximum amounts of heptachlor and heptachlor epoxide present in your drinking water and in the seafood you eat each day through your lifetime should

not exceed 2.78 ppt. In theory, this would limit the risk of developing cancer to one in 100,000. For contaminated seafood alone, the maximum amounts of heptachlor and heptachlor epoxide that your consume each day throughout your lifetime should not exceed 2.85 ppt. This recommendation is made because harmful effects may occur in people after exposure to heptachlor. Because the exact levels that might cause these effects are not known, EPA has set a very low limit as a safety factor.

For short-term exposures of up to 10 days, EPA recommends that a child weighing 22 pounds or less not drink water containing levels of heptachlor greater than 10,000 ppt. For longer exposures, EPA recommends that a child not drink water containing levels of heptachlor greater than 5,000 ppt or water containing levels of heptachlor epoxide greater than 150 ppt.

FDA controls the amount of heptachlor and heptachlor epoxide on raw food crops and on edible seafood. The limit on food crops is from 0 to 10 ppb depending on the type of food product. The limit on edible seafood is 300 ppb. FDA limits the amount of heptachlor and heptachlor epoxide in the fat of food-producing animals to 200 ppb.

EPA has named heptachlor as a hazardous solid waste material. If quantities of heptachlor or heptachlor epoxide of greater than 1 pound enter the environment, the National Response Center of the federal government must be told immediately.

The American Conference of Governmental Industrial Hygienists (ACGIH) and the Occupational Safety and Health Administration (OSHA) recommend that the highest average amount of heptachlor in workplace air over an 8-hour workday for a 40-hour workweek not be more than 0.5 mg/m^3. For more information on standards and guidelines for heptachlor and heptachlor epoxide, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of heptachlor and heptachlor epoxide and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for heptachlor and heptachlor epoxide based on toxicological studies and epidemiological investigations.

There are few studies that specifically describe the effects of heptachlor or heptachlor epoxide in humans following exposure via the oral, inhalation, or dermal routes. There are data on the health effects of chlordane from occupational studies of pesticide applicators and manufacturers, and from studies of people who consumed food contaminated with chlordane and heptachlor. Chlordane is a pesticide that is structurally similar to heptachlor, and technical-grade preparations may contain anywhere from 6% to 30% heptachlor. While the effects of two such structurally similar compounds would be expected to be essentially similar, there might not be a one-to-one correspondence of effects, and data do not exist with which to compare the toxicities. The q_1* is the numeric value that is used to provide an estimation of the carcinogenic potency of a chemical. The EPA q_l* for chlordane is lower than that for heptachlor. The q_l* for heptachlor is lower than that for heptachlor epoxide. Based on general toxicity data in laboratory animals, heptachlor would appear to be more toxic than chlordane. Heptachlor epoxide is more toxic than heptachlor.

In addition to being a component of technical-grade chlordane, heptachlor is a metabolite of chlordane. Therefore, identification of heptachlor or heptachlor epoxide does not always signify that the primary exposure was to heptachlor. Humans have been exposed occupationally to heptachlor via the inhalation and dermal routes during manufacture and application of pesticides. The general population has been exposed through the inhalation or dermal routes following the use of chlordane or heptachlor in homes, and orally through the consumption of contaminated food. Much of the human data on exposure to heptachlor is limited because of concomitant exposure to other substances. Toxicological and pharmacological animal studies have tested heptachlor primarily by the oral route of exposure. The existing animal studies share similar limitations. For example, the National Cancer Institute (NCI) bioassay on the effects of heptachlor was carried out with a formulation of technical-grade heptachlor that contained 22% α-chlordane. Chlordane, heptachlor, and heptachlor epoxide have been classified as B2 carcinogens, or possible human carcinogens (IRIS 1990).

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermaI-- and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods—acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should

also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of heptachlor and heptachlor epoxide are indicated in Figure 2-l. Because cancer effects could'occur at lower exposure levels, the figures also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1989a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, the MRLs may be derived.

2..2.1 Inhalation Exposure

2.2.1 .l Death

A retrospective mortality study conducted on 1,403 white male workers engaged for at least 3 months in the manufacture of chlordane, heptachlor, and endrin between 1946 and 1976 showed a statistically significant increase ($p<0.05$) in deaths due to cerebrovascular disease when compared to U.S. mortality data (Wang and MacMahon 1979b). No clear relationship with employment duration, duration of follow-up, or age was found. An attempt was made to examine the relationship between exposure intensity and mortality, but complete occupational histories were not available in all cases. The study is also limited by lack of quantitative exposure information, concomitant exposure to other chemicals such as aldrin, endrin, and diazinon, and lack of control measures for confounding factors such as smoking. A larger occupational cohort of male pesticide applicators followed prospectively showed that for 16,124 workers employed for 3 months or more between 1967 and 1976, the standardized mortality ratio (SMR) was less than 100, indicating that there was no increase over expected deaths due to all causes (MacMahon et al. 1988; Wang and MacMahon 1979a). Specific dose and exposure information was not provided. These occupational studies are presumed to reflect primarily inhalation exposure, with some concomitant dermal exposure. Mortality due to bladder cancer was on the border of statistical significance. The results of the study suggested that blood pressure and cerebrovascular disease were end points to follow closely.

A mortality study of a cohort of 3,827 licensed male pesticide applicators was conducted in Florida. This cohort did not exhibit the healthy worker effect, as the overall SMR was close to expected (Blair et al. 1983). Increased SMRs, although not statistically significant, were seen for leukemia, cancers of the brain, and lung cancer. Follow-up was achieved for over 95% of the identified cohort members, but no information was available for smoking history.

No studies were located regarding death in animals after inhalation exposure to heptachlor or heptachlor epoxide.

2..2.1.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide.

Cardiovascular Effects. The information regarding cardiovascular effects in humans associated with heptachlor and heptachlor epoxide exposure is limited to a case report (Pines et al. 1986). Sixty-two hospital patients with no known occupational exposure to pesticides were divided into three groups: Group A comprised 8 men and 3 women with mild to moderate arteriosclerosis; Group B comprised 18 men and 6 women with moderate to severe arteriosclerosis; and Group C comprised 19 men and 8 women without obvious signs of arteriosclerosis and served as the study control. Several organochlorine compounds, including heptachlor epoxide, were determined in the patients' blood serum. Groups A and B had higher heptachlor epoxide blood levels (7.5 and 8.0 ng/g serum, respectively) than Group C (6.5 ng/g serum). The elevation in Group B was statistically significant. This report cannot be construed as showing a causal relationship between heptachlor epoxide and arteriosclerosis because there are no data on the background levels of pesticides in this population, and no adjustments for other risk factors for arteriosclerosis were made.

No studies were located regarding cardiovascular effects in animals after inhalation exposure to heptachlor or heptachlor epoxide.

Hematological Effects. Blood dyscrasias, including production defects and thrombocytopenic purpura, were described in a case report of 25 individuals exposed for an unspecified duration to heptachlor and chlordane following home application for termite treatment (Epstein and Ozonoff 1987). The primary route of exposure was probably inhalation. This study is limited by lack of specific exposure information and concomitant exposure to other pesticides. A case-control study of 60 men who died from aplastic anemia and 120 controls showed no dose-dependent causal relationship between pesticide exposure and aplastic anemia (Wang and Grufferman 1981). The cases were all males who died of aplastic anemia between the ages of 15 and 65 years in the state of North Carolina. The controls selected were men on the mortality list who met the criteria of having died in the same year of causes other than aplastic anemia and of being of the same race and age range at death as the case group. The occupations of all but 4 of the 180 cases and controls were obtained from the death certificates. There were no significant associations between aplastic anemia and occupation, which included exterminators, gardeners, and agricultural workers. However, the pesticide usage was estimated by domestic disappearance, and not direct measurement. Domestic disappearance is calculated by subtracting exports and net changes in inventories from total annual production. Three cases of aplastic anemia associated with exposure to chlordane, which can contain heptachlor, were reported by Infante et al. (1978). The cases were three males aged 15, 28, and 68 years. These exposures were not quantitated and were assumed to be some combination of inhalation

and dermal exposure. There could also have been exposures to other chemicals. Leukemia has also been associated with exposure to heptachlor in case reports. See Section 2.2.1.8.

No studies were located regarding hematological effects in animals after inhalation exposure to heptachlor or heptachlor epoxide.

2..2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide.

2..2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide.

2..2.1.5 Developmental Effects

Placental transfer of heptachlor epoxide was reported by Polishuk et al. (1977a). Heptachlor epoxide concentration in extracted lipids of fetal plasma (0.9959 ppm) exceeded that of the maternal blood sample (0.2798 ppm) or of the uterine muscle. These data indicate that the uterus and placenta do not provide an effective barrier to the fetus for these compounds. Heptachlor epoxide has also been identified in breast milk, thus providing an additional route of exposure for infants. This compound has also been detected in stillborn infant brain, adrenal, lung, heart, liver, kidney, spleen, and adipose tissues (Curley et al. 1969). Other than determining that the women had no known direct exposure to pesticides, the authors did not attempt to quantitate maternal heptachlor exposure levels. These studies are limited by the lack of data concerning route, duration, extent of exposure, and number of cases examined. No gross malformations were described in any of the stillborn infants. Although a developing organism could potentially be exposed to heptachlor transplacentally or during lactation, the existing data are inadequate to establish a relationship between exposure to heptachlor or heptachlor epoxide and human developmental toxicity.

No studies were located regarding developmental effects in animals after inhalation exposure to heptachlor or heptachlor epoxide.

2..2.1.6 Reproductive Effects

Significantly higher levels of heptachlor epoxide were detected in the sera of a group of women identified through hospital records with premature delivery than in the sera of a control group with normal delivery (Wassermann et al. 1982). However, sera levels of 8 of the 10 organochlorine pesticides for which analytical data were obtained were all significantly higher in the premature delivery group. In addition, route, duration, and level of exposure information was not reported. Heptachlor epoxide has been reported in stillborn infant brain, adrenal, lung, heart, liver, kidney, spleen, and adipose tissue, indicating transplacental transfer of heptachlor or heptachlor epoxide (Curley et al. 1969). These studies also reported the presence of polychlorinated biphenyls, lindane, and dieldrin in the samples. Lack of control for confounding factors such as smoking and concomitant exposure to other pesticides and lack of completeness of report data make it difficult to assess the causal relationship between adverse reproductive outcome in humans and inhalation exposure to heptachlor and heptachlor epoxide.

No studies were located regarding reproductive effects in animals after inhalation exposure to heptachlor or heptachlor epoxide.

2..2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide.

Genotoxicity studies are discussed in Section 2.4.

2..2.1.8 Cancer

A series of case reports described five cases of neuroblastoma and three cases of acute leukemia associated with chlordane exposure (Infante et al. 1978). In two of the cases of neuroblastoma, the exposure to chlordane occurred during prenatal development; otherwise, the exposures .are assumed to be via inhalation in combination with dermal contact that occurred at the ages of 1 year and 11 months, 2 years and 5 months, and 3 years and 8 months. The developmental period during which the exposures occurred for the cases of leukemia was not specified. Dosages and durations of exposure were also not specified. The authors concluded that there is an association between chlordane exposure and neuroblastoma and between chlordane exposure and leukemia but did not quantify the exposure frequency. However, the association of these malignancies with heptachlor exposure cannot be confirmed from these data because the exposures were to chlordane and were not quantified. In another study, leukemia was associated with exposure to chlordane and heptachlor following home termiticide use. However, this exposure cannot be confirmed to be causal because the study was limited by concomitant exposure to other chemicals, lacked quantitative exposure data, and failed to adjust for other potential causal factors such as genetic disposition or immunologic disorders (Epstein and Ozonoff 1987).

In a large occupational cohort mortality study, 16,124 workers engaged in the manufacture of chlordane and heptachlor were followed for cause of death (Wang and MacMahon 1979a). The results of the original study found no significant increase in death from any type of cancer. The SMR for bladder cancer was of borderline significance, but no information on cigarette smoking was obtained from the participants. The follow-up of this cohort of pesticide applicators identified an increase in lung cancer, but the SMR for deaths from lung cancer for the manufacturing group with the highest chance of exposure to heptachlor was only 97, indicating no increase for lung cancer deaths in this group and suggesting that chlordane and heptachlor were not responsible for the lung cancer increase. It is possible that the sample size was not sufficient for detecting the effect by the statistical methods employed in the study. In addition, the excess in lung cancers occurred in persons employed for less than 5 years, which suggests that factors other than prolonged exposure to heptachlor were responsible (MacMahon et al. 1988).

A retrospective mortality study was conducted on 1,403 white male workers engaged in chlordane, heptachlor, and endrin manufacture between 1946 and 1976 (Wang and MacMahon 1979b). All subjects were employed for at least 3 months. A slight excess of lung cancer was seen in this cohort compared to the general U.S. population, but the increase was not statistically significant. The lack of complete occupational histories made it impossible to examine the relationship between exposure intensity and mortality. The study is also limited by lack of quantitative exposure information, concomitant exposure to other chemicals, and lack of control measures for confounding factors.

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An occupational mortality study conducted on a cohort of workers employed for at least 3 months between 1952 and 1979 at a Velsicol plant in Memphis, Tennessee, revealed no pattern of disease or medical condition that indicated that persons employed in the manufacture of chlordane and other chlorinated hydrocarbon pesticides were at greater risk of adverse outcome than the general population (Shindell and Associates 1981). In general, the workers at the plant demonstrated the healthy worker effect as evidenced by a lower incidence of cancer and other health effects compared to the control population. This study had several deficiencies. The study design did not include examination of employees by designated physicians to establish manifestations such as respiratory difficulties, anxiety, restlessness, headache, etc. The blood and urine were not analyzed to verify the presence of pesticide, and serum was not obtained to determine serum glutamic-pyruvic transaminase (SGPT) or serum glutamic-oxaloacetic transaminase (SGOT) levels. Pregnancy status and race of women employees were not determined. Many of the workers were exposed to other chemicals in addition to heptachlor. The level of exposure to heptachlor was not documented. This study achieved 92.8% complete follow-up, suggesting that these findings do in fact represent the experience of the cohort as a whole. However, it would be desirable to conduct a follow-up study on the same population.

No studies were located regarding cancer in animals after inhalation exposure to heptachlor or heptachlor epoxide.

2..2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to heptachlor or heptachlor epoxide. However, since heptachlor is a major component of the insecticide chlordane, chlordane poisoning can be considered when evaluating heptachlor toxicity data. In the case study of a woman who ingested 6 g of chlordane with suicidal intent and died 9.5 days following ingestion, no information was presented on the composition of the chlordane. Therefore, the amount of heptachlor exposure is unknown, and the effect of other components of chlordane cannot be ruled out (Derbes et al. 1955).

Acute oral LD_{50}s for heptachlor in rodents (rats, mice, hamsters, and guinea pigs) and rabbits range from 40 to 162 mg/kg (purity ranging from unspecified to 99.9%) (Ben-Dyke et al. 1970; Eisler 1968; Gaines 1969; Gak et al. 1976; Lehman 1951; Podowski et al: 1979; Sun 1972). Acute oral LDS_{50}s for heptachlor epoxide in rodents (rats and mice) and rabbits range from 39 to 144 mg/kg (Eisler 1968; Podowski et al. 1979). The studies provide little information on procedural details such as dosing, number of doses, and detailed results. AI1 studies except Gak et al. (1976) and Sun (1972) used gavage dosing. The number of animals tested was either small or not reported.

Two calves receiving 2.5 or 5 mg/kg/day of heptachlor formulation (25% heptachlor) for 15 or 6 days, respectively, died after the last doses were administered (Buck et al. 1959). In contrast, among six calves given single doses of heptachlor epoxide formulation (25% heptachlor epoxide), two received 25 mg/kg, and three received 15, 10, or 5 mg/kg/day. All died within 3 hours to 3 days. These results indicate that heptachlor epoxide is more toxic to young calves than technical-grade heptachlor.

Heptachlor can be converted to its photoisomer, photoheptachlor, in the presence of sunlight or ultraviolet light. This photolysis can take place on plant leaves. Despite the use of a small number of test animals, photoheptachlor was found to be more toxic to rats than heptachlor or heptachlor epoxide. The LD_{50} for photoheptachlor was 3.8 mg/kg (Podowski et al. 1979).

Groups of eight male minks were fed diets containing 0, 1.79, 3.11, 5.67, or 6.19 mg/kg/day heptachlor for 28 days. Three minks receiving the highest dose died, two of them in the post-exposure observation period (Aulerich et al. 1990). Thus, intermediate exposure to heptachlor was highly toxic to minks.

Groups of 10 adult Osborne-Mendel rats (5/sex) and 10 adult B6C3F$_1$ mice (5/sex) were fed technical-grade heptachlor in food (73% heptachlor, 22% chlordane, 5% nonachlor) for 6 weeks, followed by a 2-week period of observation. Dietary doses were 1, 2, 4, 8, and 16 mg/kg/day (NCI 1977) for the rats and 2.6, 5.2, and 10.4 mg/kg/day for the mice. Two of five male rats died at the highest dose; no deaths were reported at 8 mg/kg/day or less. The LOAEL for male rats was 16 mg/kg/day, and the NOAEL was 8 mg/kg/day. All of the female rats died at the 16-mg/kg/day level, and four of five died at the 8-mg/kg/day level. No deaths were reported at 4 mg/kg/day or less. All male mice died at the l0.4-mg/kg/day level, the highest dietary dose tested in mice. No deaths were reported at levels of 5.2 mg/kg/day or lower. Two of five female mice died at the highest dose; no deaths were reported at the lower doses.

Groups of 50 male and 50 female B6C3F, mice were fed diets containing technical-grade heptachlor (73% heptachlor, 22% chlordane, 5% nonachlor) for up to 80 weeks at time-weighted average (TWA) doses of 0.79 or 1.8 mg/kg/day for males and 1.1 or 2.3 mg/kg/day for females. Following treatment, the animals were observed for 10 weeks. There were no significant differences in survival between the control and treated males. In females, there was a dose-related increase in mortality, due mainly to the effect of the high dose (NCI 1977). The increased mortality in females could be due to greater susceptibility in females or to the larger dose received by females. Chronic exposure of 50 male and 50 female Osborne-Mendel rats fed the same compound for 80 weeks at TWA doses of 1.94 or 3.9 mg/kg/day for males and 1.28 or 2.56 mg/kg/day for females resulted in a 20% decrease in survival in high-dose females (NCI 1977).

A high incidence (55-60%) of mortality was reported in neonatal rats following dietary exposure of parental rats for 18 months (Mestitzova 1967).

All reliable LD_{50} values and ail reliable LOAEL values for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory effects in humans or animals ‘after oral exposure to heptachlor or heptachlor epoxide.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species ‘and duration category are recorded in Table 2-l and plotted in Figure 2-1.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to heptachlor or heptachlor epoxide. In an intermediate-duration study, increased heart-to-body-weight ratio was reported in rats following dietary exposure to 0.5 mg/kg/day heptachlor, 5 days/week, for 4 weeks (Enan et al. 1982).

Gastrointestinal Effects. Nausea and vomiting were reported in humans following accidental ingestion of chlordane (Dadey and Kammer 1953; Derbes et al. 1955). These symptoms developed within 1.5-2.5 hours after a one-time ingestion of chlordane. Histopathologic ex,amination showed that the stomach and intestimal walls were slightly hyperemic in rats exposed to 5 mg/kg/day of heptachlor for 28 days (Pelikan 1971).

TABLE 2-1. Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Compound
ACUTE EXPOSURE									
Death									
1	Rat	(GO)	1 d 1x/d				71 (LD50) 60 (LD50) 3.8 (LD50)	Podowski et al. 1979	H HE PH
2	Rat	(GO)	1 d 1x/d				100 (LD50 male) 162 (LD50 female)	Gaines 1969	H
Systemic									
3	Rat	(GO)	1 d 1x/d	Hepatic		60 (increased serum GPT and ALD, increased liver GPT and ALD at 2 hours, decreased liver GPT and ALD at 72 hours, vacuolated cells, pyknotic nuclei)		Krampl 1971	H
Reproductive									
4	Mouse	(G)	1 d 1x/d		15			Arnold et al. 1977	H/HE
5	Mouse	(G)	5 d 1x/d		8			Epstein et al. 1972	HE
6	Mouse	(G)	5 d 1x/d		10			Epstein et al. 1972	H
INTERMEDIATE EXPOSURE									
Death									
7	Rat	(F)	6 wk ad lib				16 (2/5 M) 8 (4/5 F)	NCI 1977	H

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Compound
8	Mouse	(F)	6 wk ad lib				10.4 (5/5 M) 10.4 (2/5 F)	NCI 1977	H
9	Mink	(F)	28 d ad lib				6.19 (3/8 M)	Aulerich et al. 1990	H
Systemic									
10	Rat	(F)	28 d ad lib	Hepatic		5 (steatosis, 19% increase in liver weight)		Pelikan 1971	H
				Gastro		5 (slight hyperemia of stomach and intestinal walls)			
11	Rat	(F)	4 wk 5d/wk 1x/d	Hemato		0.5 (37% increase in WBC after 7 days, 70% increase in WBC after 28 days)		Enan et al. 1982	H
				Hepatic		0.5 (increased levels of bilirubin, glucose, and acid phosphatase at 7 days, decreased glycogen at 7 days, increased cholesterol and AP at 28 days, increased liver weight)			
				Renal		0.5 (87% increase in blood urea at 7 days)			
12	Rat	(GO)	28 d 1x/d	Hepatic		7 (mononuclear necrosis, GPT and ALD decreased in liver and increased in serum, normal ALD levels by 28 days)		Krampl 1971	H

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Compound
13	Mouse	(W)	180 d ad lib	Hepatic		5.7 (increased levels of SGPT, and liver lipid peroxide, increased liver to body weight ratio)		Izushi and Ogata 1990	H
				Musc/skel		5.7 (increased serum creatinine phosphokinase)			
14	Mouse	(F)	10 wk 7d/wk 4x/d	Hepatic			6.5 (hepatitis, necrosis, granuloma, congestion)	Akay and Alp 1981	H
				Renal			26 (granuloma)		
15	Mouse	(W)	26 d	Other			80 (adrenal fibrosis, cortical cell granulation, lipid accumulation)	Akay et al. 1982	H
16	Mouse	(GO)	92 d 2x/wk	Hepatic		10 (increased SGPT, serum AP, liver triglycerides, and liver to body weight ratio)		Izushi and Ogata 1990	H
17	Pig	(F)	78 d 1x/d	Hepatic		2 (decreased glycogen)		Halacka et al. 1974	H
				Other	2	5 (16% decrease in body weight gain)			
18	Pig	(F)	78 d 1x/d	Hepatic		2 (increased agranular endoplasmic reticulum in liver cells, decreased glycogen content)		Dvorak and Halacka 1975	H

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Compound
19	Mink	(F)	28 d ad lib	Hepatic	5.67	6.19 (fatty infiltration of the liver)		Aulerich et al. 1990	H
				Renal	5.67	6.19 (granulation, kidney discoloration, decreased kidney to body weight ratio)			
				Other		5.67 (22% decrease in body weight)			
Immunological									
20	Rat	(F)	28 d ad lib			5 (enlarged, congested hyperemic spleen)		Pelikan 1971	H
21	Mouse	(F)	10 wk 7d/wk 4x/d				26 (splenic fibrosis, increased spleen erythrocytes and eosinophilic leukocytes)	Akay and Alp 1981	H
22	Mink	(F)	28 d ad lib		3.11	6.19 (49% decrease in spleen/brain weight)		Aulerich et al. 1990	H
Neurological									
23	Mouse	(F)	10 wk 7d/wk 4x/d		6.5		13 (ataxia, tremors, self-mutilation, in females)	Akay and Alp 1981	H
24	Mink	(F)	28 d ad lib		5.67	6.19 (hyperexcitability, incoordination, paralysis in hind quarters)		Aulerich et al. 1990	H
Developmental									
25	Rat	(F)	60 d				0.25 (16% embryo survival in F1 generation)	Green 1970	H

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Compound
Reproductive									
26	Rat	(F)	60 d				0.25 (F1 generation: 30% decrease in fertility, increased resorption, F2 generation: 100% infertility)	Green 1970	H
27	Mouse	(F)	10 wk 7d/wk 4x/d				6.5 (100% infertility)	Akay and Alp 1981	H
CHRONIC EXPOSURE									
Death									
28	Rat	(F)	80 wk ad lib				2.56 (20% decrease in survival of females)	NCI 1977	H
29	Mouse	(F)	80 wk ad lib				2.3 (18% decrease in survival of females)	NCI 1977	H
Systemic									
30	Rat	(F)	18 mo 1x/d	Ocular			6 (lens cataracts)	Mestitzova 1967	H
Developmental									
31	Rat	(F)	18 mo 1x/d				6 (55-62% neonatal, death)	Mestitzova 1967	H
Reproductive									
32	Rat	(F)	80 wk ad lib			1.28 (vaginal bleeding)		NCI 1977	H

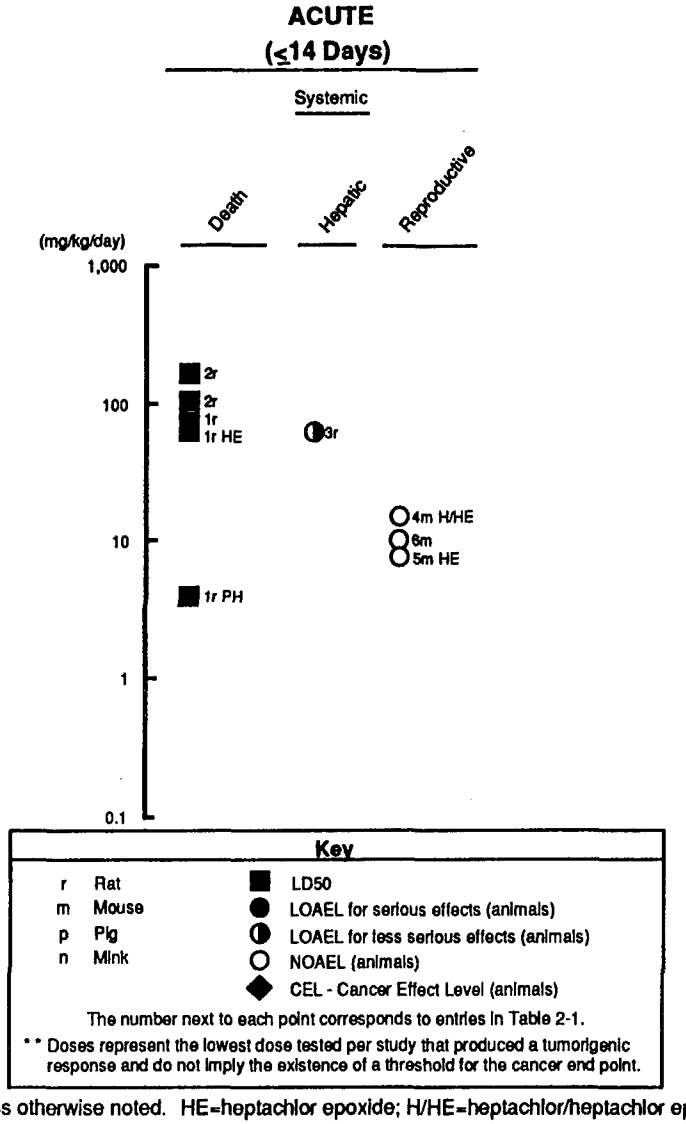
TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Compound
33	Rat	(F)	18 mo 1x/d				6 (23% decrease in mean litter size, 57% mortality at one month)	Mestitzova 1967	H
Cancer									
34	Mouse	(F)	80 wk ad lib				1.8 (hepatocellular carcinoma in males) 2.3 (hepatocellular carcinoma in females)	NCI 1977	H

[a]The number corresponds to entries in Figure 2-1.

ad lib = ad libitum; ALD = aldolase; AP = alkaline phosphatase; d = day(s); F = female(s); (F) = feed; F1 = first filial generation; F2 = second filial generation; (G) = unspecified gavage; Gastro = gastrointestinal; (GO) = oil gavage; GPT = glutamate pyruvic transaminase; H = heptachlor; HE = heptachlor epoxide; H/HE = mixture of heptachlor and heptachlor epoxide; Hemato = hematological; (LD50) = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; PH = photoheptachlor; SGPT = alanine aminotransferase; (W) = water; WBC = white blood cell(s); wk = week(s); x = time(s)

FIGURE 2-1. Levels of Significant Exposure to Heptachlor and Heptachlor Epoxide - Oral *



* All exposures were to heptachlor unless otherwise noted. HE=heptachlor epoxide; H/HE=heptachlor/heptachlor epoxide mixture; PH=photoheptachlor

FIGURE 2-1 (Continued)

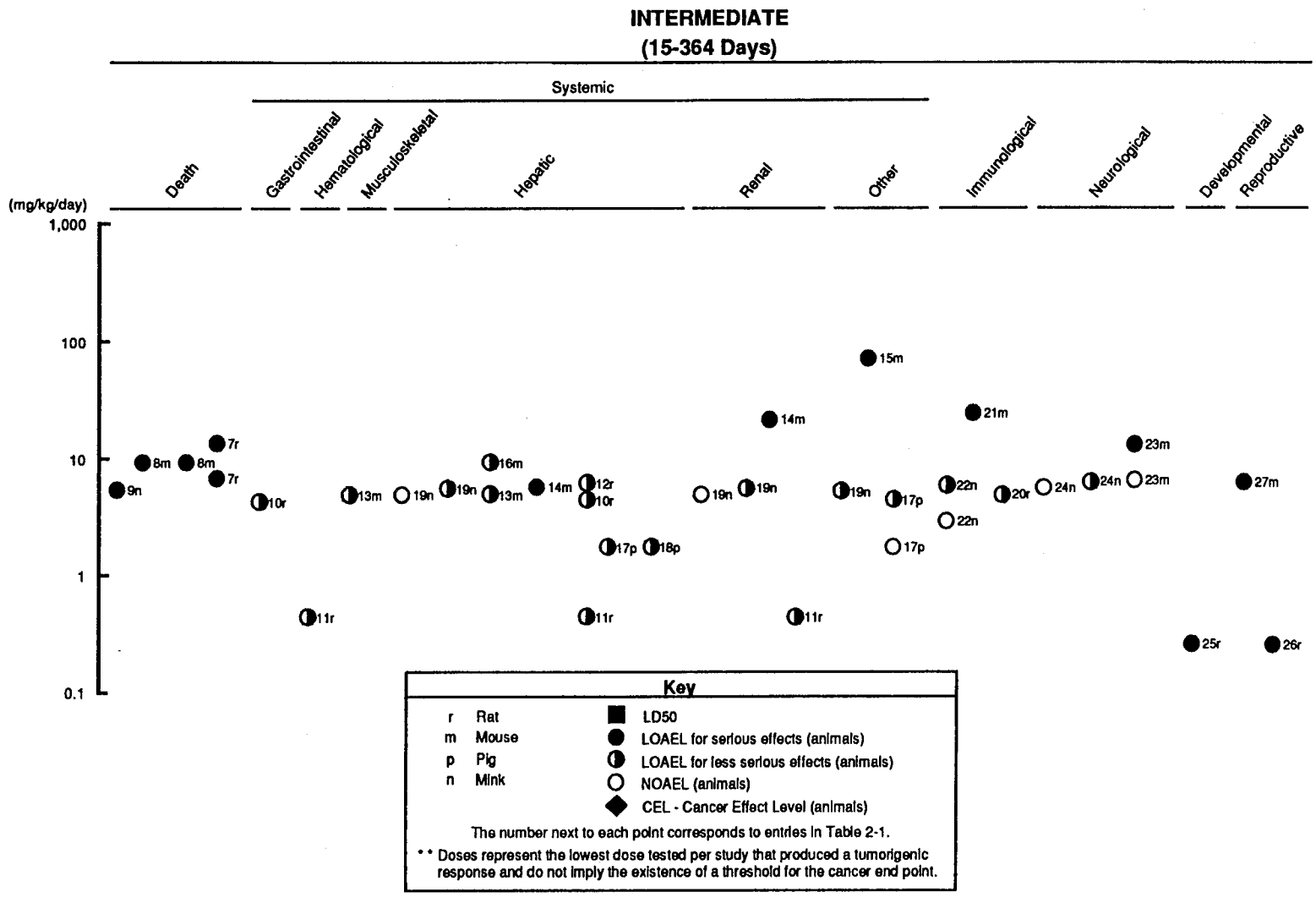
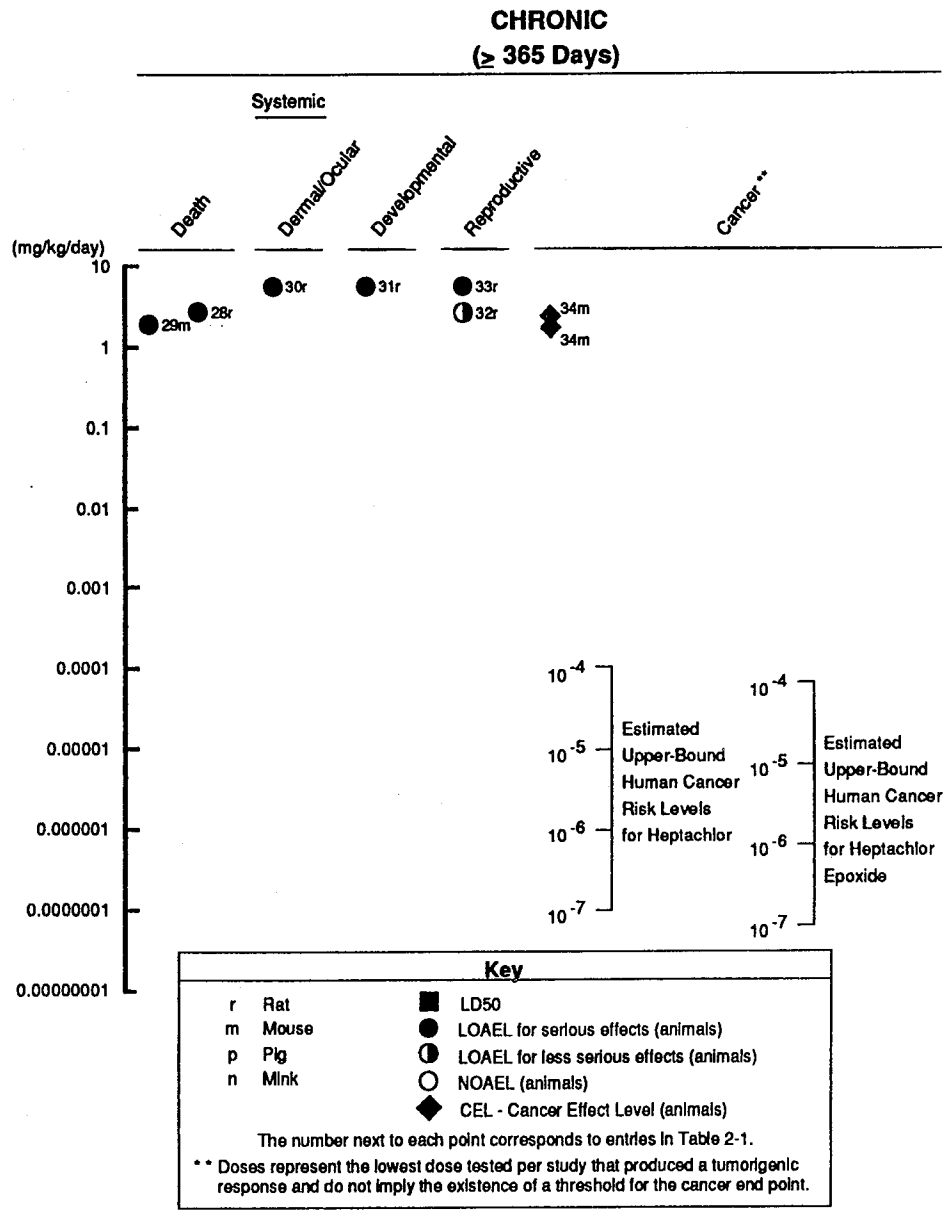


FIGURE 2-1 (Continued)



Calves fed multiple doses of heptachlor (2.5, 5, or 10 mg/kg/day for 16, 6, and 3 days, respectively) or heptachlor epoxide (2.5 and 3.5, or 15 mg/kg/day for 3 or 5 days, respectively) had hyperemic or hemorrhagic gastrointestinal tracts (Buck et al. 1959).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to heptachlor or heptachlor epoxide. See Section 2.2.1.2 for information on hematological effects from exposures thought to be by the inhalation route.

Rats that received 0.5 mg/kg/day of heptachlor (96% purity) in the diet in an intermediate-duration study (5 days/week for 4 weeks) showed a statistically significant increase in total white blood count and bilirubin at 1, 7, and 28 days post-exposure (Enan et al. 1982). This study is limited by the use of insufficient dose levels to establish a dose response.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to heptachlor or heptachlor epoxide. Calves given multiple doses of heptachlor (2.5, 5, or 10 mg/kg/day for 15, 6, and 3 days, respectively) and heptachlor (2.5, and 3.5, or 15 mg/kg/day for 3 and 5 days, respectively) exhibited muscle spasms as secondary effects to central nervous stimulation (Buck et al. 1959). In another study, an increase in serum creatinine phosphokinase was observed in mice fed 5.7 mg/kg heptachlor for 180 days (Izushi and Ogata 1990). This suggests that muscle damage may have occurred, but supporting histopathology was not presented by the authors.

Hepatic Effects. In a study of 45 individuals exposed for an unspecified period of time to contaminated raw milk products from cattle fed heptachlor-contaminated feed, 23-31% were found to have significantly elevated serum levels of heptachlor metabolites. Results of liver function tests and assays for hepatic microsomal enzyme induction did not differ from those of the local comparison cohort (Stehr-Green et al. 1986). In a follow-up study of the same families approximately 18 months later, heptachlor epoxide was found in the blood of 7 out of 39 subjects who drank raw milk contaminated with heptachlor at concentrations as high as 89.2 ppm and in the blood of 3 out of 79 controls. The exposed group had significantly higher mean serum levels of heptachlor epoxide (0.84 ppb) compared to the control group (0.50 ppb). However, no evidence of related acute or subacute hepatic effects such as hepatomegaly was found in the exposed subjects, regardless of their serum residue concentrations (Stehr-Green et al. 1988).

Oral exposures in rats and mice have been shown to increase hepatic micxosomal enzymes (Den Tonkelaar and Van Esch 1974; Krampl 1971) and to alter hepatic carbohydrate metabolism (Enan et al. 1982; Kacew and Singhal 1973). At week 1, the blood glucose levels increased by 48% while liver glycogen decreased. AlI measured liver gluconeogenic enzymes were increased over control levels by 41% (Kacew and Singhal 1973). This study, however, used only one dose that was above the LD_{50}, and only four animals per group were used. In addition, the dose is above the solubility limit for heptachlor, so there is some question as to the actual dose administered Single oral exposure of heptachlor (60 mg/kg) to female rats increased serum and liver GPT and ALD at two hours and decreased liver GPT and ALD at 72 hours; histology revealed vacuolated cells with pyknotic nuclei. Histologic examination of liver tissue from female rats given 7 or 12 mg/kg/day heptachlor (98% purity) for 28 days revealed slight morphologic changes that increased with increasing dose. The authors concluded that there could be a correlation between cellular leakage and necrosis and serum enzyme levels (Krampl 1971). Increased liver weight and an increase in hepatic lipid content occurred in rats that received 5 mg/kg/day heptachlor for 14 or 28 days (Pelikan 1971). No clinical signs were observed in any of the groups. This study used only one dose level and a control and did not report statistical significance. Mice that received 6.5, 13, or 26 mg/kg/day heptachlor showed toxic hepatitis with liver granuloma, hepatic cellular degeneration,

necrosis, fibrosis, and congestion in all treatment groups (Akay and Alp 1981). No statistical Lanalyses were presented and microsomal enzymes were not measured.

Three pigs receiving 2 or 5 mg/kg/day heptachlor showed a depletion of liver glycogen and increased agranular endoplasmic reticulum beginning at 78 and 27 days of exposure, respectively. Pigs receiving 5 mg/kg/day also showed an increase in lysosomes (Dvorak and Halacka 1975; Halacka et al. 1974). Activity of the 5th fraction of liver lactate dehydrogemase increased at the highest dose, as did swelling of the liver (without a change in liver weight) and slight steatosis of the hepatocytes (Halacka et al. 1974). Fatty infiltration of liver was observed in minks fed 6.19 mg/kg/day heptachlor for 28 days (Aulerich et al. 1990).

Oral exposure of mice to heptachlor for 92 days (10 mg/kg/day) or 180 days (5.7 mg/kg/day) increased SGPT and decreased phospholipids and total serum cholesterol (Izushi and Ogata 1990). Triglyceride content wIas increased at 92 days only. Evidence of liver damage was seen as a significant increase in SGPT. An increase in the liver-to-body-weight ratio was also observed.

Physiological responses following chronic dietary administration of heptachlor epoxide were investigated in five groups of beagle dogs (2 males and 3 females per group) fed diets containing 0, 0.013, 0.062, 0.13, or 0.19 mg/kg/day heptachlor epoxide continuously for 60 weeks (University of Cincinnati 1958). The body weight gain of male dogs decreased with the increasing concentration: this effect was margimally significant. There was a statisticdly significant, dose-dependent increase in termimal liver weights in both sexes of dogs. However, this increase wras not accompanied by histological changes and, therefore, could have been an adaptive response to treatment-related toxicity. No treatment-related clinical signs were noted. Moreover, the animals suffered from pneumonia which suggests poor animal husbandry. The other study limitations included an insufficient number of animals for meaningful statistical analysis, improper diet preparation, lack of analytical chemistry data, short experimental duration, and individual variations among animals reflecting genetic variability of the dog colony stock. Thus, chronic exposure to low concentrations of heptachlor epoxide produced minimal physiological changes in beagle dogs.

Renal Effects. Urimary output was severely reduced and uremia was present in a woman 24 hours after intentional ingestion of about 6 g of chlordane. After 9.5 days, she died; autopsy revealed nephrosis of the kidneys (Derbes et al. 1955).

Heptachlor was shown to alter renal carbohydrate metabolism in male Wistar rats that received a single dose of 200 mg/kg heptachlor. All measured gluconeogenic enzymes in the kidney cortex were significantly increased compared to controls. Heptachlor also elevated cyclic adenosine monophosphate (AMP) levels in the kidney cortex (Kacew and Singhd 1973). Granulomas were observed in the kidneys of mice that received 26 mg heptachlor/day in an intermediate-duration study (Akay and Alp 1981). Granuloma is a general term used to describe modular inflammation lesions that frequently contain proliferated macrophages. The inflammation characteristics as well as the increase in macrophages suggest some immune involvement, which is supported by the observation of splenic fibrosis.

Granulation and discoloration of kidneys and a decrease in kidney-to-brain-weight ratio was reported in minks fed 6.19 mg/kg/day of heptachlor daily for 28 days (Aulerich et al. 1990). Rats receiving 0.5 mg/kg/day of heptachlor in the diet in an intermediate-duration study showed a statistically significant increase in blood urea (Enan et al. 1982). Increased blood urea may indicate renal inefficiency in metabolism and clearance of protein by-products. This study is limited in that histologic examination was not included in the study design and insufficient dose levels were utilized to establish a dose response.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after oral exposure to heptachlor or heptachlor epoxide.

Of 50 adult rats used in a reproductive/developmental study, 22% of those that received 6 mg/kg/day heptachlor in the diet developed lens cataracts 4.5-9.5 months following exposure. In addition, 6-8% of the F_1, offspring and 6% of the F_2 offspring of these rats also developed cataracts 19-21 days after birth (Mestitzova 1967). The author of this study eliminated the possibility of a vitamin B deficiency or a recessive genetic trait as the cause of the cataracts. She could not rule out the possibility of altered vitamin B metabolism caused by heptachlor.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to heptachlor or heptachlor epoxide. A reduction in body weight was reported in minks fed heptachlor in the diet for 28 days (Aulerich et al. 1990). The observed effects were proportional to the concentration of heptachlor in the diet. Three pigs receiving 5 mg/kg/day of heptachlor for 78 days had a 16% decrease in body weight gain compared to controls (Halacka et al. 1974). Female mice receiving 80 mg/kg/day heptachlor (89% purity) showed increased incidences of cortical atrophy and slight hypertrophy in the zona glomerulosa of the adrenal gland compared to controls. Heavy lipid accumulation and granulation were observed in cortical cells on day 26 of exposure. Congestion, cell degeneration, and fibrosis in the adrenal cortex were reported at the end of the study in treated mice only; lack of these effects in controls suggest that they were not stress related (Akay et al. 1982). The interpretation of these findings is limited because the l00-ppm concentration reportedly used exceeds the solubility of heptachlor in water (0.05 ppm) (EPA 1987a). This implies that either the dose was reported incorrectly or that the heptachlor was present in suspension, calling into question the uniformity of dosing.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to heptachlor or heptachlor epoxide.

No animal studies were located that specifically investigated the effects on the immune system of oral exposure to heptachlor. However, systemic findings in three studies included some reference to changes that may reflect an effect on the immune system. Wistar rats fed 5 mg/kg/day heptachlor for 28 days developed enlarged, congested, and hyperemic spleens (Pelikan 1971). Female rats fed 0.5 mg/kg/day heptachlor for 4 weeks showed a significant increase in white blood cell count and an increased spleen-to-body-weight ratio (Enan et al. 1982). Mice fed 26 mg/kg/day heptachlor in food for 10 weeks showed kidney and liver granuloma, splenic fibrosis, and an increase in the number of erythrocytes and eosinophilic leukocytes in the spleen (Akay and Alp 1981). A decreased spleen-to-brain-weight ratio was reported in minks receiving 6.19 mg/kg/day heptachlor in the diet for 28 days (Aulerich et al. 1990).

The highest LOAEL values for immunological effects in each species following intermediate exposure are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.4 Neurological Effects

A case report of oral exposure to technical-grade chlordane reported neurological effects including irritability, salivation, dizziness, muscle tremors, and convulsions (Dadey and Kammer 1953). However, exposure measurements were not provided in the report, and technical-grade chlordane contains varying amounts of heptachlor. The effects cannot be said to have resulted from exposure to heptachlor only.

Tremors and convulsions were reported to occur in rats given 90 mg/kg heptachlor (oral LD_{50}) in a single dose. Neurotoxic signs appeared 30-60 minutes after dosing and lasted 2 days (Lehman 1951). This study was limited because procedural details were omitted, compound purity was not reported, and the number of animals tested was not reported. Hyperexcitability and incoordination were reported in minks fed 6.19 mg/kg/day heptachlor for 28 days; one had paralysis of the hind legs (Aulerich et al. 1990). Mice that received 13 mg/kg/day heptachlor for 10 weeks had difficulty in walking and standing and lost the righting reflex. Whole-body tremors and self-mutilation also occurred (Akay and Alp 1981).

Statistically significant changes in electroencephalogram (EEG) patterns were reported in female adult Wistar rats administered heptachlor in the diet at levels of 1 and 5 mg/kg/day for three generations (Formanek et al. 1976). Interpretation of these findings is difficult because details of the dosing, the procedures used, and conditions of the rats were not described.

Young calves fed multiple doses of heptachlor (2.5, 5, or 10 mg/kg/day for 15, 6, and 3 days, respectively) or heptachlor epoxide (2.5 and 3.5, or 15 mg/kg/day for 3 and 5 days, respectively) had muscle spasms in the head and neck region, convulsive seizures, elevated body temperatures, and engorged brain blood vessels (Buck et al. 1959).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species following intermediate exposure are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.5 Developmental Effects

The only study located regarding developmental effects reported no adverse effects on human fetal development following transplacental exposure to heptachlor based on birth certificate information and hospital discharge data (Le Marchand et al. 1986). The study was conducted on women of child-bearing age from Oahu, Hawaii, who ingested milk containing heptachlor for 27-29 months. The study did not provide data on the heptachlor level in the milk of nonexposed women. Therefore, the data are inadequate to establish a relationship between exposure to heptachlor and human developmental toxicity. Milk fat levels of heptachlor measured in Hawaii during this time ranged from 0.12 to 5.00 ppm (EPA's "worst case" estimates on record range from 0.10 to 1.20 ppm). No increase in fetal or neonatal deaths or incidence of low birth weight infants were found in this study cohort. Of the 23 categories of major congenital malformations evaluated, 22 were found to be decreased in the study population when compared with comparison cohorts from the other Hawaiian islands and from the U.S. general population for the same time period. One type of malformation (anomalies of the abdominal wall) was found to be slightly increased in the study cohort during the period of known exposure compared with the control cohorts. However, the baseline data for this type of malformation were not available prior to study initiation, and birth defects may be underreported. It was, therefore, not possible to document the temporal change in the incidence of this type of malformation. Since women who might not have consumed the contaminated milk were included in the study group, positive findings may have been diluted as a result of misclassification bias.

Cataracts and decreased postnatal survival were reported in the progeny of rats fed diets containing heptachlor. However, the data were insufficient to further evaluate these studies. Because cataracts also developed in the adult rats post-exposure, there is reason to question whether cataracts actually are a developmental effect. These studies are discussed below.

Transplacental exposure to heptachlor (98% purity) also significantly shortened the life-span of sucklings with the death rate being highest in the first 24-48 hours (Mestitzova 1967). Cataracts were noted in the progeny 19-21 days after eye opening. This study had several deficiencies including lack of details regarding the strain and number of rats, dosing methodology, duration of treatment period, and statistical analysis. Use of a single dose level precludes assessment of dose response.

Four male and 15 female Sprague-Dawley rats were fed diets containing 0.25 mg/kg/day heptachlor (purity not reported) for 60 days prior to mating and treatment continued during gestation of the females (Green 1970). Reduced fertility and increased resorptions were seen in the treated group, but statistical significance was not reported. The number of abnormal embryos was not significantly different. Postnatal survival in the F, progeny was reduced. Only 19 out of 122 offspring of treated rats survived 21 days postpartum compared to 179 out of 288 offspring of controls. The LOAEL for decreased embryo survival was 0.25 mg/kg/day. The study was conducted using only one dose level, and therefore, a NOAEL was not established.

The reliable LOAEL values for developmental effects in rats following intermediate and chronic exposure are recorded in Table 2-1 and plotted in Figure 2-l.

2.2.2.6 Reproductive Effects

No adverse effects on reproduction (no decrease in fertility, no increase in fetal or neonatal deaths) were reported by Le Marchand et al. (1986) among women of child-bearing age following ingestion of heptachlor-containing milk in excess of 0.1 ppm for 27-29 months.

In a dominant lethal assay, eight male Charles River CD-l mice received single oral doses of 7.5 or 15 mg/kg/day of a heptachlor:heptachlor epoxide mixture (25%:75%) and were bred with three untreated females each week for 6 weeks (Arnold et al. 1977). No adverse effect on the reproductive capacity of male mice was noted; therefore, the NOAEL was 15 mg/kg. A LOAEL was not established. Both heptachlor and heptachlor epoxide were also tested separately in another dominant lethal assay in mice. Heptachlor was tested at 5 and 10 mg/kg and heptachlor epoxide at 8 mg/kg/day. Neither agent produced early fetal deaths or preimplantation losses outside the control limits (Epstein et al. 1972).

Male and female Sprague-Dawley rats were fed diets containing 0.25 mg/kg/day heptachlor for 60 days; the females continued receiving the test diet through gestation (Green 1970). Increased numbers of resorptions were seen, although the number of abnormal embryos was not increased. During the second phase of the study, rats receiving 0.25 mg/kg/day for two generations showed a marked decrease in pregnancy rates. In the first generation, only 18 out of 25 heptachlor-treated females (compared to 30 out of 32 controls) became pregnant. In the second generation, none of 12 females receiving heptachlor became pregnant. Treatment seems to be more likely to affect male than female rats; treated females conceived and had normal litters when bred to males fed control food. The absence of normal viable sperm in the vaginal smear of heptachlor-fed females after copulation and the presence of normal spermatogenesis in the testes suggest that sperm are possibly killed (Green 1970). The LOAEL for decreased fertility in females was 0.25 mg/kg/day. A NOAEL was not established.

Male and female mice that were fed 6.5, 13, or 26 mg/kg/day of heptachlor for 10 weeks failed to produce a new generation after the 10 weeks of exposure (Akay and Alp 1981). No microscopic alterations were found in ovaries or testes. The study was limited by lack of details and statistical analysis.

When rats were fed 6 mg/kg/day heptachlor (98% purity) for an unspecified portion of an l8month study, there was a 23% decrease in size of successive generations (Mestitzova 1967). Vaginal bleeding was reported in rats fed 1.28 mg/kg/day heptachlor for 80 weeks (NCI 1977).

In a 2-year chronic rat study, daily dietary exposure of rats (20/sex) to heptachlor at concentrations of 0, 0.38, 0.075, 0.125, 0.175, and 0.25 mg/kg/day resulted in a failure of animals to reproduce (Witherup et al. 1955). Because of the lack of confirmation of copulation plugs, this effect cannot be definitely attributed to heptachlor exposure. The variations in weaning weight were inversely related to the numbers of pups nursed by the mothers. Growth of the offspring during the preweaning period was normal. Treatment-related high mortality was noted among offspring of mothers fed heptachlor at 0.125, 0.175, or 0.25 mg/kg/day but was not dose-dependent. Overall, the findings of the study are of little significance because of severe deficiencies (refer to Section 2.2.2.8 for details).

All reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.7 Genotoxic Effects

One case report was located involving a woman who ingested more than one-half gallon of heptachlor-contaminated milk per day during and after her pregnancy (Chadduck et al. 1987); the level of heptachlor in milk was not provided in the report. Her child was delivered normally and appeared to be healthy. Two weeks after birth, however, the child was diagnosed as having a cerebral gliosarcoma. Cytogenetic analyses of tumor cells revealed chromosomal anomalies including translocations, rearrangements, and breaks. The presence of chromosomal abnormalities suggests the possibility of either environmental or familial causes. However, most tumor cells exhibit abnormal karyotypes. Therefore, heptachlor is only a potential factor in the etiology of the cerebra1 gliosarcoma (Chadduck et al. 1987).

In two dominant lethal studies, neither heptachlor nor heptachlor epoxide proved to be clastogenic in the germ-line cells of male Charles River or Swiss mice (Arnold et al. 1977; Epstein et al. 1972). Mice in one study were given a single oral dose of heptachlor:heptachlor epoxide (25:75) at 7.5 or 15 mg/kg (Arnold et al. 1977). The other study involved five daily oral doses at 5 or 10 mg/kg for heptachlor or 8 mg/kg for heptachlor epoxide (Epstein et al. 1972).

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to heptachlor or heptachlor epoxide.

Dietary administration of heptachlor (97.6% purity) at 0.65 or 1.3 mg/kg/day for 25 weeks promoted the development of hepatocellular foci and hepatocellular neoplasms in male $B6C3F_1$ mice previously initiated with 3.8 mg/kg/day diethylnitrosamine in drinking water for 14 weeks (Williams and Numoto 1984). These results indicate that heptachlor acts as a liver tumor promoter in male mice.

Hepatocellular carcinoma was significantly increased in mice of both sexes following a chronic feeding study in which the mice received technical-grade heptachlor (73%) at 1.8 mg/kg/day heptachlor for males and 2.3 mg/kg/day heptachlor for females for 80 weeks. These were the highest doses for each sex that were

tested. Body weights were similar for exposed animals and controls. However, signs of toxicity including alopecia, rough coats, and palpable masses were seen in both treated and control animals. A dose-related decrease in survival was noted in high-dose females (NCI 1977).

Osborne-Mendel rats were fed technical-grade heptachlor (73%); males received TWA doses of 1.94 and 3.9 mg/kg/day and females received TWA doses of 1.28 and 2.56 mg/kg/day for 80 weeks (NCI 1977). The results of this study showed a statistically significant increase in follicular cell neoplasms in the thyroid (adenomas and carcinomas) in females fed the high dose compared to controls. This finding was discounted by the investigators, however, because the incidence rates were low and are known to be variable in the control rat population. Rates of tumor incidences in males were not increased.

In a 2-year chronic study, dietary exposure of CF rats to heptachlor failed to produce biologically and statistically significant treatment-related effects (Witherup et al. 1955). Six groups of rats (20/sex) were fed diets containing heptachlor at concentrations of 0, 0.038, 0.075, 0.125, 0.175, or 0.25. mg/kg/day. The mortality noted among animals was not dose-dependent and may have been age related or due to ill health since animals developed pneumonia and in some cases hepatitis or other diseases. Daily food intake varied among treated animals, varied from period to period, and displayed no uniformity. Variation in the body weight followed very closely the variation in food consumption, irrespective of the amounts of heptachlor ingested. The occurrence of various types of tumors primarily among dead animals was unrelated to the treatment and may have been spontaneous in origin and age related. The study had several deficiencies including a faulty diet preparation method, improper dose selection, and crude and insensitive methods for evaluation of toxicity. Moreover, it was conducted in the 1950s when test guidelines were not established. There was a lack of dose-response patterns in the reported results, and the concentrations of heptachlor used were too low to produce toxicologically significant effects, which suggests that the maximum tolerated dose was not achieved.

EPA has classified heptachlor and heptachlor epoxide in Group B2 (possible human carcinogen) (IRIS 1990). The International Agency for Research on Cancer (IARC) has classified heptachlor and heptachlor epoxide as Group 3 chemicals (not classifiable as to human carcinogenicity) (IARC 1979).

The Cancer Effect Level (CEL) inmice from chronic exposure to heptachlor is recorded in Table 2-l and plotted in Figure 2-l.

2.2.3 Dermal Exposure

There is very little information on dermal exposures in either humans or animals. Most occupational exposures to heptachlor and heptachlor epoxide are assumed to be some combination of inhalation and dermal exposure, but there are no data to quantitate the relative contribution of each route. The occupational studies on pesticide workers are discussed in Section 2.2.1.

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to heptachlor or heptachlor epoxide.

For heptachlor dissolved in xylene and administered once, Gaines (1969) reported LD_{50} values in Sherman rats of 195 mg/kg (males) and 250 mg/kg (females). Therefore, the dermal LD_{50} for heptachlor in rats is between 195 and 250 mg/kg heptachlor (Ben-Dyke et al. 1970; Gaines 1969). The studies are limited by

the lack of procedural details regarding the vehicle used for administration and the absence of data on the purity of the test compounds.

2.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans or animals after dermal exposure to heptachlor or heptachlor epoxide.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to heptachlor or heptachlor epoxide.

2.2.3.4 Neurological Effects

One human case report was located that described confusion and convulsions occurring about 40 minutes after a woman spilled an unknown amount of chlordane on her clothing (Derbes et al. 1955). The woman died shortly after the onset of convulsions; autopsy showed congestion and edema of the brain and scattered petechiae. Technical-grade chlordane contains varying amounts of heptachlor. However, exposure measurements were not provided in the report.

No studies were located regarding neurological effects in animals after dermal exposure to heptachlor or heptachlor epoxide.

No studies were located regarding the following health effects in humans or animals after dermal exposure to heptachlor or heptachlor epoxide:

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to heptachlor or heptachlor epoxide.

2 . 3 TOXICOKINETICS

2.3.1 Absorption

2.3.1 .l Inhalation Exposure

No studies were located regarding absorption in humans after inhalation exposure to heptachlor or heptachlor epoxide.

Although the database is extremely limited, one study has examined inhalation exposure in rabbits under environmental conditions (Arthur et al. 1975). One group of 20 white rabbits (10 male, 10 female; strain not reported) was housed outdoors in an area of high pesticide use, in cages under an aluminum roof allowing free air movement. A second, equal-sized group was housed inside a building in an area of low pesticide use. During the 3-month exposure, weekly air sampling revealed the heptachlor epoxide concentration to be 1.86 ng/m^3 in the high-exposure area. Heptachlor epoxide was not measured in the indoor area and was assumed negligible based on previous low measures of DDT. Respiratory intake of heptachlor epoxide was calculated to be 0.002 μg day; heptachlor epoxide was not detectable in the feed. At the end of the exposure period, serum and fat concentrations of heptachlor epoxide were measured. It was found that heptachlor epoxide in the fat of exposed rabbits was significantly higher than that measured in control animals (0.039-±-0.002 versus 0.016±0.001). No heptachlor epoxide was detected in any serum sample.

2.3.1.2 Oral Exposure

In order to assess the potential extent of human exposures and health effects, members of dairy farm families who consumed raw dairy products known to be contaminated with heptachlor epoxide were studied (Stehr-Green et al. 1986). These individuals and an unexposed urban reference population were compared with regard to serum pesticide levels and liver toxicity. The farm family members had significantly higher mean serum levels of heptachlor epoxide (0.81±0.94 ppb), oxychlordane (0.70±0.75 ppb), and transnonachlor (0.79±.60 ppb) than the unexposed population. This study is limited because exposure level, duration, and frequency of exposure are not known. There was no increase in prevalence of abnormal liver function tests in the dairy farm families compared to the urban population. There are insufficient data to make a quantitative estimate for. absorption of heptachlor in humans following oral exposure.

Heptachlor is absorbed from the gastrointestinal tract of rats (Radomski and Davidow 1953; Tashiro and Matsumura 1978) and cattle (Harradine and McDougall 1986) as indicated by the presence of heptachlor and/or its metabolites in serum, fat, liver, kidney, and muscle (Radomski and Davidow 1953) and by its oral toxicity in several animal species including rats, mice, hamsters, guinea pigs, and rabbits (LD_{50}, 40-162 mg/kg/day) (Ben-Dyke et al. 1970; Eisler 1988; Gaines 1969; Gak et al. 1976; Lehman 1951; Podowski et al. 1979; Sun 1972). Heptachlor epoxide is also absorbed after oral administration to rats (Gillett and Chan 1968). However, no quantitative data that specifically describe absorption of heptachlor epoxide following oral exposure were found in the literature.

Only 6% of the radioactivity from radiolabeled (^{14}C) heptachlor was found in the urine while 60% was found in the feces of male rats 10 days after a single oral dose indicating that most of the radioactive material was not absorbed and was excreted in the feces (Tashiro and Matsumura 1978). These data strongly suggest that a large percentage of heptachlor is absorbed from the gastrointestinal tract and eliminated via the bile into the feces. More than 72% of the radioactivity eliminated in the feces was present as metabolites of heptachlor (heptachlor epoxide, 13.1%; H-2, <0.1%; l-OH-chlordene, 19.5%; l-OH-chlordene epoxide, 17.5%; 1,2-OH-chlordene, 3.5%; H-6, 19.0%).

Three groups of four Australian Hereford steers were placed in a paddock that had been previously treated twice, 3 years earlier, with 0.275 kg heptachlor/hectare (Harradine and McDougall 1986). The mean heptachlor and heptachlor epoxide residues measured in soil samples averaged 0.136 ppm and 0.117 ppm, respectively. Soil samples showed substantial variability about the mean with no relation to date of sampling; this was attributed by the authors to uneven applications of heptachlor to the pasture, resulting

in "hot spots" which were not always sampled. Biopsies of fat from the steers were taken to monitor heptachlor uptake. Within 4 weeks of grazing in the contaminated paddock, one group of animals had heptachlor epoxide present in their body fat at levels that exceeded the Australian maximum residue limit of 0.2 mg/kg. In all groups of cattle, adipose tissue levels of heptachlor epoxide were inversely related to pasture grass length. The authors believe that when pasture grasses are shorter than 50 mm, ruminants ingest a great amount of pasture soil through close grazing, thus accounting for the relationship between pasture grass length and heptachlor and heptachlor epoxide intake. Although this study supports oral absorption of heptachlor and/or heptachlor epoxide in cattle, there are insufficient data to make a quantitative estimate of absorption fraction or absorption rate.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to heptachlor or heptachlor epoxide.

Heptachlor is absorbed through the skin following topical application as indicated by its dermal toxicity in rats (LD_{50}, 195-250 mg/kg) (Gaines 1969), but quantitative data are not available. Rats were given heptachlor dissolved in xylene (concentration of heptachlor unspecified), formulated to give a dose at a rate of 0.0016 mL/g body weight. The rats were not restrained and no attempt was made to remove the heptachlor from the shaved area of skin following the exposure, and therefore, some absorption following ingestion may also have occurred.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide.

2.3.2.2 Oral Exposure

No human studies were located regarding the distribution of heptachlor and its metabolites after oral exposure. However, there is an abundance of information reporting heptachlor and heptachlor epoxide in various tissues sampled at autopsy or during surgery, and in serum and milk from humans after exposure via unknown routes. Since the majority of data are from the period when heptachlor was widely used in agriculture, making the ingestion of heptachlor through contaminated agricultural products likely, human tissue, serum, and milk levels are presented in this section. It is possible, however, that other routes of exposure may have contributed to the overall body burden of heptachlor and heptachlor epoxide.

In the human studies described below, levels of organochlorine pesticides were measured in various tissues of adults at autopsy; in stillborn infants and newborns at autopsy; and in body fat, human milk, and serum. With the exception of one study (Stehr-Green et al. 1986), all of the studies are limited by the unknown exposure history of the individuals.

Autopsies of 77 Hawaiian individuals between 1966 and 1968 found heptachlor epoxide in tissues at levels ranging from 1 to 32 ppb (Klemmer et al. 1977). The highest levels of heptachlor epoxide occurred in bone marrow and liver, although the actual levels were not provided in the study. Autopsies of 271 patients with various terminal diseases detected heptachlor epoxide concentrations in fat

(0.21±0.11-0.48±0.37 ppm) and to a lesser degree in liver and brain (trace to 0.05 ppm and trace to 0.01 ppm, respectively) (Radomski et al. 1968). There appeared to be no correlation between the cause of death and the heptachlor epoxide concentration or pesticide usage during the lifetime of the individual.

Heptachlor epoxide was measured in a strip of skin, fat, and subcutaneous tissue from 68 children who died in the perinatal period and ranged from not detected (nondetectable) to 0.563 ppm (mean 0.173) (Zavon et al. 1969). In 10 other stillborn infants, heptachlor epoxide levels measured in various tissues were as follows: brain (nondetectable), lung (0.17±0.07 ppm), adipose (0.32±0.10 ppm), spleen (0.35±0.08 ppm), liver (0.68±0.50 ppm), kidney (0.70±0.28 ppm), adrenal (0.73±.27 ppm), and heart (0.80±0.30 ppm) (Curley et al. 1969). In another study, the following heptachlor epoxide levels were measured in extracted lipids from mothers and newborn infants: maternal adipose tissue (0.28±.31 ppm), maternal blood (0.28±0.46 ppm), uterine muscle (0.49±.51 ppm), fetal blood (1.00±0.95 ppm), placenta (0.50±0.40 ppm), and amniotic fluid C0.67±1.16 ppm) (Polishuk et al. 1977a). These data provide evidence of transplacental transfer to the fetus.

Heptachlor and heptachlor epoxide were measured in 51 human milk samples at average concentrations of 0.0027 and 0.019 ppm, respectively, from women with unknown exposure histories (Jonsson et al. 1977). Heptachlor epoxide was found in 24% of the samples, and heptachlor in 6%. Other investigators have reported the presence of heptachlor epoxide in human milk at concentrations ranging from not detected to 0.46 ppm (Kroger 1972; Polishuk et al. 1977b; Savage et al. 1981; Takei et al. 1983), suggesting a potential for lactational transfer to the fetus.

Unchanged heptachlor has not been detected in human adipose tissue; however, heptachlor epoxide was measured in adipose tissue at levels ranging from 0.0001 to 1.12 ppm (Barquet et al. 1981; Burns 1974; Greer et al. 1980; Radomski et al. 1968; Wasserman et al. 1974) and in plasma at 0.0136±0.0057 ppm (Polishuk et al. 1977b).

Animal studies regarding heptachlor and heptachlor epoxide distribution in body tissues are limited. When 20 adult female rats were fed heptachlor in their diet at a level of 35 ppm for 3 months, examination of the body fat revealed a high concentration of heptachlor epoxide at 3 months but no heptachlor (Radomski and Davidow 1953). Further studies in rats showed that accumulation of heptachlor epoxide was directly related to the dose of heptachlor given. A more detailed examination of the deposition of heptachlor epoxide in body tissues after oral administration under similar exposure conditions showed that the highest concentrations were found in the fat; markedly lower amounts were found in liver, kidney, and muscle; and none was found in the brain. In a parallel study, three dogs were also examined. Doses of 1 mg/kg/day for 12-18 months revealed the same distribution picture as in rats, but the livers of dogs contained more heptachlor epoxide than the kidneys and muscle tissue. Levels in all tissues were higher in female dogs than in males. This is interesting in light of the fact that male rats were more sensitive than female rats to heptachlor toxicity (Gaines 1969), suggesting a species difference.

The rate of heptachlor epoxide accumulation in, and elimination from, fat was determined in rats fed diets containing 30 ppm heptachlor for 12 weeks, then fed untreated diets for 12 more weeks (Radomski and Davidow 1953). Animals were sacrificed at various times during treatment, and it was shown that the residue in the fat of males reached a plateau at approximately 2-8 weeks. Thereafter, the levels decreased and were below the detection limit by the end of week 6 postdosing. In females, the heptachlor epoxide level in fat was much higher than males by the second week and throughout the remainder of the study. By the end of the 8th week postdosing, the heptachlor epoxide was below the detection limit in females.

Heptachlor and heptachlor epoxide residues were found in the fat (≥0.16 ppm and ≥18.25 ppm, respectively), liver (≥0.08 ppm and ≥2.11 ppm, respectively), and muscle (0 and ≥0.03 ppm, respectively) of pigs fed 2 mg/kg/day heptachlorine (purity unspecified) for 78 days (Halacka et al. 1974). When pigs were fed 5 mg/kg/day, the levels of heptachlor and heptachlor epoxide were higher: 0.37 and 25.82 ppm, respectively, in the fat; 0.23 and 4.94 ppm, respectively, in liver; and 0 and 0.7 ppm, respectively, in muscle.

Detection of heptachlor epoxide may indicate either recent or past exposure. This compound has a long half-life, particularly in adipose tissue, because it is very lipophilic. Because of its highly lipophilic nature, heptachlor epoxide remains accumulated in adipose tissue for months to years. However, it is eventually mobilized into the serum and subsequently to the liver for further breakdown. Blood serum levels are often taken to indicate a recent exposure. Following long-term exposure, the level in the blood may be very low, but because of an equilibrium between fat and blood, it can be used to detect exposure to heptachlor epoxide. Thirty-five human adipose tissue samples were obtained during autopsy between 1987 and 1988 from residents of North Texas (Adeshina and Todd 1990). In 97% of these samples, there were measurable levels of heptachlor epoxide that were positively correlated with age for the age groups 41-60 years and 61 and older. No differences between sexes were noted. These results indicate that the tissue levels of heptachlor epoxide in the human population from the above geographical region have not significantly decreased since 1970.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to heptachlor or heptachlor epoxide.

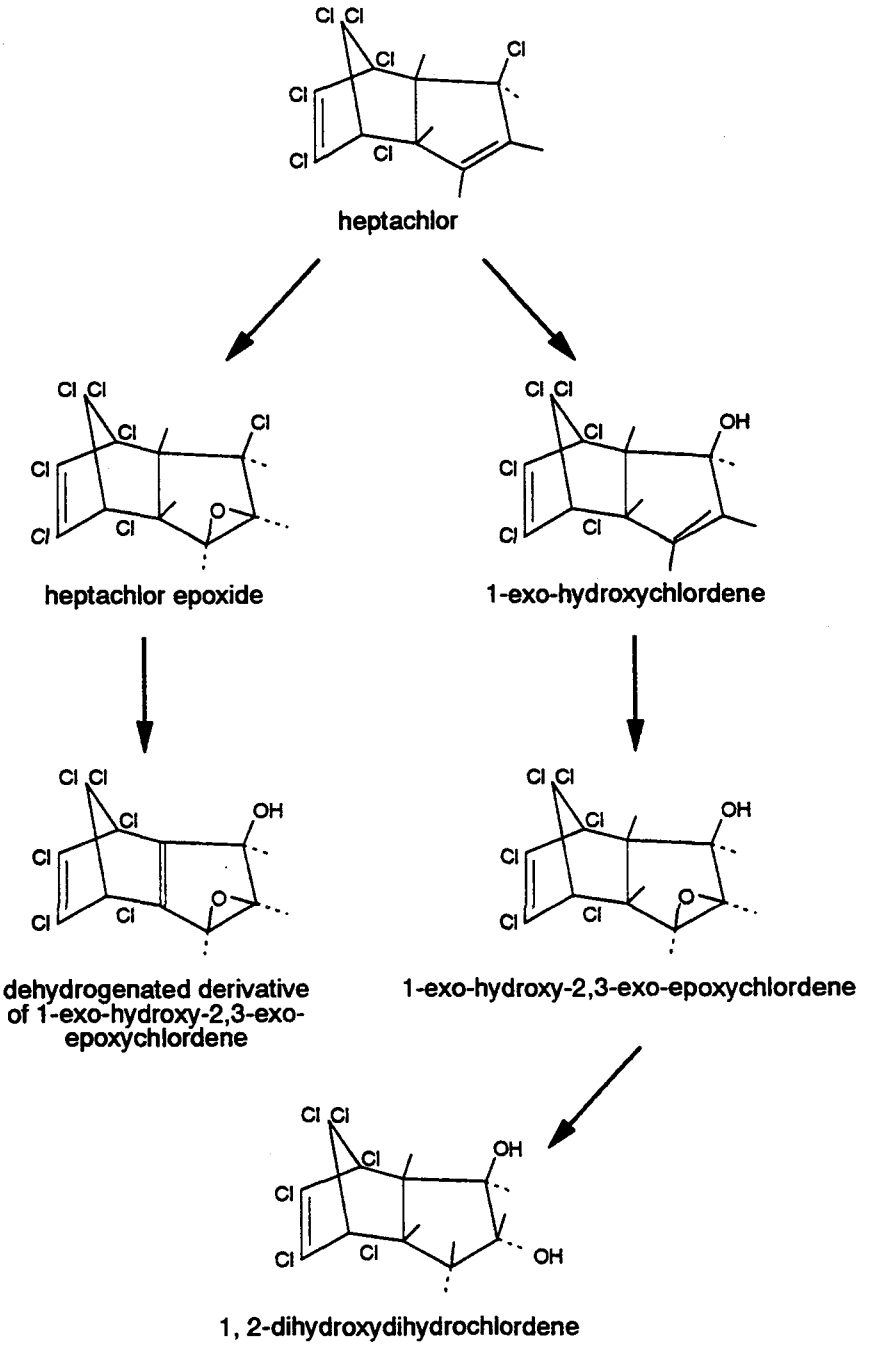
2.3.3 Metabolism

No studies were located regarding metabolism of heptachlor or heptachlor epoxide in humans. However, animal studies have shown that heptachlor undergoes epoxidation to produce heptachlor epoxide, which is more toxic than its parent compound. Heptachlor epoxide is further metabolized and excreted. In an in vitro liver study, human and rat liver microsomes metabolized heptachlor to the same products but in different proportions (Tashiro and Matsumura 1978). It was also shown in this study that rat microsomal preparations were four times more efficient in the metabolic conversion of heptachlor to heptachlor epoxide than were human microsomal preparations.

The major fecal metabolites in male rats administered a single oral dose of ^{14}C-heptachlor are heptachlor epoxide, l-exo-hydroxychlordene,1-exo-hydroxy-2,3-exo-epoxychlordene,and1,2 dihydrovdihydrochlordene, as well as two unidentified products (Figure2-2) (Tashiro and Matsumura 1978). By day 3, 50% of the dose was excreted in the feces. About 72% of the radioactivity was eliminated in the feces in the form of metabolites and 26.2% as parent compound by day 10. The same metabolites were identified in the comparative in vitro study using rat and human microsomal preparations (Tashiro and Matsumura 1978). Heptachlor epoxide is metabolized one step further to a dehydrogenated derivative of l-exo-hydroxy-2,3-exoepoxychlordene. Less than 0.1% of radiolabel was seen of this compound in an in vitro study using human liver microsomes (Tashiro and Matsumura 1978).

Heptachlor is formed through the metabolism of chlordane. Heptachlor epoxide is formed through the epoxidation of heptachlor and has been shown to be a cosubstrate of the same enzyme responsible for the epoxidation of aldrin to dieldrin (Gillett and Chan 1968). Heptachlor epoxide is considered more toxic

FIGURE 2-2. Metabolic Scheme for Heptachlor in Rats*



*** Adapted from Tashiro and Matsumura 1978**

than its parent compound and, like heptachlor, is primarily stored in adipose tissue (Barquet et al. 1981; Burns 1974; Greer et al. 1980; Harradine and McDougall 1986).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals after inhalation exposure to heptachlor or heptachlor epoxide. Based on the data from oral studies, heptachlor is expected to be excreted primarily in the form of metabolites and also as unchanged parent compound.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to heptachlor or heptachlor epoxide.

The elimination of a single oral dose of ^{14}C-heptachlor in male rats showed that most of the radioactivity was eliminated in the feces (Tashiro and Matsumura 1978). One day after dosing, 36% of the dose had been eliminated, and by day 10, approximately 62% had been eliminated in the feces. Elimination of the radioactive label in urine accounted for only 6% of the total dose in 10 days. Approximately 26.2% of the total radioactivity recovered from the feces was the parent compound and the remainder was in the form of metabolites.

Elimination of heptachlor epoxide via milk production was found to maximize within 3-7 days in cows that had grazed on pastures immediately following treatment of the grasses with heptachlor. The level of heptachlor epoxide in the milk was 0.22 ppm (Gannon and Decker 1960).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to heptachlor or heptachlor epoxide. Based on the data from oral studies, heptachlor is expected to be excreted primarily in the form of metabolites and also as unchanged parent compound.

2.4 RELEVANCE TO PUBLIC HEALTH

Although few quantitative data on exposures and measurable adverse health effects exist for humans, there is evidence that heptachlor and heptachlor epoxide can cause adverse effects if exposure is sufficient in duration and/or dose. Heptachlor is one of the cyclodiene pesticides designed to act as a neurotoxicant in insects. It is not surprising, therefore, that the central nervous system can be identified as one of the target systems of this compound in humans and animals. The liver is also a target organ for heptachlor and heptachlor epoxide. The findings of changes in liver enzymes and histopathology in several animal species indicate that the liver would be a target for humans also. There is some evidence from the few metabolic studies available that male rats may be more sensitive than female rats. Interestingly, a study on dogs provided evidence that the livers and other tissues of the females concentrated higher levels of heptachlor epoxide, although no differences in response were noted.

Heptachlor was classified by IARC as having some evidence for carcinogenicity although it tested negative in in vitro tests for deoxyribonucleic acid (DNA) repair (Williams et al. 1989). This evidence against

heptachlor having a direct effect on the DNA molecule is consistent with evidence from other chemicals that some chemicals act as epigenetic carcinogens and produce neoplasia by nongenotoxic mechanisms. Additional analysis based on the structure-activity relationships of 189 chemicals supports the possibility that heptachlor may contain non-electrophilic structures in common with other nongenotoxic carcinogens (Rosenkranz and Klopman 1990).

Death. Occupational mortality studies of pesticide workers exposed to heptachlor have not revealed an excess number of deaths in these cohorts compared to the general U.S. population. This may possibly be explained as a healthy worker effect. The EPA has described human case reports in which convulsions and death were reported following suicidal ingestion of technical-grade chlordane, which typically contains 6-30% heptachlor, but these effects cannot be attributed to heptachlor or heptachlor epoxide. There are no controlled, quantitative human data for any route of exposure. Acute lethality data were located for animals exposed via the oral and dermal routes. Both heptachlor and heptachlor epoxide may be considered very toxic via the oral route on the basis of acute animal data in rats and mice. Intermediate oral exposure to these compounds also caused up to 40% and 100% mortality in rats and mice, respectively. There appear to be differences in sensitivity in males and females in some species with the males being most sensitive. Heptachlor epoxide is more toxic than heptachlor. Heptachlor may be considered very toxic to extremely toxic via the dermal route on the basis of acute lethabty data in rats and mice. The severity of acute effects may possibly depend upon the extent of formation of heptachlor epoxide and the species tested.

Systemic Effects

Cardiovascular Effects. There is evidence to suggest that the effects of heptachlor on the atherosclerotic process are involved in both cardiovascular and cerebrovascular disease. The incidence of cerebrovascular disease was significantly increased in workers engaged in the manufacture of chlordane, heptachlor, and endrin, but was not increased in pesticide applicators and termite control operators thought to have the potential for high-level exposures to chlordane and heptachlor by unspecified routes. These studies were limited because of the lack of control for confounding variables such as preexisting cardiovascular disease and other risk factors such as smoking and dietary habits. There are no animal studies that confirm or refute cardiovascular effects following heptachlor or heptachlor epoxide exposure from any route. The effects of heptachlor on liver function, gluconeogenic enzymes, and steatosis could potentially be involved in the atherosclerotic process. Increases in gluconeogenic enzymes and hepatocyte production of lipids could cause increased serum levels of lipids, which in turn contribute to atherosclerosis.

Hematological Effects. Intermediate and chronic inhalation exposure of humans to mixtures of heptachlor, chlordane, and other chemicals has been associated with leukemia and aplastic and hemolytic anemias. These exposures were either occupational or followed the use of termiticides in homes. These exposures were probably primarily inhalation combined with dermal. There are oral animal studies that confirm that the hematopoietic system, specifically the white cells, can be affected by heptachlor exposure. Rats fed 0.5 mg/kg/day heptachlor in the diet showed a statistically significant increase in total white blood count (Enan et al. 1982). It appears that although the hematopoietic system is not a primary target for heptachlor or heptachlor epoxide, it can be measurably affected.

Hepatic Effects. There are a few epidemiological studies that have attempted to identify hepatic changes in humans exposed primarily via the inhalation route to heptachlor; so far these have been negative. On the basis of animal data, hepatotoxicity may be the most sensitive systemic end point for heptachlor and heptachlor epoxide; signs of toxicity in animals following short- or long-term oral exposure include

histologic evidence of liver damage, a statistically significant increase in liver weight, and increased levels of serum enzymes such as alanine aminotransferase (ALT), glutamine aminotransferase (GLT), and lactate dehydrogenase (LDH) indicative of hepatic damage. Decreased body weight gain has often been reported in conjunction with the induction of hepatotoxicity by intermediate or chronic oral exposure to heptachlor or heptachlor epoxide. Although these animal studies have limitations in either design or conduct, the hepatic effects seen are generally consistent across species. Heptachlor also induces cytochrome P-450 enzymes, which in turn aid the metabolism of heptachlor to heptachlor epoxide, a more toxic product. This, in effect, constitutes "self" bioactivation.

There are data from animal studies in mice, rats, and pigs that indicate that both carbohydrate metabolism and lipid metabolism may be affected by exposure to heptachlor or heptachlor epoxide (Enan et al. 1982; Halacka et al. 1974; Kacew and Singhal 1973, Pelikan 1971). Alterations in gluconeogenic enzymes and an increase in cellular steatosis in the liver have been reported. Granulomas and fibrotic liver have also been observed. In addition, hepatocellular carcinoma was identified as causally related to heptachlor in the diet in a mouse study conducted by the National Cancer Institute (NCI 1977). The existing evidence suggests that heptachlor and heptachlor epoxide are hepatic toxicants.

Chronic intramuscular injection of rats with heptachlor, heptachlor epoxide, or endrin (cyclodiene compounds) for 45 consecutive days significantly elevated the concentration of blood glucose and the levels of liver pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose l,Bdiphosphatase, and glucose 6-phosphatase. In addition, a significant decrease in hepatic glycogen content was noted in the animals receiving either of the three cyclodiene compounds (Kacew et al. 1973). However, in vitro studies of heptachlor epoxide in mouse liver homogenates showed no effects on enzyme succinic dehydrogenase activity at molar concentrations of 0.166×10^{-5}, 0.332×10^{-5}, 1.66×10^{-5}, and 3.32×10^{-5} (Gasper and Kawatski 1972). At a molar concentration of 1.66×10^{-5}, heptachlor epoxide caused slight inhibition of the enzyme system.

Renal Effects. There are some data that provide evidence of renal effects (uremia, nephrosis) in humans after deliberate oral exposure to heptachlor in chlordane. Target organ toxicities observed in rats and mice during long-term oral exposures include renal effects. Intramuscular injection with heptachlor, heptachlor epoxide, or endrin in rats for 45 consecutive days significantly elevated the concentration of blood urea and increased gluconeogenic enzyme activity in the kidney cortex (Kacew et al. 1973). While these enzyme changes do not necessarily indicate toxicity, they do indicate that heptachlor exposure may affect renal function. Granulomas of the kidney have also been associated with oral heptachlor exposure in mice. There are no extensive histopathologic data, but the human and animal data are consistent in the presence of renal effects.

Other Systemic Effects. Adrenal fibrosis with lipid accumulation was reported in one study in mice, but these effects have not been observed in humans known to be exposed to heptachlor and have not been verified in other species. There has been no measurement of adrenal hormone in exposed humans or animals. Body weight changes have, in general, been accompanied by a decrease in food consumption, due possibly to taste aversion.

Neurological Effects. In human case studies, signs of neurotoxicity (irritability, salivation, lethargy, dizziness, labored respiration, muscle tremors, and convulsions) were reported following exposure (route not specified) of humans to technical-grade chlordane, which contains between 6% and 30% heptachlor. These effects cannot, however, be attributed solely to heptachlor (Dadey and Kammer 1953). Neurotoxic signs, including tremors, convulsions, ataxia, and changes in EEG patterns, have been induced in animals

by chronic oral intake of heptachlor and heptachlor epoxide (Formanek et al. 1976). Studies in rat brain suggest that the neurotoxic effects of heptachlor or heptachlor epoxide may involve, in part, (1) interference with nerve action or release of nemotransmitters as the result of inhibition of either Na^{+}-K^{+} ATPase or Ca^{2+}-Mg^{2+} ATPase activity (inhibition of this enzyme results in reduction of Ca^{2-} binding capacity) (Yamaguchi et al. 1979), or (2) inhibition of the function of the receptor for γ-aminobutyric acid (GABA) (Yamaguchi et al. 1980). Because heptachlor was designed to be an insect neurotoxicant, it is not surprising that the central nervous system is a primary target for this chemical. These results could explain the neurotoxic effects observed in humans exposed -to chlordane, which may be partially attributed to heptachlor content.

Neurological damage following exposure to heptachlor and heptachlor epoxide was also observed in young calves. Central nervous system stimulation was manifested early by muscle spasms in the neck and head. These spasms progressed posteriorly and increased in severity, resulting in convulsions and finally death (Buck et al. 1959). The level of intake influenced the amount of heptachlor epoxide storage in the body fat. Heptachlor epoxide was 10 times as toxic to young calves as technical-grade heptachlor. The maximum nontoxic oral dose of heptachlor epoxide was l-2.5 mg/kg compared with 15-25 mg/kg for heptachlor. The authors characterized these symptoms as typical of those produced by other cyclodiene chlorinated hydrocarbon insecticides.

Cyclodiene insecticides produce intense nerve excitation in both vertebrate and invertebrate species (Matsumura 1985; Matsumura and Tanaka 1984). It has been suggested that the biochemical mechanisms by which these chemicals induce hyperexcitation in the central nervous system are due to the release of neurotransmitters caused by the interactions of the insecticide with the picrotoxinin receptor.

Developmental Effects. Heptachlor epoxide was detected in tissues of stillborn infants (Curley et al. 1969). A negative study was conducted in women of child-bearing age who ingested heptachlor-contaminated milk (Al-Omar et al. 1986). However, the authors did not examine or monitor developmental effects in the infants. The resulting data from the above studies were considered inadequate to establish a relationship between exposure to heptachlor and human developmental toxicity. A large cohort of births was investigated in Oahu, Hawaii, following more than a year of heptachlor-contaminated milk consumption by the mothers.. No evidence of an increase in the incidence of malformations was observed in the study population when" compared to equivalent cohorts from other islands of Hawaii and the general U.S. population (Le Marchand et al. 1986). These studies suggest that heptachlor can cross the placenta; in addition, heptachlor epoxide has been detected in breast milk.

Cataracts (Mestitzova 1967) and decreased postnatal survival (Green 1970) were reported in the progeny of rats fed diets containing heptachlor in intermediate- and chronic-duration studies. Data were insufficient to further evaluate these studies. Although the authors did not offer a mechanism, they did rule out vitamin B deficiency in the development of the cataracts. Because cataracts have also been observed in adult rats following oral exposure to heptachlor, there is reason to question whether cataracts actually are a developmental effect. No data were located for other routes of exposure in animals.

There are no data available that suggest that heptachlor or heptachlor epoxide are developmental toxicants at the levels measured in human populations.

Reproductive Effects. The existing data in humans are insufficient to establish a causal relationship between premature delivery and higher levels of heptachlor epoxide found in pregnant women (Wassermann et al. 1982). Because the ascertainment was based on premature delivery and other risk factors were not

controlled, it is not possible to relate the levels found in these women to those seen in the general population.

Following oral or intraperitoneal administration of heptachlor or heptachlor epoxide to male mice that were then bred with untreated females, the preimplantation losses and resorptions were within control limits (Arnold et al. 1977; Epstein et al. 1972). However, lack of corpora lutea counts may have resulted in inaccurate identification of preimplantation losses. On the other hand, when both sexes of mice or rats were fed diets containing heptachlor in multigeneration studies, resorptions were increased relative to controls, and fertility was markedly decreased (Green 1970), in some instances to zero (Akay and Alp 1981). These results seem to suggest that heptachlor affects the female reproductive system and/or the fetuses and may also affect the male reproductive system. No studies were found in which only female rodents were dosed.

Genotoxic Effects. No conclusive data exist to suggest that either heptachlor or heptachlor epoxide are genotoxic to humans. Only one case study was located that reported a possible link between prenatal heptachlor exposure and the chromosomal anomalies associated with an infant gliosarcoma (Chadduck et al. 1987). However, hereditary factors are also possible in this case. Human SV-40 transformed fibroblasts were exposed to heptachlor and heptachlor epoxide in an in vitro study (see Table 2-2). An increase in unscheduled DNA synthesis (UDS) was observed for both chemicals only in the presence of metabolic activators (Ahmed et al. 1977). According to this investigation, certain metabolites of heptachlor may be the genotoxic agents.

There are very few in vivo genotoxicity studies. Only two in vivo studies were located, and both assessed the dominant lethal effects. The results were negative for both studies, implying that neither heptachlor nor heptachlor epoxide are genotoxic to the germ-line cells of male mice when tested alone or as a mixture (Arnold et al. 1977; Epstein et al. 1972). Refer to Table 2-3 for a summary of these results of in vivo studies.

Most of the research regarding the genotoxicity of heptachlor and heptachlor epoxide comes from in vitro studies. The majority of these studies suggest that neither heptachlor nor heptachlor epoxide are genotoxic. One Salmonella typhimurium Ames assay reported gene mutation in the presence of metabolic activators (Gentile et al. 1982). The remaining gene mutation studies involving prokaryotic organisms reported negative responses both with and without metabolic activation (Glatt et al. 1983; Marshall et al. 1976; NTP 1987; Probst et al. 1981; Zeiger et al. 1987). Another prokaryotic study investigated heptachlor's capacity to cause DNA damage. Both S. tynhimurium and Escherichia coli were tested, and the results were negative for both bacteria (Rashid and Mumma 1986). However, since metabolic activators were not employed, it is impossible to know whether or not metabolites of heptachlor would have damaged DNA In fungi, Saccharomvces cerevisiae was negative for gene conversion following heptachlor exposure with and without activation (Gentile et al. 1982), and Aspergillus nidulans was negative for both gene mutation and chromosome malsegregation following exposure to heptachlor epoxide (Crebelli et al. 1986). Metabolic activators were again not utilized with A. nidulans. In vitro studies for mammalian species show mixed results. Rat, mouse, and hamster hepatocytes were negative for UDS (Maslansky and Williams 1981; Probst et al. 1981). Heptachlor without metabolic activation reportedly caused gene mutations in mouse lymphoma cells but not in adult rat liver cells (Telang et al. 1982). Chromosomal aberrations were observed in Chinese hamster ovary cells following exposure to heptachlor with metabolic activation; sister chromatid exchange was also observed both with and without metabolic activation (NTP 1987). Refer to Table 2-2 for a further summary of these results.

TABLE 2-2. Genotoxicity of Heptachlor and Heptachlor Epoxide In Vitro

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium (histidine reversion)[a]	Gene mutation	–	–	Zeiger et al. 1987
S. typhimurium (Ames assay)[b]	Gene mutation	–	–	Marshall et al. 1976; NTP 1987
S. typhimurium (Ames assay)[a]	Gene mutation	+	–	Gentile et al. 1982
S. typhimurium (modified Ames assay)[a]	Gene mutation	–	–	Probst et al. 1981
S. typhimurium (modified Ames assay)[c]	Gene mutation	–	–	Glatt et al. 1983
Escherichia coli (modified Ames assay)[a]	Gene mutation	–	–	Probst et al. 1981
S. typhimurium (disc assay)[a]	DNA damage	No data	–	Rashid and Mumma 1986
E. coli (DNA repair assay)[a]	DNA damage	No data	–	Rashid and Mumma 1986
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae (ade, trp loci assay)[a]	Gene conversion	–	–	Gentile et al. 1982
Aspergillus nidulans (strain 35/liquid medium)[c]	Gene mutation	No data	–	Crebelli et al. 1986
A. nidulans (strain P1/liquid medium)[c]	Chromosome malsegregation	No data	–	Crebelli et al. 1986

TABLE 2-2 (Continued)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Mammalian cells:				
Mouse (L5178Y tk^+/tk^- lymphoma cell forward mutation assay)[a]	Gene mutation	No data	+	McGregor et al. 1988
Rat (ARL-HGPRT assay)[a]	Gene mutation	–	NA	Telang et al. 1982
Chinese hamster (ovary cells)[a]	Chromosomal aberrations	+	–	NTP 1987
Chinese hamster (ovary cells)[a]	Sister chromatid exchange	+	+	NTP 1987
Rat (primary hepatocytes)[a]	Unscheduled DNA synthesis	–	NA	Probst et al. 1981
Rat (primary hepatocytes)[a]	Unscheduled DNA synthesis	–	NA	Maslansky and Williams 1981
Mouse (primary hepatocyte)[a]	Unscheduled DNA synthesis	–	NA	Maslansky and Williams 1981
Syrian hamster (primary hepatocytes)[a]	Unscheduled DNA synthesis	–	NA	Maslansky and Williams 1981
Human (SV-40 transformed fibroblasts)[b]	Unscheduled DNA synthesis	+	–	Ahmed et al. 1977

[a]Tested effects of heptachlor only
[b]Tested effects of both heptachlor and heptachlor epoxide individually; result applies to both compounds.
[c]Tested effects of heptachlor epoxide only

– = negative result; + = positive result; ade = adenine; ARL = adult rat liver epithelial cell line; DNA = deoxyribonucleic acid; HGPRT = hypoxanthine-guanine phosphoribosyl transferase; NA = not applicable; tk = thymidine kinase locus; trp = tryptophan

TABLE 2-3. Genotoxicity of Heptachlor and Heptachlor Epoxide *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
CD-1 mouse (dominant lethal assay)	Dominant lethal	–[a,b]	Arnold et al. 1977
Swiss mouse (dominant lethal assay)	Dominant lethal	–[a,c]	Epstein et al. 1972

[a]Result applies to both oral and intraperitoneal routes of exposure.
[b]Heptachlor/heptachlor epoxide mixture (25:75) was used.
[c]Results reflect separate exposures to both heptachlor and heptachlor epoxide.

– = negative result

Several studies were located involving heptachlor genotoxicity in plants. A positive response was noted for the waxy gene mutation in maize (Zea mavs) following exposure to heptachlor in situ (Gentile et al. 1982). A micronucleus test in Tradescantia produced a significant positive dose-related response at 1.88 ppm heptachlor (Sandhu et al. 1989). This study suggests that heptachlor has clastogenic potential in plants. Two researchers conducted a series of studies to determine the effects of certain pesticides (heptachlor included) on mitotic and meiotic chromosomes in Lens culinaris, Lens esculenta, Pisum sativum, and Pisum arvense (Jain and Sarbhoy 1987a, 1987b). For the mitotic segment, positive responses were observed after heptachlor treatment for the following chromosomal abnormalities: early separation during metaphase, condensation, stickiness, and chromatin bridges (Jain and Sarbhoy 1987a). For the meiotic study, heptachlor reportedly caused such chromosomal abnormalities as stickiness, non-orientation during metaphase I, fragments, multivalents, and bridges (Jain and Sarbhoy 1987b). These studies by Jain and Sarbhoy report no statistical comparisons with which to interpret the results; therefore, it is difficult to evaluate the significance of their research. Even though these plant studies suggest that both heptachlor and heptachlor epoxide are potentially genotoxic, the applicability to mammalian genotoxicity remains questionable.

Cancer. Existing epidemiological studies on heptachlor are considered inadequate to establish a clear qualitative or quantitative assessment of heptachlor exposure and human risk of developing cancer. The large occupational cohort mortality studies conducted on workers engaged in the manufacture of heptachlor have not identified a statistically significant increase in cancer deaths. Chronic oral exposure to heptachlor and heptachlor epoxide increased the incidence of liver carcinomas in CFN rats and C3H, CD-l, and $BGC3F_1$, mice. Heptachlor and heptachlor epoxide are classified as possible human carcinogens, Group B2, under EPA's guidelines for carcinogen risk assessment based on the positive cancer findings in animal studies. Heptachlor and heptachlor epoxide are classified as Group 3 by IARC. A Group 3 classification indicates that it is not possible at present to determine the human carcinogenicity of these compounds.

Heptachlor appears to be a promoter of hepatocarcinogenesis in mice. Consistent with this finding, low concentrations of heptachlor inhibited intercellular communication in Chinese hamster cells and rat liver cells, a property common to many known promoters (Williams and Numoto 1984). Of note was the demonstration of assay specificity for detection only of agents that interfere with cell-to-cell communication (epigenetic effect), as opposed to chemicals that induce a genotoxic effect. Overall, therefore, it may be postulated that heptachlor acts .through an epigenetic mechanism rather than one that is genetic.

In vitro treatment of human myeloblastic leukemia ML-l cells with low concentrations of heptachlor (<30 nmol) induced them to differentiate into monocyte and macrophage-like cells (Chuang et al. 1991). These cell types resemble those produced after treatment with 12-0-tetradecanoylphorbal-13-acetate (TPA), a known tumor promoter. Similar to TPA, heptachlor has been shown to inhibit intracellular communication between cultured liver cells (Telang et al. 1982). Based on these similarities, it is speculated that heptachlor and TPA may act by a common mode of action and that heptachlor acts not as a chemical mutagen, but as a tumor promoter (Chuang et al. 1991).

Most of the evidence from genotoxicity assays indicates that neither heptachlor nor heptachlor epoxide act directly on the DNA molecule. The exact mechanism by which these chemicals produce their effects remains unclear, but several lines of investigation are being pursued. Both chlordane and heptachlor have been shown to be potent inducers of protein kinase C activity in both rat and mouse brain. Several other chlorinated hydrocarbons were also positive for this effect; chlordane was the most potent of this set of chemicals (Moser and Smart 1989).

Other work has indicated that chlordane and heptachlor are energy transfer inhibitors as evidenced by marked decreases in oxidative phosphorylation of rat hepatic mitochondria following in vitro incubation of the mitochondria with the pesticides (Ogata et al. 1989). Interestingly, even though heptachlor epoxide is more toxic than either chlordane or heptachlor in tests of general toxicity, it was less effective in inhibiting mitochondrial respiration.

Heptachlor, chlordane, and endosulfan (another cyclodiene pesticide) were shown to inhibit hepatocyte gap junctional interceliular communication (Ruth et al. 1990). All three pesticides showed similar doseresponse relationships. Further testing with chlordane and heptachlor indicated that inhibition of the cytochrome P-450 system had no effect on this response. These results suggest that the interference with intercellular communication is not directly tied into the effects of these cyclodienes on the P-450 system.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NASNRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NASNRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to heptachlor and heptachlor epoxide are discussed in Section 2.51.

Biomarkers of effect are defined as .any measurable biochemical, physiologic, or other alteration within an organism that, depending *on* magnitude, can be recognized as an esrablished or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by heptachlor/ heptachlor epoxide are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to identify or Quantify Exposure to Heptachlor and Heptachlor Epoxide

Extremely sensitive analytical methods have been developed for the detection of heptachlor and heptachlor epoxide in various environmental and biological samples (detection limits as low as 10 ng/L). Although most methods were developed for detecting heptachlor and heptachlor epoxide in environmental media, the technology is readily adaptable to biological materials including breast milk, adipose tissue, and serum. These methods can be used to determine whether exposure has occurred. The presence of heptachlor may reflect an exposure to heptachlor or chlordane because it is a metabolite of chlordane. The presence of heptachlor epoxide may reflect an exposure to heptachlor or to chlordane since it is a metabolite of both these pesticides. However, in the absence of stable chlordane residues (e.g., nonachlor and oxychlordane), the heptachlor epoxide would most likely have been derived from heptachlor.

Detection of heptachlor or heptachlor epoxide may indicate either recent or past exposure. Heptachlor epoxide has a long half-life, particularly in adipose tissue, because it is very lipophilic and can remain for months to years. However, it is eventually mobilized into the serum and subsequently to the liver for further breakdown. Blood serum levels are often taken to indicate a more recent exposure, but heptachlor epoxide does become mobilized into the serum after being stored in adipose tissue for substantial periods. Thirty-five human adipose tissue samples were obtained during autopsy between 1987 and 1988 from residents of north Texas. In 97% of these samples, there were measurable levels of heptachlor epoxide that were positively correlated with age for the age groups 41-60 years and ≥61 years. No differences between sexes were noted. These results indicate that levels of heptachlor epoxide in human tissues from this region have not significantly decreased since 1970 (Adeshina and Todd 1990).

Pesticide residues were analyzed in 183 milk samples from 165 Finnish women. Heptachlor was found in 12% of the samples; heptachlor epoxide was found in 6.6%. Five percent of the samples contained levels of heptachlor epoxide in excess of 0.0005 mg/kg body weight, an acceptable daily intake (Mussalo-Rauhamaa et al. 1988). Fifteen milk and fat specimens from residents of Grand Forks, British Columbia, and 16 milk and 17 fat specimens from residents of Prince George, British Columbia, were analyzed for pesticide residues. Heptachlor epoxide was found in one milk sample and nine fat samples in the Grand Forks group (>0.004 ppm) and in no milk samples and two fat samples in the Prince George group (>0.004 ppm) (Larsen et al. 1971). The residue was not detectable at levels lower than 0.004 ppm because of limitations of the analytical methods and faulty techniques. It is possible that the potential exposure of the residents to heptachlor may also have occurred via food contaminated with heptachlor.

Organochlorine insecticide residues were determined in samples of human milk, evaporated milk, and prepared baby formulas from various regions of Canada (Ritcey 1972). A mean concentration of 0.003 mg/kg of heptachlor epoxide was detected in human milk, with significantly lower levels in evaporated milk and prepared baby formulas.

No studies were found correlating levels to which humans were exposed with actual body burdens. However, an attempt was made to correlate blood levels of chlordane, which may contain from 6% to 30% heptachlor, to duration of occupational exposure. Blood samples from 51 male pest control operators who were occupationally exposed to chlordane were tested for the presence of chlordane and its metabolites trans-nonachlor, oxychlordane, and heptachlor epoxide. The blood of 19 male workers with no experience : spraying chlordane was also tested as a control. Heptachlor epoxide was detected (from not detectable to 1.6 ppb) in 20% of the blood samples from pest control operators exposed to chlordane (concentration not reported). The total chlordane in the blood was low but demonstrated sizable correlation with the number of spraying days and the amount of chlordane sprayed (Saito et al. 1986).

2.5.2 Biomarkers Used to Characterize Effects Caused by Heptachlor and Heptachlor Epoxide

No specific tests for the effects of heptachlor or heptachlor epoxide were found. The neurological and hepatic effects seen from heptachlor and heptachlor epoxide exposure are typical of exposure to other chlorinated pesticides. An attempt was made to correlate blood residues of heptachlor epoxide to sperm count in a group of 29 infertile men and 14 controls matched for age and smoking (Pines et al. 1987). No correlation could be shown, however. Heptachlor epoxide was found in the blood of 7 out of 39 subjects who drank raw milk contaminated with heptachlor at concentrations as high as 89.2 ppm (fat basis) and in the blood of 3 out of 79 controls (Stehr-Green et al. 1988). The exposed group had significantly higher mean levels of heptachlor epoxide (0.84 ppb) compared to the control group (0.50 ppb). However, no evidence of related hepatic effects in the exposed subjects could be identified. In addition, the study authors were unable to identify a relationship between pesticide levels and dairy fat consumption. The levels of heptachlor found in the milk of four Iraqi women ranged from nondetectable to less than 1 ppm (Al-Omar et al. 1986). No health effects could be associated with these levels.

Although there are no data from human studies that indicate that hepatic effects occur in humans exposed to heptachlor, the animal studies indicate that the liver is a target organ for this chemical and is more sensitive to low doses than the neurological system. Decreased glycogen, increased cholesterol, GOT, and AP enzyme levels, and increased liver weight were reported in mice fed heptachlor at 0.5 mg/kg/day. In contrast, neurological effects such as convulsions were observed in a cow fed 2.5 mg&/day heptachlor daily for 15 days (Buck et al. 1959). Increased liver enzymes could indicate exposure to heptachlor, but this would not be a marker specific to this chemical. Refer to Section 2.2 for a detailed discussion of the effects caused by heptachlor and heptachlor epoxide.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Dietary administration of heptachlor (97.6% purity) at 0.65 or 1.3 mg/kg/day in diet for 25 weeks promoted the development of hepatocellular foci and hepatocellular neoplasms in male B6C3F mice previously initiated with 3.8 mg/kg/day diethylnitrosamine given in the drinking water for 14 weeks (Williams and Numoto 1984).

Nutritional factors may influence the toxicity of pesticides. Research in this area has primarily focused on the role of dietary proteins, particularly sulfur-containing amino acids, trace minerals, and vitamins A, C, D, and E. Studies in rats show that inadequate dietary protein enhances the toxicity of most pesticides but decreases, or fails to affect, the toxicity of a few. ‘The results of these studies have shown that at oneseventh or less normal dietary protein, the hepatic toxicity of heptachlor is diminished as evidenced by fewer enzyme changes (Boyd 1969; Shakman 1974). The lower-protein diets may decrease metabolism of heptachlor to heptachlor epoxide.

Male weanling rats were fed a 5%, 20%, or 40% casein diet for 10 days and then given heptachlor intraperitoneally. The animals receiving the 5% casein diet showed a three-fold tolerance to heptachlor toxicity, but the toxicity of heptachlor epoxide was not affected (Weatherholtz et al. 1969). This was probably due to inability of weanling rats to metabolically convert heptachlor to the more toxic heptachlor epoxide. This fact is further supported by the observation that changes in protein percentage in diet did not affect the toxicity of heptachlor epoxide itself.

Walter Reed-Wistar and Charles River male adult rats were exposed to oral doses of turpentine or to turpentine vapors, which consisted of α- and β-pinene. These exposures were followed by oral

administration of heptachlor epoxide or of one of three pesticides, paraoxon, heptachlor, or parathion, or by an intraperitoneal injection of hexobarbital. The studies revealed that pretreatment with turpentine reduced hexobarbital sleeping time, reduced the parathion LD_{50}, and increased the heptachlor LD_{50}. The paraoxon and heptachlor epoxide LD_{50} values were unchanged. α-Pinene and ß-pinene vaporized from turpentine had no effect on either hexobarbital sleeping time or parathion, paraoxon, or heptachlor epoxide mortality but did increase the heptachlor LD_{50} (Sperling et al. 1972). The authors speculated that increases in hepatic microsomal enzyme activity are responsible for these differences.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to heptachlor and heptachlor epoxide than will most persons exposed to the same level of heptachlor and heptachlor epoxide in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect that the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

No studies were located indicating that any populations are unusually susceptible to heptachlor or heptachlor epoxide. There is a possibility that very young children may exhibit particular susceptibility to hepatic effects because of the immaturity of the hepatic microsomal system. Heptachlor is bioactivated to produce heptachlor epoxide which is more toxic than heptachlor. Pre-adolescent children have a greater rate of glutathione turnover, and they are expected to be more susceptible to heptachlor epoxide–induced toxicity. Their susceptibility would probably depend upon their ability to detoxify heptachlor epoxide. Individuals who show reduced liver function for other reasons, such as glutathione deficiency, might also be unusually susceptible (Calabrese 1978). However, Harbison (1975) observed that heptachlor was less toxic in newborn rats than in adult rats. Newborn rats pretreated with phenobarbital were more sensitive to the effects of heptachlor than those not pretreated. Thus, the ability to metabolize and bioactivate heptachlor correlates with its toxicity in the newborn. The difference in blood heptachlor epoxide levels among Asians and U.S. residents (Rodomski et al. 1971b) may suggest the involvement of a genetic factor in the susceptibility to heptachlor epoxide toxicity.

There is some evidence in laboratory animals that high-protein diets cause more rapid conversion of heptachlor to heptachlor epoxide and therefore increase the toxicity resulting from exposure to heptachlor. The lack of corroborating data in humans on this phenomenon, however, makes it difficult to postulate that high- or very high–protein diets would significantly increase susceptibility to heptachlor toxicity.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to heptachlor and heptachlor epoxide. However, because some of the treatment discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to heptachlor or heptachlor epoxide. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Human exposure to heptachlor or heptachlor epoxide can occur by inhalation, oral, or dermal contact. Treatment of exposure to these substances is primarily supportive. Following a significant inhalation exposure, the patient is removed from the source to fresh air. Treatment may include administering oxygen and, if needed, maintaining ventilation with artificial respiration (Stutz and Janusz 1988; Bronstein and Currane 1988). General recommendations for reducing absorption of heptachlor following acute dermal exposure have included removal of contaminated clothing followed by washing the skin and hair with soap and water, then with alcohol, then again with soap and water (HSDB 1992; Morgan 1982; Stutz and Janusz 1988). Since leather absorbs pesticides, it has been recommended that leather not be worn while using heptachlor or heptachlor epoxide, and that any leather contaminated with these substances be discarded (HSDB 1992). Oils have not been recommended as dermal cleansing agents because they could increase absorption (Haddad and Winchester 1990). If the eyes have been exposed, they are flushed with water (Bronstein and Currance 1988; Stutz and Janusz 1988). Treatment for ingestion of this substance may require gastric emptying by gastric lavage (Haddad and Winchester 1990) and administration of activated charcoal and cathartic (HSDB 1992; Morgan 1982; Stutz and Janusz 1988; Haddad and Winchester 1990). Heptachlor may be present with a hydrocarbon vehicle which could result in aspiration pneumonitis following the induction of emesis. Therefore, emesis may not be indicated. Some sources do not recommend the use of emetics (Bronstein and Currance 1988), although others do under some circumstances (HSDB 1992; Morgan 1982; Stutz and Janusz 1988). Treatments such as emesis and lavage may be most appropriate following ingestion of large quantities; it is unlikely that the types of exposure likely to occur at hazardous waste sites would require such measures. Treatment with milk, cream, or other substances containing vegetable or animal fats, which enhance absorption of chlorinated hydrocarbons, has not been recommended (Haddad and Winchester 1990; Morgan 1982). If seizures occur, diazepam administration, followed if necessary by additional anticonvulsant medicines such as phenytoin, pentobarbital, thiopental, or succinylcholine, may be recommended (Bronstein and Currance 1988; HSDB 1992; Morgan 1982; Stutz and Janusz 1988). As adrenergic amines, such as epinephrine, may further increase myocardial irritability and produce refractory ventricular arrhythmias, their use has not been recommended (Bronstein and Currance 1988; HSDB 1992; Morgan 1982; Haddad and Winchester 1990).

2.8.2 Reducing Body Burden

Heptachlor is rapidly metabolized by the body, mostly to heptachlor epoxide. Most of the metabolites are rapidly excreted in the feces, with the adipose tissue serving as the major storage depot for the remainder. From the fat, heptachlor epoxide can be slowly released into the bloodstream for further metabolism and excretion. Cholestyramine resin may accelerate the biliary-gastrointestinal excretion of the more slowly eliminated organochlorine compounds, and its use has been suggested (Morgan 1982). Because of the lipophilicity of heptachlor and heptachlor epoxide, dialysis and exchange transfusion are thought to be ineffective (HSDB 1992).

Because heptachlor epoxide is lipophilic, it is likely that the loss of adipose tissue, as may occur during fasting, will mobilize the stored compound and increase the rate of its elimination. However, this mobilization is also likely to temporarily increase the blood levels of heptachlor epoxide. Hence, any possible benefits due to a reduced body burden accompanying fat reduction would need to be balanced against potential harmful results due to the expected temporary increase in blood levels.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Since the metabolized form of heptachlor, heptachlor epoxide, is the most toxic, it may be possible to reduce the toxic effects of heptachlor by inhibiting the enzyme catalyzing this conversion. This is the same enzyme that catalyzes the epoxidation of aldrin to dieldrin (Gillett and Chan 1968). Further research into the specificity of this enzyme, drugs that could inhibit the enzyme, and any side effects of these drugs could help to determine the feasibility of such a treatment strategy.

In the central nervous system, symptoms observed in animals following exposure include tremors, convulsions, ataxia, and changes in EEG patterns (Formanek et al. 1976). These central nervous system symptoms could be due either to (1) inhibition of the Na^+/K^+ ATPase or the Ca^+/Mg^+ ATPase activity, which can then interfere with nerve action or release of neurotransmitters (Yamaguchi et al. 1979) and/or (2) inhibition of the function of the receptor for GABA (Yamaguchi et al. 1980). In support of the latter possibility, another study showed that heptachlor epoxide inhibited the GARA-stimulated chloride uptake in the coxal muscle of the American cockroach and directly competed against [^{3}H]a-dihydropierotoxinin for binding in the rat brain synaptosomes. These results indicate that some of the nerve excitation symptoms that insecticides cause are probably due to their interaction with the picrotoxinin receptor (Matsumura and Ghiasuddin 1983). A more detailed understanding of the mechanism of heptachlor/heptachlor epoxide action on the central nervous system may lead to new approaches for reducing the toxic effects.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of heptachlor and heptachlor epoxide is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of heptachlor and heptachlor epoxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessmen*t.* This definition should *not* be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing information on Health Effects of Heptachlor and Heptachlor Epoxide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to heptachlor and heptachlor epoxide are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of heptachlor and heptachlor epoxide. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as “data needs” information (i.e., data gaps that must necessarily be filled).
Most of the data located concerning the health effects of heptachlor and heptachlor epoxide in humans come from case reports and occupational epidemiology studies of workers engaged either in the

FIGURE 2-3. Existing Information on Health Effects of Heptachlor and Heptachlor Epoxide

	Death	SYSTEMIC Acute	SYSTEMIC Intermed.	SYSTEMIC Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation	●		●	●		●				●
Oral	●	●		●		●	●	●		
Dermal										

HUMAN

	Death	SYSTEMIC Acute	SYSTEMIC Intermed.	SYSTEMIC Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation										
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●									

ANIMAL

● Existing Studies

manufacture or application of pesticides. There is. some information on people who have consumed heptachlor-contaminated food or dairy products, but no adverse health effects have been related to these exposures. The occupational studies involve exposures that are predominantly inhalation with contributions from dermal exposure, whereas all the animal studies were conducted using oral or intraperitoneal exposures. The occupational and case reports provide no quantitation of dose or duration of exposure, which makes it impossible to determine with any precision the effect levels for humans. There are no data that indicate that heptachlor or heptachlor epoxide are carcinogenic to humans. However, human studies are limited by the long latency period of carcinogenesis and by ascertainment and follow-up biases.

The animal studies for oral exposure to heptachlor and heptachlor epoxide are almost all limited to some extent by the number of doses used, the lack of appropriate statistics, or the small number or lack of controls. No information was located regarding the health effects of inhalation or dermal exposure, with the exception of a dermal LD_{50} in rats. Exposure of the general population via the inhalation and dermal routes may result from contaminated soil or vapors from treated houses. Some exposures from contaminated soil or water may occur in populations located near hazardous waste sites in which these chemicals have been stored or from food grown in contaminated soil.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. Quantitative methods for the estimation of exposure in humans would be useful. A usable model to estimate the exposure levels from the residue in blood and adipose tissue at various time intervals from the time of exposure would be useful. There are limited data on renal effects from acute exposure of humans to heptachlor or heptachlor epoxide (Derbes et al. 1955). There are a few case reports of neurological and hematological effecfs from occupational or residential inhalation and/or oral exposure to chlordane, a pesticide that typically contains about 10% heptachlor, but there is no way to accurately define the duration of exposure (Dadey and Kammer 1953; Epstein and Ozonoff 1987; Infante et al. 1978). Heptachlor is accumulated in body fat. Acute exposure is likely to result in a delayed effect when the pesticide is subsequently released into the circulation. The liver and the central nervous system appear to be the most sensitive target organs for acute oral toxic effects of heptachlor in animals (Akay and Alp 1981; Aulerich et al. 1990; Kacew and Singhal 1973; Krampl 1971; Lehman 1951,). Although the studies that show hepatic effects are limited (lack of histopathologic examination, enzyme changes that may be adaptive rather than adverse, lack of statistical analyses), the overall pattern of effects indicates that the hepatic function of laboratory animals is altered by acute exposure to heptachlor or heptachlor epoxide.
Acute inhalation studies in animals would be useful for confirming the liver as a target organ by this exposure route, and for providing information about the potential effects on humans exposed in accidents during manufacture or application, or exposed at NPL sites. No acute oral or inhalation MRLs for heptachlor or heptachlor epoxide have been determined because of the shortcomings of the existing database. More information on the effects observed in different species after acute exposure at several dose levels would be particularly helpful. There are no data on acute dermal exposures currently available other than LD_{50} values for heptachlor and heptachlor epoxlde. Since there is a risk of exposure to heptachlor and heptachlor epoxide at NPL sites or from direct contact from residential pesticide application, more information on acute dermal exposures would be useful for determining target organs and health effects from exposure via this route.

Intermediate-Duration Exposure. Because the human studies do not report quantitative information on dose or duration, it is not possible to know with certainty whether the combined inhalation and dermal exposures were of intermediate duration. There are intermediate-duration oral exposure data from animal studies that indicate that the liver and the hematologic systems are affected by heptachlor exposure (Enan

et al. 1982, Halacka et al. 1974; Pelican 1971). The liver is probably the more sensitive of the two. No intermediate-duration oral or inhalation MRLs for heptachlor or heptachlor epoxide have been determined because of limitations in the studies, including lack of statistical comparisons, insufficient number of dose levels, no identification of NOAELs, and the description of effects that may be considered adaptive and not adverse.

There are no data on intermediate-duration inhalation or dermal exposures in either humans or animals. Data on intermediate inhalation and dermal exposures would be useful since the inhalation of vapors or direct contact with residual heptachlor from residential pesticide application or at NPL sites may be potential routes of exposure for the general population.

Chronic-Duration Exposure and Cancer. There are no data on chronic oral exposures in humans. There are occupational studies of workers engaged in the manufacture of heptachlor in which the exposures are presumed to be predominantly inhalation with contributions from the dermal route. No adverse health effects have been identified in these cohorts that could be positively associated with heptachlor exposure (Infante et al. 1978; MacMahon et al. 1988; Stehr-Green et al. 1988). The liver appears to be the most sensitive target organ for the chronic oral toxic effects of heptachlor in animals (University of Cincinnati 1958). Chronic inhalation studies in animals would be useful for determining whether the target organ is the same for both oral and inhalation exposures. There are human case reports that describe neurotoxic and hematologic effects following chronic exposure to technical-grade chlordane from oral or other unspecified routes. Chronic animal studies would be useful for confirming these target organs.

There are occupational mortality studies that have collected data appropriate for determining whether those engaged in the manufacture or application of heptachlor are at increased risk for dying of cancer. These studies have not shown an increased risk of cancer mortality (Infante et al. 1978; MacMahon et al. 1988). Occupational studies that collected cancer incidence data, rather than just mortality data, would be useful for further exploration of this issue.

Other data available for assessing carcinogenicity come from animal studies of rats and three strains of mice (NC1 1977; Williams and Numoto 1984; Witherup et al. 1955). These data show increases in tumorigenesis following exposure to heptachlor. Chronic studies of inhalation exposure in relation to oncogenesis in animals might be useful for determining mechanism of action and the consistency of effect across routes of exposure. There are no pharmacokinetic data that indicate that there will be route-specific differences. There are some data that indicate that male dogs may be more susceptible than females, and female rats store greater amounts of heptachlor epoxide in the liver than do males. Studies that address gender differences would be useful for determining whether these differences may occur in other species.

Genotoxicity. There is very little information on the in vivo genotoxic effects of heptachlor or heptachlor epoxide. This is true for both humans and animals. More case reports and epidemiology studies are needed to properly evaluate genotoxic effects in humans exposed to heptachlor or heptachlor epoxide. In addition, in vivo animal research into the effects of heptachlor and heptachlor epoxide on sister chromatid exchange, chromosomal aberrations and anomalies, DNA adduct formation, gene mutation, and other genotoxic parameters would be helpful in assessing the genotoxic potential of these chemicals. More information is also needed concerning relevant routes of exposure, especially the inhalation and dermal routes.

Reproductive Toxicity. No adverse effects on human reproduction were reported following ingestion of heptachlor-contaminated milk for 27-29 months by women of child-bearing age (Le Marchand et al. 1986).

Given the uncertain exposure data and the relatively short observation period (relative to human conception and prenatal development), a clear assessment of the relationship between heptachlor exposure and human reproductive toxicity cannot be made. Studies in rodents orally exposed to heptachlor are inconsistent. No adverse effects in mice were reported for acute heptachlor exposure. In an intermediate oral exposure study (60 days), increases in the number of resorptions were seen in the first generation (Green 1970). In the second generation, all females receiving heptachlor at 0.25 mg./kg/day failed to become pregnant. No adverse effects on reproductive capacity were seen in a dominant lethal assay in which eight male mice were exposed to a single oral dose of 25% heptachlor/75% heptachlor epoxide (Arnold et al. 1977). Because the human data do not adequately assess reproductive toxicity and the animal data are inconclusive, additional animal studies evaluating female reproductive end points would be useful for assessing this health effect for all three routes of exposure.

Developmental Toxicity. There are no conclusive data on developmental effects of heptachlor or heptachlor epoxide exposure in humans. Case reports exist that indicate that no adverse developmental effects occurred in the offspring of women who drank heptachlor-contaminated cow's milk (see discussion above on reproductive toxicity). However, heptachlor epoxide has been found in the blood and several tissues of stillborn human infants (Stehr-Green et al. 1986). The identification of heptachlor in amniotic fluid, placenta, and fetal blood provides good evidence of transplacental transfer of this chemical. The relationship of these measurements to exposure is unclear; no data exist that indicate a causal effect. A 60-day oral study in rats showed decreased postnatal survival, but no teratogenic effects were noted (Green 1970). Reproductive studies in rats yielded offspring that developed cataracts at 2-3 weeks after birth, but cataracts also developed in the exposed adults (Mestitzova 1967). Verification of these findings would be useful. Studies that examined both reproductive and developmental effects after intermediate oral or inhalation exposures would be useful because they 'would provide better evidence for establishing the developmental risks in humans.

Immunotoxicity. No studies were located that specifically addressed immune function parameters following heptachlor or heptachlor epoxide exposure. Intermediate and chronic multichemical exposures of humans by inhalation to heptachlor, chlordane, and other substances have been associated with hematologic effects, including aplastic anemia, hemolytic anemia, and leukemia (Epstein and Ozonoff 1987; Infante et al. 1978). The only animal data come from intermediate oral exposure studies in which rats showed a significant elevation of the white blood count (Enan et al. 1982). Rats fed heptachlor for 10 weeks showed increased red blood cells and eosinophils (Enan et al. 1982). Alterations of the hematopoietic system observed following intermediate or chronic multiple chemical exposure suggest that there is at least potential for effects on the immune system. Ninety-day studies examining immune function end points would be useful in establishing whether or not the immune system is a target for heptachlor or heptachlor epoxide toxicity.

Neurotoxicity. The only human data on neurotoxicity come from case reports of occupational exposures to chlordane in which the route was not specified, and for which the effects could not be related directly to heptachlor or heptachlor epoxide alone (Dadey and Kammer 1953). Signs of neurotoxicity, such as irritability, salivation, lethargy, dizziness, labored respiration, muscle tremors, and convulsions, were reported. No data exist describing neurologic effects in animals following inhalation exposure of any duration. Acute and intermediate oral studies in animals provide support for the supposition that the neurotoxicity of chlordane seen in humans may be due in part to heptachlor or heptachlor epoxide. Although there are no reasons to suspect that neurotoxic effects are route-specific, more quantitative data on inhalation effects would be useful because there are no inhalation data and people are exposed by this route in pesticide-treated houses and at NPL sites.

2. HEALTH EFFECTS

Epidemiological and Human Dosimetry Studies. The existing epidemiological studies are primarily of occupational cohorts or case reports of health effects seen in groups exposed to contaminated milk (Chadduck et al. 1987). These studies have generally not included good quantitation of the exposure to heptachlor or heptachlor epoxide. In many cases, it is not possible to determine the exact identity of the contaminants involved. Although use of this compound has been discontinued, exposure could nevertheless occur through food grown in contaminated soil, through contact with applied residential pesticides, or from hazardous waste sites. Analytical methods are available to determine exposure to heptachlor or heptachlor epoxide (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968). However, no information is available that correlates levels of heptachlor epoxide in tissue with either level or duration of exposure. Occupational exposure levels are likely to be high enough to enable distinction from background levels. However, many epidemiologic4 studies examining outcomes of exposure are limited by the accuracy of determining the exposure status of those individuals who show adverse health effects and those who show none. The precision and reliability of categorizing exposed individuals and non-exposed individuals contribute significantly to the statistical power of a study and greatly assist in accurate estimation of an increased risk. If data on exposure parameters are sparse or show very wide variation, it is difficult to determine what constitutes an exposure. More data on the correlation of tissue levels to exposure parameters would be useful for increasing the power of epidemiological studies to measure statistically significant associations between heptachlor exposure and health effects in cohorts from both occupational or contaminated community environments.

Biomarkers of Exposure and Effect. Exposure to heptachlor and heptachlor epoxide is currently measured by determining the level of these chemicals in the blood or adipose tissue in living organisms (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968). This measure is specific for both heptachlor and heptachlor epoxide. Heptachlor epoxide is also a metabolite of chlordane, and thus its presence is not specific for exposure to heptachlor alone. However, in the absence of stable chlordane residues (e.g., nonachlor and oxychlordane), the heptachlor epoxide would most likely have been derived from heptachlor. Because heptachlor is believed to be converted rapidly in the body to heptachlor epoxide, it is impossible to determine whether the exposure was to one or the other of these two compounds. Heptachlor and heptachlor epoxide accumulate in adipose tissue and are released slowly over long periods of time. Therefore, it is not possible to accurately identify whether the exposure was recent or what the duration of exposure was. However, the ratio of heptachlor epoxide to heptachlor increases over time and therefore may be used as a biomarker of possible exposure to heptachlor. The sensitivity of the methods for identifying these compounds in human tissue appears to be only sufficient to measure background levels of heptachlor epoxide in the population. Additional biomarkers of exposure to heptachlor would be helpful at this time.

There is no clinical disease state unique to heptachlor. A major problem in developing a biomarker of effect for heptachlor or heptachlor epoxide is that human exposures to these compounds have occurred concomitantly with exposures to other chemicals, and it is difficult to attribute the health effects to heptachlor or heptachlor epoxide alone. More data that quantify the biological effects as well as data that distinguish heptachlor and heptachlor epoxide exposures from those of other chemicals would be useful for developing biomarkers of effect for population monitoring. Biomarkers that could indicate the length of time since exposure would also be useful.

Absorption, Distribution, Metabolism, and Excretion. There are very few data available to assess the relative rates of pharmacokinetic parameters with respect to route of exposure for either heptachlor or heptachlor epoxide. There are no human or animal inhalation or dermal studies on absorption, distribution, metabolism, or excretion. The only human data on metabolism come from in vitro studies

using liver microsomes that indicate that, qualitatively, human microsomes metabolize heptachlor to the same end products as do rat microsomes (Tashiro and Matsumura 1978). Oral exposure in members of farm families led to elevated serum levels of heptachlor metabolites (Stehr-Green et al. 1986), indicating that the compound is absorbed through the gastrointestinal tract. Animal studies also suggest that uptake occurs through the gastrointestinal tract following oral dosing; excretion of these doses occurs primarily through the bile duct into the feces (Tashiro and Matsumura 1978). Animal studies also indicate that heptachlor can be absorbed through the skin to acutely toxic doses, but there are no data on distribution, metabolism, or excretion of dermally absorbed doses. Substantial amounts of data would be useful in order to gain a thorough understanding of the pharmacokinetic parameters of these compounds. Heptachlor epoxide is more toxic than heptachlor and has a longer half-life. Additional pharmacokinetic data on absorption of heptachlor epoxide would be helpful.

Comparative Toxicokinetics. There are limited available data with which to compare humans and other animal species. There are, for example, no inhalation studies in humans and one poorly controlled rabbit inhalation experiment. For the dermal route of exposure, the data are limited to only one rat study (Gaines 1969). With oral exposure, however, heptachlor and heptachlor epoxide seem to have essentially the same absorption and distribution properties in both humans and animals. Although there are no human kinetic data and scanty animal data with which a comparison between humans and animals can be made, the oral distribution data in human cadavers and rats suggest that target organs are similar. The single in vitro comparative study that specifically addresses metabolism indicates that the metabolites produced in humans and rats are identical, but the amounts differ (Tashiro and Matsumura 1978). Moreover, the rate of metabolism is not similar in both species. Thus, the rat may not be an appropriate metabolic model for humans. No information was located regarding human excretion of heptachlor or heptachlor epoxide, and only one study in rats was located. Finally, there is a lack of information regarding kinetic changes after prolonged exposure. This kind of information would be useful because most exposures in the general population (e.g., from contaminated food or improperly applied pesticides) are likely to be long-term and low-dose.

Methods for Reducing Toxic Effects. The mechanism by which heptachlor and heptachlor epoxide are absorbed from the gastrointestinal tract is unknown. Current methods for reducing absorption from the gastrointestinal tract involve removing these chemicals from the site of absorption (Haddad and Winchester 1990; HSDB 1992; Morgan 1982; Stutz and Janusz 1988). Additional studies examining the method of absorption would provide valuable information for developing methods that can interfere with gastrointestinal absorption. Numerous studies have examined the distribution of heptachlor and heptachlor epoxide (Barquet et al. 1981; Burns 1974; Curley et al. 1969; Greer et al. 1980; Jonssan et al. 1977; Polishuk et al. 1977b; Rodomski et al. 1968). Additional studies on distribution are not necessary at this time. No established methods exist for reducing body burden of heptachlor and heptachlor epoxide. However, available information suggests that removal of these compounds via biliary-gastrointestinal excretion can be accelerated (Morgan 1982). Reducing enterohepatic recirculation before these chemicals partition to tissues may be effective (Haddad and Winchester 1990; HSDB 1992). Thus, studies examining the effectiveness of repeated doses of activated charcoal or cholestyramine in reducing body burden would be useful. Adipose tissue serves as a major storage repository for both heptachlor and heptachlor epoxide (Barquet et al. 1981; Burns 1974; Greer et al. 1980; Harradine and McDougall 1986). Losing fat can : mobilize the stored compound and increase the rate of its elimination. However, it may temporarily increase the blood levels of heptachlor epoxide. Studies that would examine the benefits of reducing body burden with accompanying fat reduction while balancing against harmful effects from temporary increase in blood level would be useful. Since heptachlor undergoes epoxidation to produce heptachlor epoxide which is more toxic than the parent compound, studies examining drugs that would inhibit the enzyme

catalyzing this conversion would be helpful. Neurotoxicity of heptachlor epoxide is believed to result, at least in part, from interference with GABA receptor function (Yamaguchi et al. 1980). The available data suggest that benzodiazepenes and barbiturates may be useful in mitigating some of the neurological symptoms of heptachlor epoxide (Bronstein and Currance 1988; HSDB 1992; Morgan 1982; Stutz and Janusz 1988). However, additional studies examining the effectiveness of GABAergic function in mitigating heptachlor epoxide's neurologic effects would be useful. The liver also appears to be a major target organ for the toxic effects of heptachlor and heptachlor epoxide in animals (Akay and Alps 1981; Krampl 1971; Pelikan 1971). An understanding of the mechanism of action in the liver may identify new approaches for reducing the toxic effects.

2.9.3 On-going Studies

EPA is currently examining the systemic and organ toxicity of heptachlor at its Health Effects Research Laboratories in Research Triangle Park, North Carolina (NTP 1990). The testing was scheduled for completion in fiscal year 1990.

L.B. Willett and C.P. Hodgson of Ohio State University, in collaboration with the U.S. Department of Agriculture, are currently investigating reproductive, metabolic, and nutritional disorders following heptachlor exposure from contaminated food in cattle (FEDRIP 1990). These investigators will also determine the cellular alterations that can influence reproductive or other homeostatic mechanisms.

J. Worebey and M. Lewis of Rutgers University are currently investigating a relationship between prenatal exposure to organochlorine pesticides and heavy metals and the subsequent behavioral development of the exposed infants (CRIS/USDA 1990). Infants of 18 months of age will be examined. Behavioral assessment will be primarily focused on three areas: (1) habituation and recovery of attention, (2) lateral@, and (3) emotionality and attachment (CRIS/USDA 1990).

F. Matsumura, sponsored by the National Institute of Environmental Health Sciences (NIEHS), plans to study the toxic effects of chlorinated and pyrethroid pesticides primarily on calcium and sodium regulating processes in the nervous system. To examine the interactions of the pesticides with calcium regulating processes, researchers will use synaptosomal preparations from the brains of rats and the central nervous systems of squid. To examine the interactions of the pesticides with sodium regulating processes, they will collect antibodies directed against sodium channel proteins.

J.E. Trosko (Michigan State University) is studying. the inhibitory action of heptachlor and heptachlor epoxide on cell-to-cell communication in conjunction with their cancer promoting activities.

3. CHEMICAL AND PHYSICAL INFORMATION

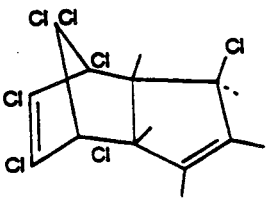
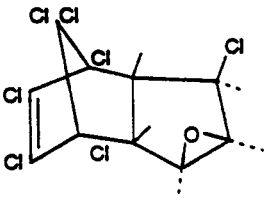
3.1 CHEMICAL IDENTITY

Information regarding the chemical identities of heptachlor and heptachlor epoxide is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of heptachlor and heptachlor epoxide is located in Table 3-2.

TABLE 3-1. Chemical Identity of Heptachlor and Heptachlor Epoxide[a]

Characteristic	Heptachlor	Heptachlor epoxide
Chemical name	Heptachlor	Heptachlor epoxide
Synonym(s)	2-Chlorochlordene; 1,4,5,6,7,8,8a-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; 1,4,5,6,6a-heptachloro-dicyclopentadiene; and others	Epoxyheptachlor; 1,4,5,6,7,8,8a-hepta-chloro-2,3-epoxy-3a,4,7,7a-tetra-hydro-4,7-methanoindene
Registered trade name(s)	Heptagran; Heptamul; Heptagranox; Heptamak; Basaklor; Drinox[b]; Soleptax; Gold Crest H-60; Termide; Velsicol 104	Velsicol 53-CS-17
Chemical formula	$C_{10}H_5Cl_7$	$C_{10}H_5Cl_7O$
Chemical structure		
Identification numbers:		
CAS registry	76-44-8	1024-57-3
NIOSH RTECS	PC0700000	PB9450000[c]
EPA hazardous waste	P059	No data
OHM/TADS	7216526	833300216
DOT/UN/NA/IMCO shipping	NA 2761	No data
HSDB	554	6182
NCI	C00180	

[a]All information obtained from HSDB 1990a for heptachlor or 1990b for heptachlor epoxide unless otherwise noted.
[b]OHM/TADS 1985a
[c]OHM/TADS 1985b

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Heptachlor and Heptachlor Epoxide[a]

Property	Heptachlor	Heptachlor epoxide
Molecular weight	373.35	389.40
Color	White (pure); tan (technical grade)[b]	White[b]
Physical state	Crystalline solid	Crystalline solid[b]
Melting point	95–96°C (pure); 46–74°C (technical grade)[c]	160–161.5°C
Boiling point	145°C	No data
Density:		
at 9°C	1.57 g/cm^3	No data
Odor	Camphor-like	No data
Odor threshold:		
Water	No data	No data
Air	0.3 mg/m^3	0.3 mg/m^3
Solubility:		
Water at 25°C	0.05 mg/L[d]	0.275 mg/L[d]
Organic solvent(s)	Soluble in most organic solvents	Soluble in most organic solvents[b]
Partition coefficients:		
Log K_{ow}	5.44[e]	5.40[f]
Log K_{oc}	4.34[e]	3.34–4.37[g]
Vapor pressure		
at 20°C	3x10^{-4} mmHg[h]	2.6x10^{-6} mmHg[i]
at 25°C	3x10^{-4} mmHg	No data
Henry's law constant:		
at 25°C	1.48x10^{-3} atm-m^3/mol[d]	3.2x10^{-5} atm-m^3/mol[d]
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	Noncombustible but may be dissolved in flammable liquids	No data
Conversion factors	1 ppm = 15.27 mg/m^3 at 25°C, 1 atm	1 ppm = 15.93 mg/m^3 at 25°C, 1 atm
Explosive limits	Stable[j]	Stable[i]

[a]All information obtained from HSDB 1990a for heptachlor or 1990b for heptachlor epoxide unless otherwise noted
[b]IARC 1974
[c]Worthing and Walker 1987
[d]EPA 1987a
[e]Chapman 1989
[f]MacKay 1982
[g]Estimated from Lyman et al. 1982
[h]ACGIH 1986
[i]OHM/TADS 1985b
[j]OHM/TADS 1985a

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Heptachlor was first registered for use in the United States as an insecticide in 1952 and commercial production began the following year (EPA 1986a). Nearly all registered uses of heptachlor were canceled in 1974 by EPA because of its potential cancer risk and its persistence and bioaccumulation throughout the food chain (EPA 1986a). The sale of heptachlor was voluntarily canceled in 1987 by its sole U.S. manufacturer, the Velsicol Chemical Corporation. The sale, distribution, and shipment of existing stocks of all canceled chlordane and heptachlor products were prohibited in the United States as of April 1988 (EPA 199Ob; SRI 1990). Heptachlor is a constituent of technical-grade chlordane, approximately 10% by weight (HSDB 199Oa). Heptachlor epoxide is an oxidation product of heptachlor and of chlordane; it is not produced commercially in the United States (IARC 1979).

Table 4-1 summarizes the facilities in the United States that manufacture or process heptachlor. It also lists the maximum amounts of heptachlor that are allowed at these sites and the end uses of the heptachlor. This information is based on the release data reported to the Toxics Release Inventory (TRI) in 1988 (TM88 1990).

Heptachlor is produced commercially by the free-radical chlorination of chlordene in benzene containing from 0.5% to 5.0% of fuller's earth. The reaction is run for up to 8 hours. The chlordene starting material is prepared by the Diels-Alder condensation of hexachlorocyclopentadiene with cyclopentadiene (Sittig 1980). Technical-grade heptachlor usually consists of 72% heptachlor and 28% impurities such as trans-chlordane, cis-chlordane, and nonachlor (HSDB 1990a).

The U.S. International Trade Commission (USITC) did not report the domestic production volume of heptachlor separately for the years 1981-1985 (USITC 1982b, 1983b, 1984b, 1985, 1986). Only yearly totals were reported for all cyclic insecticides. The USITC reports production volume data only for chemicals for which three or more manufacturers report volumes that exceed certain minimum output levels.

4.2 IMPORT/EXPORT

The USITC did not report separate.import data for heptachlor for the years 1981, 1982, and 1983 (USITC 1982a, 1983a, 1984a). The U.S. Department of Commerce did not report separate importation data for heptachlor for the year 1985 (USDOC 1986). The sale, distribution, and shipment of existing stocks of all canceled heptachlor products were prohibited by EPA in 1988 (EPA 1990b). No information was located that provided specific information about heptachlor or heptachlor epoxide importation following the 1988 ban.

No information was located regarding the exportation of heptachlor or heptachlor epoxide.

4.3 USE

Heptachlor is a persistent dermal insecticide with some fumigant action. It is nonphytotoxic at insecticidal concentrations (Worthing and Walker 1987). Heptachlor was used extensively from 1953 to 1974 as a soil and seed treatment to protect corn, small grains, and sorghum from pests. It was used *to control* ants, cutworms, maggots, termites, thrips, weevils, and wireworms in both cultivated and uncultivated soils. Heptachlor was also used nonagriculturally during this time period to control termites and household insects (EPA 1986a; Worthing and Walker 1987).

TABLE 4-1. Facilities That Manufacture or Process Heptachlor[a]

Facility	Location[b]	Range of maximum amounts on site in pounds	Activities and uses
Velsicol Chemical Corp.	Memphis, TN	10,000-99,999	Produce

[a]Derived from TRI88 (1990)
[b]Post office state abbreviations used

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

EPA proposed cancellation of nearly all registered uses of heptachlor in 1974 because of its potential cancer risk and its persistence and bioaccumulation throughout the food chain. The few uses that were not canceled in 1974, treatment of field corn, seed (for corn, wheat, oats, barley, rye, and sorghum), citrus, pineapple, and narcissus bulbs, were phased out gradually over a 5-year period ending on July 1, 1983 (EPA 1986a). Certain uses of heptachlor.were specifically exempted from EPA's suspension and cancellation actions because they were believed to result in insignificant exposure and, consequently, insignificant risk. Registrations were retained for subsurface termite control, fire ant control in buried cable closures, and dipping of roots or tops of nonfood plants (a use subsequently canceled voluntarily by the registrant,Velsicol Chemical Corporation) (EPA 1986a).

In 1988, EPA prohibited the sale, distribution, and shipment of existing stocks of all canceled chlordane and heptachlor products. Subsequently, virtually all uses of heptachlor products were voluntarily canceled by the registrant, Velsicol Chemical Corporation (EPA 199Ob). The only commercial use of heptachlor products still permitted is fire ant control in power transformers. Use of existing stocks of heptachlorcontaining termiticide products in the possession of homeowners is also permitted (EPA 1990b).

4.4 DISPOSAL

Heptachlor and heptachlor epoxide are Resource Conservation and Recovery Act (RCRA) hazardous wastes and hazardous constituents (EPA 1986c); as such, they must be disposed of in secure landfills in compliance with all federal, state, and local regulations. They may also be incinerated at 1,500°F for 0.5 second for primary combustion and at 3,200°F for 1 second for secondary combustion, with adequate scrubbing of incinerator exhaust and disposal of ash (Sittig 1985).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Heptachlor was used extensively until the 1970s as a broad-spectrum insecticide on a wide variety of agricultural crops, with the major use on corn. It also had nonagricultural uses including seed treatment, home and garden uses, and termite control. In 1974, EPA proposed cancellation of neaily all registered uses of heptachlor except termite and fire ant control and dipping of roots or tops of nonfood plaxits, a use that was subsequently voluntarily canceled by the registrant in 1983 (EPA 1986a). In 1988, the sale, distribution, and shipment of existing stocks of all heptachlor products were prohibited in the United States. As of April 1988, heptachlor could no longer be used for the underground control of termites. The only commercial use of heptachlor still permitted is fire ant control in power transformers (EPA 1990b).

Heptachlor is converted to heptachlor epoxide and other degradation products in the environment. Heptachlor epoxide degrades more slowly and, as a result, is more persistent than heptachlor. Heptachlor epoxide has been found in food crops grown in soils treated with heptachlor many years before. Both heptachlor and heptachlor epoxide adsorb strongly to sediments, and both are bioconcentrated in aquatic and terrestrial organisms. Biomagnification of heptachlor and heptachlor epoxide in aquatic food chains is significant. Because heptachlor is readily metabolized to heptachlor epoxide by higher trophic level organisms, biomagnification of heptachlor itself is not significant. Because of the more persistent nature of heptachlor epoxide and its lipophilicity, biomagnification of heptachlor epoxide in terrestrial food chains is significant.

In the past (prior to 1974), exposure of humans to heptachlor and heptachlor epoxide was directly related to the application of heptachlor as an insecticide. However, because of the persistence and bioaccumulation of heptachlor and heptachlor epoxide, exposure of the general population can occur through ingestion of contaminated food (especially cow's or maternal human milk), inhalation of vapors from contaminated soil and water, or direct contact with residual heptachlor from pesticide application. People whose homes have been treated may continue to be exposed to these chemicals in the air over long periods. Occupational exposure can occur in the manufacture of the chemical or from use of heptachlor to control fire ants. The most likely routes of exposure at hazardous waste sites are unknown. Heptachlor has been found infrequently in soil and groundwater at hazardous waste sites. Children who eat contaminated soil or people who obtain tap water from wells located near hazardous waste sites might be exposed to heptachlor. Also, since both compounds can volatilize from soil, people living near hazardous waste sites may be exposed to the compounds in the air.

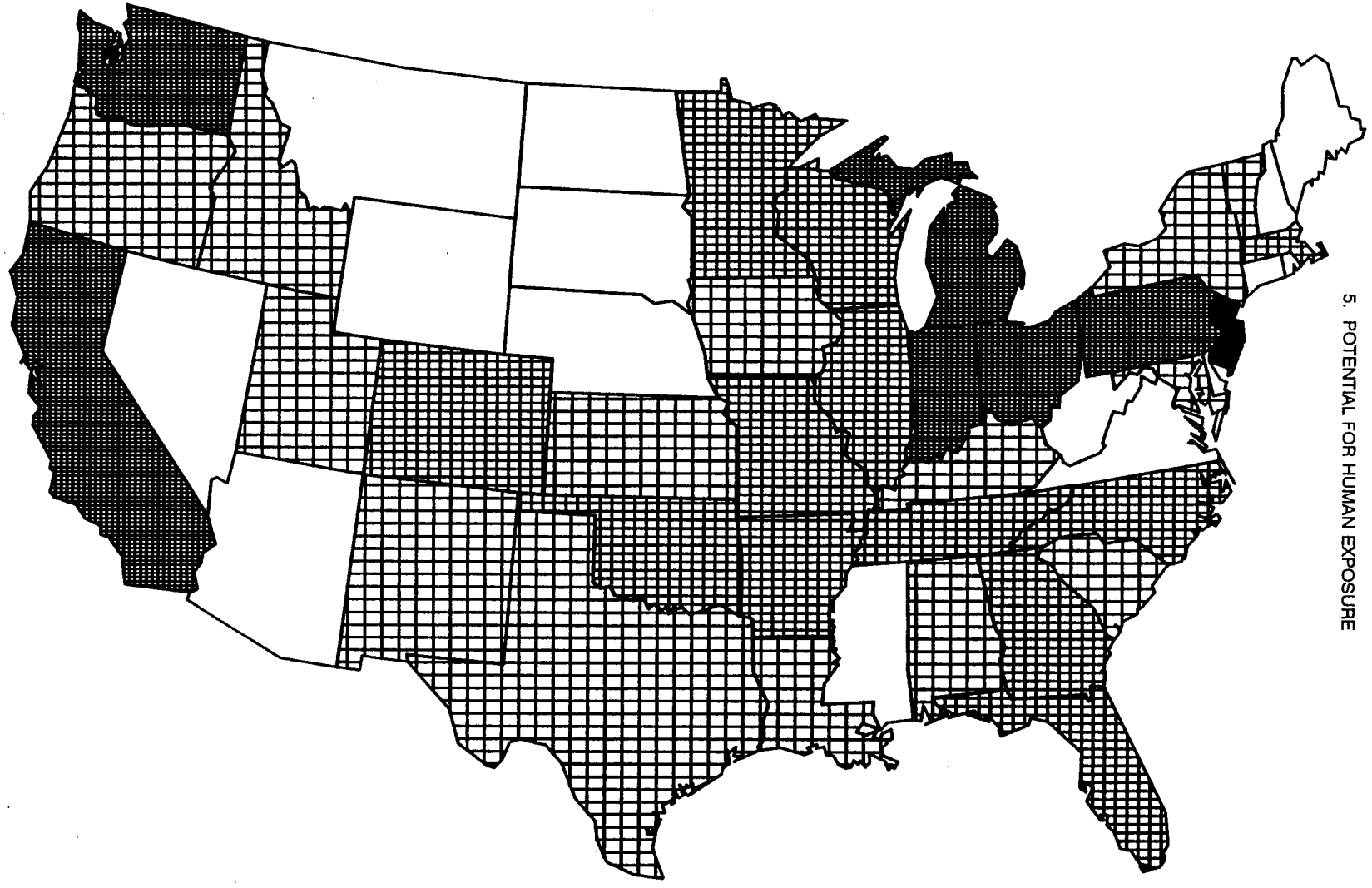
Heptachlor and heptachlor epoxide have been identified in at least 129 and 87 sites of the 1,300 NPL hazardous waste sites, respectively (HAZDAT 1992); however, the total number of sites evaluated for these compounds is not known. Of the identified sites, 1 site for heptachlor and 2 sites for heptachlor epoxide are located in the Commonwealth of Puerto Rico (not shown). The frequency of these sites within the United States can be seen in Figures 5-l and 5-2.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

People whose homes have been professionally treated for termites, either by spraying or subsurface injection, may continue to be exposed to heptachlor and possibly to its transformation product, heptachlor

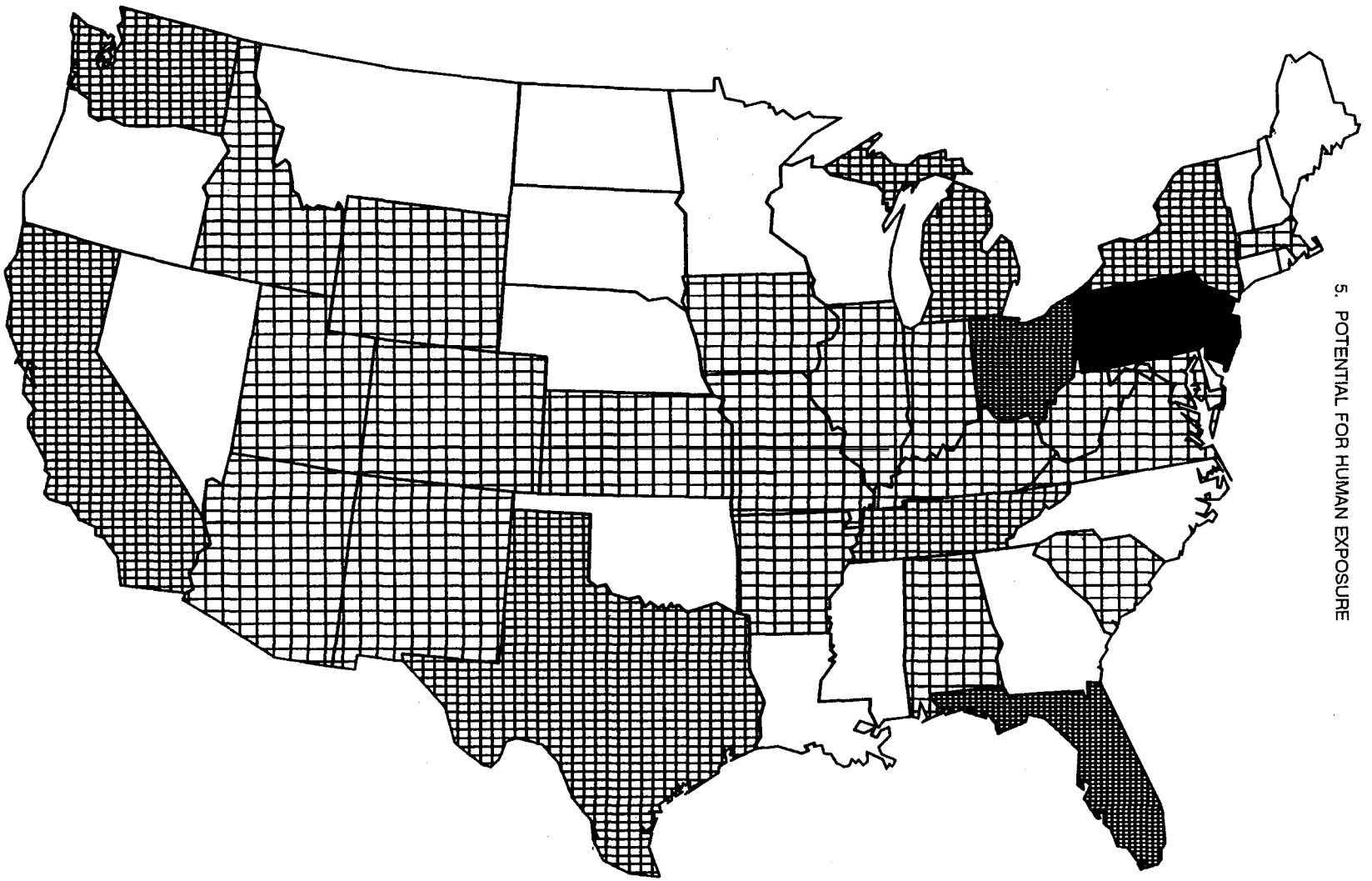
FIGURE 5-1. FREQUENCY OF NPL SITES WITH HEPTACHLOR CONTAMINATION *



FREQUENCY
1 TO 2 SITES
3 TO 4 SITES
6 TO 11 SITES
19 SITES

*Derived from HAZDAT 1992

FIGURE 5-2. FREQUENCY OF NPL SITES WITH HEPTACHLOR EPOXIDE CONTAMINATION *



FREQUENCY
1 TO 2 SITES
3 TO 4 SITES
5 TO 7 SITES
11 TO 12 SITES

*Derived from HAZDAT 1992

epoxide, in the indoor air over long periods. Releases can also occur from use of existing stocks in the possession of homeowners (EPA 199Ob). According .to TRI, an estimated total of at least 49,055 pounds of heptachlor was released to outdoor air from manufacturing and processing facilities in the United States in 1988 (TR188 1990). This is also the total amount of heptachlor released to the environment since no releases to water or land were reported by these facilities. Table 5-l lists the amounts of the releases from these facilities. TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Both compounds can be released to the air by volatilization from contaminated soil and surface water such as might be found at a hazardous waste site.

5.2.2 Water

Heptachlor and heptachlor epoxide may enter surface water and groundwater in runoff from contaminated soils or in discharges of waste water from production facilities.

Heptachlor has been detected in an estimated 1.4% of the groundwater samples taken at NPL hazardous waste sites included in EPA's Contract Laboratory Program (CLP) at an estimated geometric mean concentration of 0.78 ppb for the positive samples (CLPSD 1989). The compound was not listed in the CLP Statistical Database (CLPSD) of chemicals detected in surface water samples collected at NPL sites. Heptachlor epoxide was not listed in the CLPSD of chemicals detected in groundwater or surface water samples collected at NPL sites. Note that the information from the CLPSD includes data from NPL sites only.

5.2.3 Soil

Possible releases of heptachlor to soil may occur at h&ardous waste sites or as a result of landfill leachate. Residues of heptachlor or heptachlor epoxide exist in soil as a result of past usage of heptachlor for both agricultural and nonagricultural purposes. Heptachlor was detected in 0.71% of the soil samples taken from the NPL sites included in the CLPSD at an estimated mean concentration of 4.07 ppb in the positive samples (CLPSD 1989). Heptachlor epoxide was not listed in the CLPSD of chemicals detected in soil samples collected at NPL sites. Note that the information from the CLPSD includes data from NPL sites only.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Heptachlor has a low vapor pressure (3.0×10^{-4} mmHg at 25°C) and a low water solubility (0.056 mg/L,) (EPA 1987a; Jury et al. 1987). The experimental value for Henry's law constant is 1.48×10^{-3} suggesting that heptachlor partitions somewhat rapidly to the atmosphere from surface water and that volatilization is significant (EPA 1987a; Lyman et al. 1982). Heptachlor is also subject to long-range transport and wet deposition.

The log soil organic carbon adsorption coefficient (log K_{oc}) for heptachlor was estimated to be 4.34 (Chapman 1989). The log K_{oc} value indicates a very high sorption tendency, suggesting it will adsorb strongly to soil and is not likely to leach into groundwater in most cases (Chapman 1989). The leaching potential at 15 cm (concentration in soil water/concentration in soil) for heptachlor is 0.06, and the volatilization potential at 15 cm (concentration in soil air/concentration in soil) determined in laboratory studies is 5.5×10^{-3}, again suggesting that heptachlor is unlikely to leach appreciably in soil but has some

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Heptachlor[a]

		Reported amounts released in pounds						
Facility	Location[b]	Air	Underground injection	Water	Land	Total environment[c]	POTW transfer	Off-site waste transfer
Velsicol Chemical Corp.	Memphis, TN	1,537	0	2	0	1,539	37	51,935

[a]Derived from TRI88 (1990)
[b]Post office state abbreviations used
[c]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

POTW = publicly owned treatment works

volatilization potential (McLean et al. 1988). These are important properties since heptachlor can remain deep in soil for years. The organic matter content of the soil is another factor affecting mobility. Heptachlor is less likely to leach from soil with a high organic matter content. When released into water, it adsorbs strongly to suspended and bottom sediment.

Volatilization from soil particles to the atmosphere is possible (McLean et al. 1988). Volatilization is an important mechanism of transport of heptachlor from land surfaces (Jury et al. 1987). When heptachlor was applied to orchard grass, approximately 90% was lost in 7 days. When it was applied to moist soil surfaces, 50% was lost in 6 days. When it was applied to dry soil surface, 14-40% was lost in approximately 2 days (50 hours). Volatilization was much less--only 7% in 167 days--when incorporated to a shallow depth of 7.5 cm (Jury et al. 1987). Temperature and humidity affect the persistence of heptachlor and total heptachlor (heptachlor plus heptachlor epoxide) in soil (Shivankar and Kavadia 1989). An increase in temperature resulted in a decrease in the volatilization half-lives of heptachlor and total heptachlor. For example, at 18±1°C (90±50% relative humidity [RH]) and 35±1°C (90±5% RH), the halflives of heptachlor (6 ppm) were 44.8 days and 38 days, respectively. Persistence of heptachlor and total heptachlor was found to be greater at higher humidity, irrespective of temperature. At the combination of higher temperature (25±1°C and low humidity (55±5% RH), faster dissipation of heptachlor occurred (half-life = 24.67 days). At lower temperatures (18±1°C) and low humidity (55±5% RH), greater persistence of heptachlor was found (40.67 days). Half-lives of total heptachlor (6 ppm) were longer because of the more persistent nature of heptachlor epoxide (Shivankar and Kavadia 1989).

The logarithm of the n-octanol/water partition coefficient (log K_{ow}) is a useful preliminary indicator of bioconcentration potential of a compound. The log K_{ow} for heptachlor is 5.44 (Chapman 1989; MacKay 1982), suggesting a high potential for bioaccumulation and biomagnification in the aquatic food chain. The bioconcentration factor for heptachlor was 10,630 in 'Asiatic clam fat (Corbicula manilensis), 2,570 in soft clams (Mya arenaria), and 8,511 in oysters (Crassostrea virginica) (Hawker and Connell 1986).

Heptachlor epoxide is soluble in water at a concentration of 0.275 mg/L (EPA 1987a). The experimental value for Henry's law constant is 3.2×10^{-5} (EPA 1987a), suggesting that heptachlor epoxide partitions slowly to the atmosphere from surface water (Lyman et al. 1982). Based on regression equations, the log K_{oc} for heptachlor epoxide was estimated to range between 3.34 and 4.37 (Lyman et al. 1982). These log K_{oc} values suggest a high sorption tendency, meaning that this compound is not mobile in soil and has a low potential to leach. The organic matter content of soil affects the mobility of heptachlor epoxide. Heptachlor epoxide is less likely to leach from soil with a high organic matter content. If released into water, it adsorbs strongly to suspended and bottom sediments.

Heptachlor and heptachlor epoxide are subject to long-range transport and removal from the atmosphere by wet deposition. Snowpack samples were collected at 12 sites in the Northwest Territories, Canada, in the winter of 1985-1986. Heptachlor epoxide was present in 20 of 21 samples at a mean concentration of 0.18 ng/L (1.8×10^{-4} ppb) with reported concentrations ranging from 0.02 to 0.41 ng/L (from 2×10^{-5} to 4.1×10^{-4} ppb). No data for heptachlor were reported. There were no known local sources for heptachlor in the Canadian Arctic snow (Gregor and Gummer 1989).

Heptachlor and heptachlor epoxide are also taken up by plants (translocated into plants by absorption through the roots). Loamy soils were treated with heptachlor at a total of 25 pounds per 5-inch acre over a 5-year period (1958-1962) (Lichtenstein et al. 1970). The commercial formulation of heptachlor used also contained y-chlordane and nonachlor. Insecticide residues were absorbed by crops grown in these soils, with carrots absorbing the largest amounts. Although residue levels in soils increased up to 1962,

the residue concentrations in both carrots and potatoes peaked during the 1960 growing season. During that year, the concentration of total heptachlor in carrots was 1,900 ppb. Residue levels of total heptachlor on potatoes never exceeded 540-510 ppb (1960-1962). Apparently a threshold had been reached beyond which the content of insecticidal residues remained constant in these two crops. When insecticide residue levels in soil started to decline (1963), both carrots and potatoes also contained proportionally smaller amounts of residue. In the fall of 1968, residues of total heptachlor were found in the following crops: carrots--413 ppb (92% heptachlor epoxide), potatoes--70 ppb (98% heptachlor epoxide), beets--60 ppb (100% heptachlor epoxide), radishes--140 ppb (100% heptachlor epoxide), and cucumbers--90 ppb (95% heptachlor epoxide) (Lichtenstein et al. 1970).

The log K_{ow} for heptachlor epoxide is 5.40 (MacKay 1982), indicating a high potential for bioconcentration and biomagnification in the aquatic food chain. Estimated bioconcentration factors for heptachlor epoxide are 1,698 in mussels (Mytilus edulis), 851 in oysters (Crassostrea virdnica) (Hawker and Connell 1986; Geyer et al. 1982), and 2,330 in Asiatic clam fat (Corbicula manilensis) (Hartley and Johnston 1983). The bioconcentration potentials of heptachlor and heptachlor epoxide differ, with the more polar epoxide being concentrated to a lesser degree than the parent compound (Hartley and Johnston 1983). Biomagnification of heptachlor and heptachlor epoxide in aquatic food chains is significant. Because heptachlor is readily metabolized to heptachlor epoxide by higher trophic level organisms, biomagnification of heptachlor itself is not significant. Because of the more persistent nature of heptachlor epoxide and its lipophilicity, biomagnification of heptachlor epoxide in terrestrial food chains is significant.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Heptachlor may undergo direct photolysis in sunlight and is also susceptible to photosensitized reactions (Graham et al. 1973; Ivie et al. 1972). Heptachlor epoxide is converted to intermediate and final photoproducts when exposed to sunlight or ultraviolet light on the surface of plants (Podowski et al. 1979). From 40% to 50% conversion occurred in 4 hours on bean leaves treated with rotenone, an insecticide, acting as a photosensitizer. No detectable photoproducts (photoheptachlor epoxide) were formed in the absence of rotenone. The photolysis products were ketones. The intermediate photoproduct has a reduced toxicity in mice as compared to heptachlor epoxide, and it is completely nontoxic to houseflies. The final photoproduct is more toxic to flies and mice than the parent heptachlor epoxide (Ivie et al. 1972). The photoisomers of heptachlor epoxide are not expected to form in appreciable amounts in the environment unless a potent photosensitizer is present (Ivie et a1. 1972). The photolysis of heptachlor epoxide as a solid (pressed) disk, as a powder, and as 0.5% heptachlor epoxide in a potassium bromide (a photosensitizer) disk was studied. The physical nature of the sample and the intensity of illumination affected the rate of photolysis. After 121 hours of exposure to sunlight in July, 93%, 98%, and 0% heptachlor epoxide remained in the solid disk, powder, and potassium bromide disk, respectively. When a powdered sample of heptachlor epoxide was irradiated on a rooftop of an unspecified location from January through mid-September, degradation was almost negligible until May, then increased through July, reaching a maximum decomposition rate of 1% per day at the end of July. By the end of the experiment (8.5 months), 39% of the original sample has decomposed (Graham et al. 1973).

5.3.2.2 Water

Heptachlor is hydrolyzed in surface water and distilled water to 1-hydroqchlordene. When heptachlor was added to a sample of river water maintained at room temperature and exposed to sunlight, only 25%

remained after 1 week, and no heptachlor remained after the 2nd week. The 75% loss of heptachlor after 1 week corresponds to a half-life of 3.5 days. The products formed were identified as 1-hydroxychlordene and heptachlor epoxide. It was observed that an equilibrium exists at the end of 4 weeks between 1-hydroxychlordene and heptachlor epoxide, so that approximately 60% of the converted heptachlor remained as I-hydroxychlordene and 40% was converted to the epoxide. When heptachlor epoxide was added to a sample of river water (pH 7.3-8) and to distilled water, it remained unchanged for 8 weeks. A half-life of at least 4 years was calculated for heptachlor epoxide (Eichelberger and Lichtenberg 1971).

When a ^{14}C-heptachlor-treated model aquatic ecosystem was examined for transformation of heptachlor in water, the relative amounts of various transformation products in water were determined as the percentage of the total ^{14}C label in the water sample. Heptachlor was found to decrease from 100% to approximately 10% of total ^{14}C material in 1 day (Lu et al. 1975). After 1 day, I-hydroxychlordene epoxide was present as 50% of the total ^{14}C, rose to 70% on day 3, and then remained constant until day 13 of the experiment. The heptachlor hydrolysis product, 1-hydroxychlordene, reached a maximum of 10% of the total ^{14}C at day 1 and decreased thereafter. A relatively small proportion of heptachlor epoxide was formed. Heptachlor epoxide was never found to be greater than 10% of the total ^{14}C in the water sample. The authors concluded that the major pathway of heptachlor in aquatic systems is rapid abiotic hydrolysis of heptachlor to 1-hydroxychlordene followed by metabolism to 1-hydroxychlordene epoxide (Lu et al. 1975).

Heptachlor is metabolized by the freshwater microcrustacean, Danhnia magna, to heptachlor epoxide or I-hydroxychlordene. I-Hydroxychlordene is then converted to I-ketochlordene, l-hydroxy-2,3-epoxychlordene, and their glucosides, sulfates, and other conjugates (Feroz et al. 1990).

5.3.2.3 Soil

Incubations of heptachlor with a mixed culture of soil microorganisms for 12 weeks showed conversion of heptachlor to chlordene, l-exohydrolcychlordene, heptachlor epoxide, and chlordene epoxide. A mixed culture of soil microorganisms, obtained from a sandy loamy soil, degraded heptachlor epoxide to the less toxic l-exohydroxychlordene. Conversion was about 1% per week during the 12-week test period (Miles et al. 1971).

Samples for analysis were taken from five locations selected to represent typical soil types and rainfall patterns in portions of the United States where subterranean termites were a major problem and where heptachlor was applied for treatment (Carter and Stringer 1970). Insecticide residues were found in the soil 1, 2, and 3 years after application of heptachlor. Relatively high values for 1-hydroxychlordene, representing approximately 60% of the insecticide in the soil, were obtained from extracts of a Quincy loamy fine sand from Oregon 2 years after application. Significant amounts of 1-hydroxychlordene were also found in extracts of Lakeland sand from Florida. Generally, heptachlor epoxide represented only a small fraction of the insecticide present in the soils (Carter and Stringer 1970). Large variations were found in residue concentrations in these soils where distribution and penetration of heptachlor were uneven; therefore no general trends were recognized (Carter and Stringer 1970).

Loamy soils treated with heptachlor at 25 pounds per 5-inch acre, over a 5-year period from 1958 through 1962, contained about 5% of the applied dosages in the fall of 1968, primarily in the form of heptachlor epoxide. In addition to y-chlordane and nonachlor, which were present in the original heptachlor formulation, two toxic metabolites (heptachlor epoxide and a-chlordane) and three unidentified compounds

were detected, thus indicating the breakdown in soils of heptachlor and related compounds (Lichenstein et al. 1970).

Experiments with thick anaerobically digested waste water sludge at 35°C showed that heptachlor was converted to an extractable degradation product that was more persistent than the initial heptachlor. About a 50% loss of heptachlor epoxide was found in anaerobic thick sludge after approximately 60 days. No information was given as to the identity of the product. No heptachlor epoxide loss occurred in aerobic dilute sludge, and only slight heptachlor epoxide loss occurred in anaerobic dilute sludge (Hill and McCarty 1967).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Indoor air levels of heptachlor were measured in various homes in Bloomington, Indiana, that had been professionally treated with a termiticide either by spraying or subsurface injection. Heptachlor was detected at concentrations ranging from 1.1 to 110 ng/m^3 (0.0001-0.007 ppb) (Anderson and Hites 1989). Three houses in North Carolina were treated with a termiticide containing both chlordane (0.5%) and heptachlor (0.25%). Immediately after treatment, the average ambient air level of heptachlor was 1.41±0.64 μgm3 (0.092 ppb). At 12 months post-treatment, the heptachlor level in the air was 1.00±0.70 μg./m^3 (0.065 ppb) (Wright and Leidy 1982). Heptachlor was detected at levels ranging from 1.64 to 13.2 ppb in workplace air in 1977 at the Velsicol Chemical Corporation plant in Tennessee that manufactured heptachlor (Netzel 1981). No heptachlor epoxide levels in air were detected (Netzel 1981). A study of nine households selected on the basis of high pesticide usage in an urban-suburban area in the southeastern United States found outdoor air levels of heptachlor ranging from not detectable (0.0006 ppb) to 0.003 ppb, with a mean of 0.001 ppb (Lewis et al. 1986). Heptachlor was found in seven of nine households at levels in indoor air ranging from not detectable to 0.02 ppb, with a mean of 0.006 ppb (Lewis et al. 1986).

5.4.2 Water

A statewide survey (December 1985-February 1986) was conducted in Kansas to determine the degree and extent of pesticide contamination. of drinking water from approximately 100 private farmstead wells. Heptachlor was detected in 1% of the wells tested at a concentration range of 0.023-0.026 ppb with an average concentration of 0.025 ppb (detection limit = 0.02 ppb) (Steichen et al. 1988).

Heptachlor was included in EPA's Pesticides in Groundwater Database for five states: Alabama, Idaho, Illinois, Kansas, and Massachusetts. Concentrations of heptachlor in groundwater from ,these five states ranged from 0 to 0.81 ppb with a mean concentration of 0.068 ppb (EPA 1988d). Mean heptachlor concentrations were reported for three of the states: Illinois (0.19 ppb), Kansas (0.03 ppb), and Massachusetts (0.05 ppb) (EPA 1988d).

Heptachlor and heptachlor epoxide were detected in water column samples at different depths in Lake Pontchartrain in New Orleans, Louisiana. Heptachlor was detected in the 1.5meter ebb- and flood-tide samples and in the lo-meter flood-tide samples at concentrations of 0.6, 9.1, and 9.3 ppt, respectively. Heptachlor epoxide was detected in the 1.5-meter ebb- and flood-tide samples and in the lo-meter floodtide sample at concentrations of 2, 3.9, or 2.5 ppt, respectively (McFall et al. 1985).

5. POTENTIAL FOR HUMAN EXPOSURE

Findings from the Nationwide Urban Runoff Program priority pollutant samples collected in 1982 showed that heptachlor and heptachlor epoxide were detected at a concentration of 0.1 ppb for both compounds (Cole et al. 1984). Heptachlor and heptachlor epoxide were detected in 5% and l%, respectively, of the 86 urban storm water runoff samples taken from 15 cities.

Heptachlor epoxide was detected in rain samples at concentrations ranging from 0.03 to 1 ppt at four widely separated sites in Canada from May to October in 1984. The sites are representative of overlake and shoreline locations (Strachan 1988). Snowpack samples representing snow accumulation for the winter of 1985-1986 were collected at a total of 12 widely distributed sites throughout the Northwest Territories, Canada, during the spring of 1986. Heptachlor epoxide was detected at 11 of the 12 sites at concentrations ranging from 0.2 to 0.41 ng/L ($2x10^{-4}$-4xl0^{-4} ppb). The only reasonable source for these compounds is long-range atmospheric transport and deposition (Gregor and Gummer 1989). Heptachlor was detected in wet precipitation samples (rain/snow) from Lake Erie at a volume-weighted mean concentration (based on the total volume collected over the 1Zmonth period) of 0.1 ng/L ($1x10^{-5}$ ppb) (Chan and Perkins 1989). Heptachlor epoxide was detected at volume-weighted 5 ppb), 0.24 ng /L ($2.4x10^{-4}$ ppb), and 0.02 ng/L mean concentrations of 0.05 ng/L (5x10- ($2x10^{-5}$ ppb) in wet precipitation samples from Lake Superior, Lake Erie, and Lake Ontario, respectively (Chan and Perkins 1989).

Data maintained in the STORET database for 1980-1982 included heptachlor and heptachlor epoxide concentrations in industrial effluent and ambient water. Median values for heptachlor in effluent and water samples were co.007 ppb detected in 3% (n=671) and 0.001 ppb in 34% (n=4,650) of the samples, respectively. Median values for heptachlor epoxide in effluent and water samples were <0.007 ppb detected in 4.2% (n=672) and 0.001 ppb in 36% (n=4,632) of the samples, respectively (Staples et al. 1985).

5.4.3 Soil

Data from the 1971 National Soils Monitoring Program at 1,486 sampling sites in 37 states showed heptachlor was detected in 4.9% of the samples from cropland soils at concentrations ranging from 10 to 1,370 ppb. Heptachlor epoxide was detected in 6.9% of the samples at concentrations ranging from 100 to 430 ppb (Carey et al. 1978). A survey of agricultural soils (pasture soils) in the New South Wales North Coast region in Australia (1983-1984) showed soils contaminated with organochlorine residues. Heptachlor levels in the pasture soils generally averaged <100 ppb. ‘Heptachlor epoxide residues were slightly higher. Heptachlor and heptachlor epoxide were generally highest in the top 22.5 cm of soil (McDougall et al. i987).

Heptachlor epoxide was detected in grab and core samples of southern Lake Michigan sediments (period of sampling, 1969-1970) at trace levels up to 0.7 ppb Leland et al. 1973). The U.S. Geological Survey investigated the sediment quality of the upper Rockaway River in New Jersey. Sediment samples were collected from seven stations along the upper Rockaway River. Stations 1 and 2 drain primarily forested areas of the upper Rockaway basin. Stations 3-7 drain an area consisting primarily of residential, commercial, and industrial land usage, including six NPL sites. Concentrations of heptachlor epoxide were <0.1 ppb for stations 1 and 2. Heptachlor epoxide concentrations ranged from <0.1 to 10 ppb for stations 3-7 (Smith et al. 1987).

5.4.4 Other Environmental Media

Heptachlor and heptachlor epoxide have been detected in several aquatic species. Heptachlor was measured in shrimp collected from the Calcasieu River/Lake Complex in Louisiana at concentrations

ranging from 10 to 750 ppb (Murray and Beck 1990). A survey of organic compound concentrations in whole body tissues of the Asiatic clam Corbicula manilensis was conducted on the Apalachicola River in northwest Florida in 1979-1980 as part of the Apalachicola River Quality Assessment. Heptachlor epoxide was detected in the whole body tissue of the clam at concentrations ranging from <0.1 to 0.6 ppb, with a median concentration of 0.3 ppb (Elder and Mattraw 1984).

Composite whole fish samples taken from tributary rivers around the Great Lakes in 1980-1981 had heptachlor levels of <0.002 mg/kg (<2 ppb) at all sites except the Ashtabula River where a maximum concentration of 0.30 mg/kg (300 ppb) occurred. Heptachlor epoxide was detected at concentrations ranging from 0.003 to 0.48 mg/kg (3-480 ppb) (DeVault 1985). Freshwater fish collected in 1984 for the National Contaminant Biomonitoring Program run by the U.S. Fish and Wildlife Service contained a geometric mean residue concentration of total heptachlor (heptachlor epoxide plus traces of heptachlor) of 0.01 ppm (wet weight). Heptachlor residues in fish were present in 49.1% of the collection stations (n=112) located at major rivers throughout the United States, including Alaska and Hawaii. Concentrations of heptachlor epoxide in whole fish samples remained highest in Hawaii and in the Midwest, especially in Lake Michigan and in the Mississippi, Missouri, Ohio, and Illinois rivers (Schmitt et al. 1990).

Average residue levels of total heptachlor detected in Illinois soybeans in 1980 (6.6 ppb) showed a slight increase from 1974 levels (5.3 ppb), even though the usage of heptachlor declined during that period (MacMonegle et al. 1984). Heptachlor residues above maximum residue limits were reported in Australian beef in 1987. Upon removing the animals from contaminated pastures, the proportion of samples of beef with residue levels above the permitted limits decreased from 0.42%. in 1986-1987 to 0.22% in 1987-1988 (Corrigan and Seneviratna 1989). In an earlier study, heptachlor epoxide levels in cow's milk reached a maximum of 0.22 ppm within 3-7 days after the animals had grazed on pastures immediately following treatment of the grasses with heptachlor (Gannon and Decker 1960).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is primarily exposed to heptachlor and heptachlor epoxide through diet. The food classes most likely to contain residues are milk and other dairy products, vegetables, meat, fish, and poultry. In the FDA Total Diet Study conducted between 1981 and 1982, levels of chemicals in the diet were determined by analyzing samples from retail markets in 13 cities throughout the continental United States.These samples represent the typical 1Cday diet. Approximately 120 individual food items, including drinking water, were collected for each market basket sample; the infant diet consisted of about 50 of these foods, and the toddler diet included 110. The average daily intake of heptachlor epoxide for infants was estimated to be 0.01 ,μg/kg/day. The 1981-1982 average daily intake of heptachlor epoxide for toddlers was reported to be 0.009 μg/kg/day. Whole milk, with an average concentration of 0.1 ppb, contributed the highest daily intake of heptachlor epoxide for both toddlers and infants (Gartrell et al. 1986b). In the FDA Total Diet Study conducted between 1982 and 1984, analyses were performed of 234 items depicting the diets of eight population groups with members ranging in age from infants to elderly adults. The data represent eight food collections in regional metropolitan areas during the 2-year period. Toddlers (2 years old) had the highest daily intake of heptachlor epoxide (6.1 ng/kg/day). Infants had a daily intake of heptachlor epoxide of 2.7 ng/kg/day. Daily intake from whole milk was not included in this study. Adults had heptachlor epoxide intakes that ranged from 1.5 ng/kg/day (60-65-year-old females) to 2.8 ng/kg/day (14-16-year-old males). Heptachlor epoxide was found in 8% of the food samples analyzed between 1982 and 1984. Heptachlor intake was less than 0.1 ng/kg/day for all age/sex groups. Between 1980 and

1982-1984, daily intakes of heptachlor epoxide decreased from 19 to 3 ng/kg/day for infants, from 20 to 6 ng/kg/day for toddlers, and from 7 to 2-3 ng/kg/aay for adults (Gunderson 1988).

The 1988 Acceptable Daily Intake (ADI) established by the United Nation's Food and Agriculture Organization and the World Health Organization (FAO/WHO) for total heptachlor was 0.5 μg/kg/day (FDA 1989b). Total heptachlor intakes found in the Total Diet Analysis (1988) were 0.004 μg./kg/day for 6-11-month-old infants, 0.017 μg/kg/day for 14-16-year-old males, and 0.0007 μg/kg/day for 60-63-year-old females (FDA 1989b).

Heptachlor epoxide was found in whole blood samples from nonoccupationally exposed mothers and their newborns in Argentina (Radomski et al. 1971a). The average level of heptachlor epoxide was 0.23±.29 ppb in 13 mothers and 0.06±0.01 ppb in 13 newborn infants, although no blood samples were taken from the mothers during pregnancy (Radomski et al. 1971a).

Adipose tissue samples from various body parts of people living in northeast Louisiana, an area of heavy agriculture, were taken during pathological examination. Heptachlor epoxide levels in the individual tissue samples ranged from 20 to 790 ppb (average=239 ppb) for the 1980 study and from 60 to 220 ppb (average=159 ppb) from adipose tissue samples taken from other donors for the 1984 study (Holt et al. 1986).

Heptachlor and heptachlor epoxide have been found in human milk samples (Al-Omar et al. 1986; Fytianos et al. 1985; Larsen et al. 1971; Mes et al. 1986, Ritcey 1972; Savage et al. 1981). Breast milk samples (n=210) taken from Canadian women from five different regions who had resided in Canada for at least 5 years were analyzed for chlorinated hydrocarbon contaminants as part of a monitoring program. Trends from 1967 to 1982 showed heptachlor epoxide levels -decreased from a mean of 3 ppb in 1967 to a mean of cl ppb in 1982 (maximum, 7 ppb) (Mes et al. 1986). Heptachlor epoxide was found in 62% of all samples taken in 1982 (Mes et al. 1986). Human milk samples obtained from 1,436 women residing in the United States were analyzed for chlorinated hydrocarbon insecticides. While heptachlor was recovered in less than 2% of the samples, heptachlor epoxide was found in 63% of the samples. The proportion of breast milk samples containing heptachlor epoxide varied significantly among the five geographic regions (66.1-128 ppb) with the southeastern states having the highest mean residual level. The reasons for higher levels of these chemicals in samples from women in the southeastern United States are not clear, but there may be several contributing factors. For example, more people in the southeast use pesticides in the home, lawn, and garden, and a larger proportion of southeastern U.S. homes have been treated with heptachlor for termite control. The mean residual level of heptachlor epoxide in breast milk for the whole United States was 91.4 ppb (Savage et al. 1981). A S-month follow-up study of four pregnant Iraqi women without occupational exposure to organochlorine pesticides found total heptachlor levels in the placenta immediately after delivery ranging from not detectable to 28 ppb total tissue weight. Milk samples were then taken for 20 consecutive weeks. Average total heptachlor levels in the mothers' milk ranged from 15 to 68 parts per billion parts of whole milk (Al-Omar et al. 1986). There was considerable fluctuation in the residue concentrations over the 20 weeks. The authors suggest that the fluctuations could be attributed to changes in daily diet intake of residues and daily variations in milk production and fat content of the milk.

A pilot study for EPA's Non-Occupational Exposure Study was conducted in August 1985 in order to assess nonoccupational exposures to pesticides, including heptachlor, in indoor air and personal respiratory air. The study was conducted in nine households selected on the basis of high pesticide usage in an urbansuburban area in the southeastern United States. The residents of these households were generally retired

or semi-retired persons, who spent the majority of their time indoors (average=18 hours) and, consequently, do not represent the general adult population. The results showed that heptachlor was found in seven of nine households at levels in indoor air ranging from not detectable (at 0.0001 ppb) to 0.31 μg/m^3 (0.02 ppb), with a mean of 0.088 μg/m^3 (0.006 ppb). When residents wore personal monitors, operated only during periods of activity, heptachlor was detected in six of nine households at personal exposure levels of not detectable to 0.18 μg/m^3 (0.01 ppb), with a mean of 0.06 μg/m^3 (0.004 ppb). Outdoor air levels of heptachlor were lower, ranging from not detectable to 0.048 μg/m^3 (0.003 ppb), with a mean of 0.016 μg/m^3 (0.001 ppb), and were detected in five of nine households (Lewis et al. 1986).

Data concerning occupational exposure levels of heptachlor are very limited. An industrial hygiene survey conducted in 1977 at the Velsicol Chemical Corporation, Memphis, Tennessee, a plant that manufactured heptachlor, detected heptachlor in workplace air at levels ranging from 0.025 to 0.202 mg/m^3 (1.64-13.2 ppb) (Netzel 1981). Data from the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 were not available for heptachlor or heptachlor epoxide.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Infants and toddlers are exposed to higher levels (based on their greater dose to surface area [or body weight] ratio) of heptachlor epoxide in the diet (particularly from milk) than are adults. Higher exposure rates in indoor air may occur for at least 1 year in homes that have been treated for termites with heptachlor in the past. Although the most likely routes of exposure at hazardous waste sites are unknown, exposure may result from ingestion of contaminated soil near these sites particularly by children. Since both heptachlor and heptachlor epoxide volatilize from soil, inhalation exposure may also be important for persons living near hazardous waste sites. Exposure via ingestion of contaminated drinking water obtained from wells near hazardous waste sites is unlikely. Heptachlor and heptachlor epoxide are considered too lipophilic to leach to groundwater. While some samples have been found in well water, this trend is not universal. Workers involved in the manufacture of heptachlor and in the application of heptachlor for fire ant control are at risk of exposure to heptachlor. People living in the southeastern United States may be exposed to higher than background levels of heptachlor or heptachlor epoxide because of the larger proportion of southeastern U.S. homes that have been treated with heptachlor for termite control and the greater usage of pesticides in the home, lawn, and garden. Infants living in this region may be more likely to ingest heptachlor or heptachlor epoxide from maternal breast milk, although this exposure pathway is not restricted to the southeastern United States.

Average heptachlor epoxide levels in whole blood samples from nonoccupationally exposed mothers and their newborns in Argentina were 0.23±.29 ppb in 13 mothers and 0.06±0.01 ppb in 13 newborn infants (Radomski et al. 1971a). Organochlorine pesticide levels, including heptachlor epoxide levels, in whole blood samples of an unknown number of U.S. residents (Florida) were compared to those of six Formosan and two Japanese graduate students who had been in the United States for 2-5 years. Compared to the U.S. residents, elevated blood concentrations were observed in the graduate students from Formosa and Japan (Radomski et al. 1971b). Therefore, it is possible that Formosan and Japanese residents may have been exposed to higher levels of heptachlor or heptachlor epoxide.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of heptachlor and heptachlor epoxide is available. Where adequate

information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of heptachlor and heptachlor epoxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of heptachlor and heptachlor epoxide are sufficiently well defined to allow assessments of the environmental fate of the compounds to be made (ACGIH 1986; Chapman 1989; HSDB 1990a; MacKay 1982; OHM/TADS 1985a, 1985b). Some physical and chemical properties of heptachlor epoxide that are not relevant to environmental fate are lacking. Knowledge of these properties, such as odor, flashpoint, and flammability limits, would be useful for workers involved in the manufacture, use, or clean-up of heptachlor and heptachlor epoxide.

Production, Import/Export, Use, and Release and Disposal. Currently, heptachlor use in the United States is limited to fire ant control in power transformers (EPA 1990b). However, because of former widespread use of heptachlor and the persistence of heptachlor epoxide, these compounds and their degradation products can still be found at low levels in indoor air, water, soil, and food. Disposal methods are well documented in the literature; however, more current information would be useful. Information on historical disposal practices would be helpful in evaluating the potential for environmental contamination. More information on the volume of heptachlor used in fire ant control would be useful in estimating potential occupational exposure.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to. submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1988, became available in May of 1990. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Heptachlor and heptachlor epoxide are partitioned to the air, water, and soil (EPA 1987a; Jury et al. 1987; Lichtenstein et al 1970; Shivankar and Kavadia 1989). They are both transported in air and water and sorb to soils and sediment. They are biotransformed in soil and surface water, with biotransformation occurring faster for heptachlor than for heptachlor epoxide. Current data on the biotransformation (including half-life data) of both compounds in groundwater, surface water, surface soil, and subsurface soil would be useful in assessing the environmental persistence of these substances. Data on the toxicity of the biotransformation products of both compounds would assist in better characterizing the potential public health threat. Both heptachlor and heptachlor epoxide undergo photolysis. Data regarding the half-lives for photolysis would be helpful in determining the persistence of both compounds.

Bioavailability from Environmental Media. The limited pharmacokinetic data indicate that both compounds are absorbed following inhalation, oral, and dermal exposure (Arthur et al. 1975; Gaines 1969; Harradine and McDougall 1986). Additional information on the absorption of these compounds following

inhalation and following ingestion of contaminated drinking water and soil would be useful in evaluating the relative importance of various routes of exposure to populations living in the vicinity of hazardous waste sites and those whose homes have been treated for termites with heptachlor or chlordane.

Food Chain Bioaccumulation. Heptachlor and heptachlor epoxide accumulate in aquatic and terrestrial organisms (Elder and Mattraw 1984, Murray and Beck 1990; Schmitt et al. 1990). Biomagnification of heptachlor and heptachlor epoxide in aquatic food chains is significant. Because heptachlor is readily metabolized to heptachlor epoxide by higher trophic level organisms, biomagnification of heptachlor itself is not significant. Because of the more persistent nature of heptachlor epoxide and its lipophilicity, biomagnification of heptachlor epoxide in terrestrial food chains is significant. More current information regarding biomagnification of heptachlor epoxide in terrestrial food chains would be helpful in evaluating the extent of environmental contamination.

Exposure Levels in Environmental Media. Heptachlor and heptachlor epoxide have been detected in indoor and outdoor air, surface water, groundwater, soil, sediment, and food (Larsen et al. 1971; Lewis et al. 1986). Current monitoring data on levels of both compounds in outdoor and indoor air and soil are needed. Dietary intake data for the general population were located. Intake data for other media (air and water) are needed to estimate the risk of exposure of the general population.

Exposure Levels in Humans. Heptachlor epoxide has been detected in human blood, tissues (including adipose tissue), and breast milk (AI-Omar et al. 1986; Holt et al. 1986; Larsen et al. 1971; Savage et al. 1981). The presence of heptachlor epoxide is used as an indicator of exposure to heptachlor. Current monitoring studies of heptachlor epoxide in these tissues and fluids would be helpful in assessing the extent to which populations, particularly in the vicinity of hazardous waste sites, have been exposed to heptachlor.

Exposure Registries. No exposure registries for heptachlor or heptachlor epoxide were located. These compounds are not currently among the compounds for which a subregistry has been established in the National Exposure Registry. These compounds will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to these compounds.

5.7.2 On-going Studies

No on-going studies were located for heptachlor or heptachlor epoxide regarding potential for human exposure.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring heptachlor and heptachlor epoxide in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify heptachlor and heptachlor epoxide. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect heptachlor and heptachlor epoxide in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Analytical methods exist for measuring heptachlor, heptachlor epoxide, and/or their metabolites in various tissues (including adipose tissue), blood, human milk; urine, and feces. The common method used is gas chromatography (GC) coupled with electron capture detection (ECD) followed by identification using GC/mass spectrometty (MS). Since evidence indicates that heptachlor is metabolized to heptachlor epoxide in mammals, exposure to heptachlor is usually measured by determining levels of heptachlor epoxide in biological media. A summary of the detection methods used for various biological media is presented in Table 6-1.

Heptachlor and heptachlor epoxide are measured in adipose tissue, blood, and serum using GC/ECD (Adeshina and Todd 1990; Burse et al. 1990; Polishuk et al. 1977a, 1977b; Radomski et al. 1971a, 1971b) and identified by GC/MS (LeBel and Williams 1986). Sample preparation steps for adipose tissue vary but, in general, involve a lipid extraction step followed by a clean-up procedure involving gel permeation chromatography (GPC) and/or Florisil column clean-up. Using GPC with methylene chloride cyclohexane as a solvent, individual organochlorine contaminants can be separated from adipose tissue to produce extracts clean enough for direct GC analysis. Clean-up efficiency using GPC is 99.9% (LeBel and Williams 1986). The sensitivity obtained using GC/ECD is in the low-ppb range. Recoveries for heptachlor are adequate (72-87s); recoveries for heptachlor epoxide are good (84-98s). Precision is good for both (Adeshina and Todd 1990; LeBel and Williams 1986). The preparation step used for measuring heptachlor epoxide in blood and serum involves lipid extraction, clean-up with column chromatography, and elution with acetonitrile, hexane, and methylene chloride (Burse et al. 1990; Polishuk et al. 1977a, 1977b). Recovery is adequate (80-96s). Precision is good (9-l%). Sensitivity was not reported (Burse et al. 1990).

GC/ECD and GC equipped with a microcoulometric detector have been used to determine heptachlor and heptachlor epoxide in a variety of human tissues, including the liver, brain, adrenals, lungs, heart, kidneys, spleen, and pancreas (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968). Details of a sample preparation method were not reported for GC equipped with a microcoulometric detector (Curley et al. 1969). Sample preparation steps for GC/ECD include homogenization, extraction with petroleum ether or hexane, usually followed by a clean-up procedure (Klemmer et al. 1977; Radomski et al. 1968). Recovery, sensitivity, and precision data were not reported (Curley et al. 1969; Klemmer et al. 1977; Radomski et al. 1968).

Heptachlor and heptachlor epoxide have been measured in samples of human milk using GC/ECD and GC/MS (Mussalo-Rauhamaa et al. 1988; Polishuk et al. 1977b; Ritcey et al. 1972). Sample preparation

TABLE 6-1. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Adipose tissue	Lipid extraction with acetone-hexane; fractionation from fat by gel permeation chromatography; Florisil column clean-up.	GC/ECD; GC/MS	1.4 ng/g (heptachlor); 1.1 ng/g (heptachlor epoxide)	72–87% (heptachlor); 86–98% (heptachlor epoxide)	LeBel and Williams 1986
Adipose tissue	Lipid extraction with petroleum ether; concentration; clean-up on Florisil column.	GC/ECD	0.001 ppm (heptachlor epoxide)	84%	Adeshina and Todd 1990
Human liver and brain tissue	Grind liver tissue and extract with petroleum ether. Dry brain tissue and grind with petroleum ether. Centrifuge and inject.	GC/ECD	NR	NR	Radomski et al. 1968
Human tissues	Homogenize. Extract with hexane containing anhydrous sodium sulfate. Evaporate. Redissolve in hexane. Clean-up on Florisil.	GC/ECD	NR	NR	Klemmer et al. 1977

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Lipid extraction with chloroform/methanol; clean-up with column chromatography; elution with acetonitrile, hexane and methylene chloride.	GC/ECD	NR	NR	Polishuk et al. 1977a, 1977b
Serum	Add methanol and extract with hexane/ethyl ether. Clean-up on Florisil column. Acid treatment and clean-up on silica gel column.	GC/ECD	NR	80–96%	Burse et al. 1990
Human milk	Homogenize with chloroform/methanol; lipid extract with petroleum ether or hexane; clean-up by column chromatography; elution with acetonitrile, hexane, and methylene chloride.	GC/ECD	NR	NR	Polishuk et al. 1977b
Human milk	Lipid extraction with acetone-hexane. Dissolve in benzene-acetone. Clean-up on Florisil. Elute with dichloromethane-petroleum ether. Concentrate and add hexane	GC/ECD	0.001 ppm (heptachlor epoxide)	NR	Ritcey et al. 1972

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine and feces (heptachlor, heptachlor epoxide, and metabolites)	Extract with acetone and hexane. Combine solvents and concentrate. Mix with silicic acid and air dry. Clean-up on Florisil column and silicic acid column. Metabolites extracted into hexane for GC analysis.	GC/ECD	NR	NR	Tashiro and Matsumura 1978

ECD = electron capture detector; GC = gas chromatography; MS = mass spectrometry; NR = not reported

steps for milk involve homogenization with chloroform/methanol, lipid extraction with petroleum ether, hexane or acetone-hexane, clean-up by column chromatography, and elution with acetonitrile, hexane, methylene chloride, or dichloromethane-petroleum ether. Precision, accuracy, and sensitivity were not reported for most of the studies; however, one study reported a sensitivity in the low-ppb range (Ritcey et al. 1972).

Heptachlor, heptachlor epoxide, and their metabolites have been measured in urine and feces using GC/ECD (Tashiro and Matsumura 1978). Sample preparation steps involve extraction with acetone and hexane, clean-up on Florisil and silicic acid columns, and extraction of the derivatized metabolites into hexane for GLC analysis. Precision, accuracy, and sensitivity were not reported (Tashiro and Matsumura 1978).

6.2 ENVIRONMENTAL SAMPLES

Methods exist for measuring heptachlor and heptachlor epoxide in air, water, soil, and food. The most common methods are GC/ECD and GC/MS. A summary of methods for detecting heptachlor and heptachlor epoxide in various environmental samples is presented in Table 6-2.

Heptachlor is measured in indoor and outdoor air samples using GC/ECD and GC/MS (Anderson and Hites 1989; Lewis et al. 1986; NIOSH 1979; Savage 1989). Heptachlor has also been measured in house dust (Roberts and Camann 1989). Preparation methods involve the use of a variety of air trapping samplers. Examples of these include the Greenburg-Smith impinger, Chromosorb 102, low-volume samplers, and the Millipore miniature vacuum pump with a sampling tube. The next step includes extraction with diethyl ether, acetone-hexane, or toluene (Anderson and Hites 1989; NIOSH 1989; Roberts and Camann 1989). For indoor air, precision is excellent and recovery is adequate (>75%). Sensitivity is in the sub-ppb range (NIOSH 1979). For outdoor air, precision is good (13%) and recovery is excellent (99%). Sensitivity is in the sub-ppb range (Lewis et al. 1986).

Heptachlor and heptachlor epoxide are measured in water, drinking water, waste water, soil/sediment, and solid waste using GC/ECD and GC/MS (Alford-Stevens et al. 1988; EPA 1986d; Lopez-Avila et al. 1990; McDougall et al. 1987; Smith et al. 1987). Preparation of water, waste water, and drinking water samples involves extraction with methylene-chloride, concentration, and solvent exchange to hexane or methyl *tert*-butyl ether. Mean recovery in water for heptachlor was low (52-68%) and precision was poor (48-57%) (Alford-Stevens et al. 1988). Poor recovery and precision data were thought to be attributable to chromatographic problems in some of the participating laboratories. For drinking water (EPA Method 508), recovery was excellent for heptachlor (99%) and heptachlor epoxide (95%). Precision was excellent for both compounds (<10%). Sensitivity was in the sub-ppb range (Lopez-Avila et al. 1990). Preparation of soil/sediment or solid waste samples involves extraction with methylene chloride, methylene chloride-acetone, methylene chloride-methanol, or acetone-hexane followed by clean-up with Florisil or GPC (Alford-Stevens et al. 1988, EPA 19864). Overall precision was adequate to poor, ranging from 19% to 47% for heptachlor. Recovery and sensitivity were not reported (Alford-Stevens et al. 1988). EPA Test Methods 8080 and 8250 for evaluating waste water, soil sediment, and solid waste report sensitivity in the low-ppb range for both heptachlor and heptachlor epoxide (EPA 1986d). Recovery for heptachlor is adequate (69-87%) and recovery for heptachlor epoxide is good (89-92%). Precision is adequate for both methods (EPA 1986d).

GC/ECD is the method used to detect heptachlor and heptachlor epoxide in foods (butterfat, fruits, vegetables, milk, and animal feed) (Di Muccio et al. 1988, Hopper and Griffitt 1987; Korfmacher et al.

TABLE 6-2. Analytical Methods for Determining Heptachlor and Heptachlor Epoxide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Outdoor air	Sample collected with low-volume sampler consisting of a constant flow pump and a cartridge containing polyurethane foam. Extract with diethylether in hexane.	GC/ECD; GC/MS	0.0006 ppb	99% (heptachlor)	Lewis et al. 1986
Indoor air	Sample collected through a glass tube containing Chromosorb 102. Desorption with toluene.	GC/ECD	0.1 ppb	>75% (heptachlor)	NIOSH 1979
House dust	Sample collected with high-volume surface sampler; extract with diethyl ether in hexane.	GC/ECD; GC/MS	NR	NR (heptachlor)	Roberts and Camann 1989
Water	Extract with methylene chloride.	GC/MS	NR	52–68% (heptachlor)	Alford-Stevens et al. 1988
Wastewater	Extract with methylene chloride; exchange to hexane.	GC/ECD (EPA Method 8080)	0.003 μg/L (heptachlor); 0.083 μg/L (heptachlor epoxide)	69% (heptachlor); 89% (heptachlor epoxide)	EPA 1986d
Wastewater	Extract with methylene chloride	GC/MS (EPA Method 8250)	1.9 μg/L (heptachlor); 2.2 μg/L (heptachlor epoxide)	87% (heptachlor); 92% (heptachlor epoxide)	EPA 1986d

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water	Extract with methylene chloride; solvent exchange to methyl tert-butyl ether.	GC/ECD (EPA Method 508)	0.01 μg/L (heptachlor); 0.015 μg/L (heptachlor epoxide)	99% (heptachlor); 95% (heptachlor epoxide)	Lopez-Avila et al. 1990
Soil/ sediment and solid waste	Extract with methylene chloride; clean-up extract.	GC/MS (EPA Method 8250)	1.9 μg/L (heptachlor); 2.2 μg/L (heptachlor epoxide)	87% (heptachlor); 92% (heptachlor epoxide)	EPA 1986d
Foodstuff (butterfat)	Lipid extraction with automated gel permeation chromatography; direct injection.	GC/ECD	NR	100% (heptachlor epoxide)	Hopper and Griffitt 1987
Milk	Extract on solid-matrix disposable columns by means of acetonitrile-saturated light petroleum; Florisil® clean-up.	GC/ECD	NR	99% (heptachlor epoxide)	DiMuccio et al. 1988

ECD = electron capture detector; EPA = Environmental Protection Agency; GC = gas chromatography; MS = mass spectrometry; NR = not reported

1987; Ober et al. 1987; Santa Maria et al. 1986). Preparation methods vary for the different types of foods. The sample preparation method for butterfat involves GPC. GPC is a rapid clean-up technique for separating pesticide residues from a lipid extract. It was developed into an automated clean-up apparatus for use on a wide variety of fats and oils. The automated GPC system is reproducible and reliable. After being cleaned on GPC, most samples can be analyzed by GC without additional clean-up (Hopper and Griffitt 1987). Recovery is complete (l00%), and precision is very good (<3%). Sensitivity is in the subppm range. The sample preparation for milk samples involves selective extraction on solid-matrix disposable columns by means of acetonitrile-saturated light petroleum, followed by Florisil column clean-up. Recovery is excellent (99%); precision is very good (<7%) (Di Muccio et al. 1988). Sample preparation for fruits, vegetables, and animal feed involves cyclic steam distillation extraction in hexane or isooctane with direct injection into the gas chromatograph. Recoveries for this method are very low (15~50%). This is an indication that heptachlor is not extracted quantitatively by steam distillation and is not a recommended preparation method (Ober et al. 1987; Santa Maria et al. 1986).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of heptachlor and heptachlor epoxide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of heptachlor and heptachlor epoxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods exist for determining levels of heptachlor,, heptachlor epoxide, and/or their metabolites in various tissues (including adipose tissues) (Adeshina and Todd 1990; Curley et al. 1969; Klemmer et al. 1977; LeBel and Williams 1986; Radomski et al. 1968), milk (Mussalo-Rauhamaa et al. 1988; Polishuk et al. 1977b; Ritcey et al. 1972), blood (Polishuk et al. l977a, 1977b), serum (Burse et al. 1990), urine, and feces (Tashiro and Matsumura 1978). Methods for determining levels in adipose tissue are sensitive for measuring levels at which health effects might occur as well as background levels in the population. Methods for determining heptachlor and heptachlor epoxide in adipose tissue are relatively precise. Recovery is better for heptachlor epoxide than for heptachlor. Data on the determination of heptachlor and heptachlor epoxide in tissues, blood, serum, milk, urine, and feces are limited as precision, recovery, and/or sensitivity data were not reported for the existing methods. More information on the precision, accuracy, and sensitivity of these methods is needed to evaluate the value of using levels of heptachlor and heptachlor epoxide as biomarkers of exposure. :

The methods for determining biomarkers of effect are the same as those for exposure and are subject to the same limitations. Improved methods could allow a better assessment of the relationship between levels

of heptachlor and heptachlor epoxide in body tissues, blood, and fluids and the known health effects associated with these chemicals.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Existing methods for determining levels of heptachlor in air are sensitive enough to measure background levels in the environment, as well as levels at which health effects might occur. Data on the determination of heptachlor and heptachlor epoxide in air (Anderson and Hites 1989; Lewis et al. 1986; NIOSH 1979; Roberts and Camann 1989; Savage 1989), water (Alford-Stevens et al. 1988; EPA 1986d; Lopez-Avila et al. 1990), soil (EPA 1986d; McDougall et al. 1987; Smith et al. 1987), and food (Di Muccio et al. 1988; Hopper and Griffitt 1987; Korfmacher et al. 1987; Ober et al. 1987; Santa Maria et al. 1986) are limited. Information on the accuracy, precision, and sensitivity of these methods would permit better assessment of the risk of low-level environmental exposure for these media. A preparation method for fruit and vegetable analysis that provides increased recovery would allow better assessment of the risk of dietary exposure. Research investigating the relationship between levels measured in air, water, soil, and food and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed.

6.3.2 On-going Studies

No on-going studies regarding analytical methods were located for heptachlor or heptachlor epoxide.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding heptachlor and heptachlor epoxide in air, water, and other media are summarized in Tables 7-1 and 7-2, respectively.

ATSDR has not derived an MRL for heptachlor or heptachlor epoxide. EPA (IRIS 1990) has derived an oral reference dose (RfD) for heptachlor of 5.00×10^{-4} mg/kg/day with an uncertainty factor of 300, based on liver weight increases in male rats in a 2-year feeding study (Witherup et al. 1955). EPA (IRIS 1990) assigned heptachlor epoxide an RfD of 1.30×10^{-5} mg/kg/day with an uncertainty factor of 1,000, based on increased liver-to-body-weight ratios in male and female dogs in a 60-week feeding study (University of Cincinnati 1958). No inhalation reference concentration (RfC) data exist for either chemical.

Heptachlor is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987e, 1988e).

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), all uses of heptachlor and heptachlor epoxide were canceled in 1978, except for use in subsurface control of subterranean termites and for dipping of roots and tops of nonfood plants (EPA 1985c; FDA 1989c).

FDA has established an action level of 0.3 ppm for chlorinated hydrocarbons found in the fat of the following food-producing animals: adult cattle, calves, swine, sheep, goats, and poultry (HSDB 1990). In 1989, EPA recommended a replacement action level of 0.2 ppm for heptachlor and heptachlor epoxide (EPA 1989b).

On August 25, 1989, FDA established new and revised action levels for unavoidable residues of the canceled pesticide heptachlor and its metabolite heptachlor epoxide in food and feed. The action levels were recommended by EPA following revocation of previous tolerances in raw agricultural commodities. The action levels now in effect for residues of heptachlor and heptachlor epoxide, either individually or in combination, are as follows: 0.01 ppm for processed animal feed, artichokes, asparagus, brassica, bulb vegetables, cereal grains, citrus fruits, eggs, figs, fruiting vegetables, grass forage, fodder, hay, leafy vegetables, legume vegetables, m,ilk (fat basis), nongrass animal feeds, peanuts, pome fruits, root and tuber vegetables, salsify tops, small fruits and berries, stone fruits, and sugarcane; 0.02 ppm for cottonseed, cucurbit vegetables, pineapple, and rabbit (fat basis); and 0.3 ppm for fish (edible portion) (FDA 1989a).

Effluent guidelines have been established for heptachlor and heptachlor epoxide under the Clean Water Act for the following industrial point-source categories (EPA 1988a): electroplating, steam electric, asbestos, timber products processing, metal finishing, paving and roofing, paint and ink formulating, gum and wood, pesticides, and carbon black.

TABLE 7-1. Regulations and Guidelines Applicable to Heptachlor

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC 1979
WHO	ADI in food	0.5 μg/kg/day	WHO 1984
WHO	Drinking Water Guidance Level based on a carcinogenic end point	0.1 μg/L	WHO 1984
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA (skin)	0.5 mg/m^3	OSHA 1989b (29 CFR 1910.1000); OSHA 1989a
b. Water:			
EPA ODW	RMCL in drinking water (proposed)	0.4 μg/L	EPA 1989b (40 CFR 141, 142, 143); EPA 1989a
EPA OWRS	Priority Pollutants Regulated in Subcategory 1-Organic Pesticide Chemicals Manufacturing	Yes	EPA 1978c (40 CFR 455); EPA 1985d
	Pesticides regulated by NSPS, PSES, and PSNS when formulated and packaged	Yes	EPA 1978c (40 CFR 455); EPA 1985d
	Priority Pollutants Regulated in Pesticide Active Ingredient Manufacturing Wastewater	Yes	EPA 1978c (40 CFR 455); EPA 1985d
	Priority Pollutant Effluent Limitations for BAT, NSPS, PSES, and PSNS:		EPA 1978c (40 CFR 455); EPA 1985d
	Maximum for any 1 day	0.090 mg/L	
	Monthly average shall not exceed	0.032 mg/L	
c. Food:			
FDA	Action level for edible fish and shellfish	0.3 ppm	FDA 1989a, 1989b
	Action level for raw food crops	0.01 ppm	FDA 1989b
	Recommended action level for fat from meat	0.2 ppm	FDA 1989b
d. Other:			
EPA OERR	Reportable quantity	1 pound	EPA 1985a (40 CFR 302); EPA 1985b
EPA OSW	Designation as a hazardous substance under Section 311(b)(2)(A) of the Federal Water Pollution Control Act	Yes	EPA 1978a (40 CFR 116.4); EPA 1978b
	Designated as a Toxic Pollutant under Section 307(a)(1) of the Federal Water Pollution Control Act	Yes	EPA 1979a (40 CFR 401.15); EPA 1979b
	Listing as a hazardous waste: discarded commercial chemical products off-specification species, container residues, and spill residues thereof	Yes	EPA 1980b (40 CFR 261.33); EPA 1980c

TABLE 7-1 (Continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
	Listing as a hazardous constituent	Yes	EPA 1988b (40 CFR 261, Appendix VIII); EPA 1988c
	Groundwater Monitoring Requirement	Yes	EPA 1987a (40 CFR 264, Appendix IX); EPA 1987c
EPA OTS	Toxic Chemical Release Reporting; Community Right-to-Know	Yes	EPA 1988d (40 CFR 372); EPA 1987d
Guidelines:			
a. Air:			
ACGIH	TLV TWA (skin)	0.5 mg/m^3	ACGIH 1992
	Carcinogen Category (proposed)	A2[b]	ACGIH 1992
	Excursion Limit Recommendation	Yes	ACGIH 1990
EPA	RfC (Inhalation)	No data	IRIS 1990
NIOSH	REL TWA (Ca, skin)	0.5 mg/m^3	NIOSH 1992
b. Water:			
EPA ODW	MCLG (proposed)	0.00	EPA 1989b (40 CFR 141, 142); EPA 1989a
EPA OWRS	Health Advisories		EPA 1990a
	1-day (recommended)(child)	0.010 mg/L	
	10-day (child)	0.010 mg/L	
	Longer-term (child)	0.005 mg/L	
	Longer-term (recommended)(adult)	0.0175 mg/L	IRIS 1990
	Lifetime	None[c]	
	DWEL	0.0175 mg/L	
	Ambient Water Quality Criteria for Protection of Human Health[d]		EPA 1980d
	Ingesting water and organisms:		
	10^{-5}	2.78 ng/L	
	10^{-6}	0.28 ng/L	
	10^{-7}	0.028 ng/L	
	Ingesting organisms only:		
	10^{-5}	2.85 ng/L	
	10^{-6}	0.29 ng/L	
	10^{-7}	0.029 ng/L	
	Water Quality Standards for Protection of Aquatic Life		EPA 1980d
	Concentration should never exceed:		
	Saltwater	0.053 μg/L	
	Freshwater	0.52 μg/L	
	24-hour average:		
	Saltwater	0.0036 μg/L	
	Freshwater	0.0038 μg/L	

TABLE 7-1 (Continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
c. Food:			
NAS	ADI	0-0.0005 mg/kg	HSDB 1990
d. Other:			
EPA	RfD (oral)	5.00×10^{-4} mg/kg/day	IRIS 1990
	Carcinogen classification	B2[e]	IRIS 1990
	Unit risk (air)	1.3×10^{-3} $(\mu g/m^3)^{-1}$	IRIS 1990
	Unit risk (water)	1.3×10^{-4} $(\mu g/L)^{-1}$	IRIS 1990
	q_1^* (oral)	4.5 mg/kg/day	IRIS 1990
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable Ambient Air Concentrations		NATICH 1991
California-Montana	NA	0.00	
Connecticut	(8-hour)	2.50 $\mu g/m^3$	
Florida-Tampa	(8-hour)	0.005 mg/m^3	
Florida-Fort Lauderdale	(8-hour)	0.005 mg/m^3	
Kansas	(Annual)	1.19 $\mu g/m^3$	
Kansas-Kansas City	(Annual)	0.001 $\mu g/m^3$	
Massachusetts	(24-hour)	0.140 $\mu g/m^3$	
Massachusetts	(Annual)	0.001 $\mu g/m^3$	
Maryland	NA	0.00	
North Dakota	(8-hour)	0.005 mg/m^3	
Nevada	(8-hour)	0.012 mg/m^3	
New York	(1 year)	1.70 $\mu g/m^3$	
Pennsylvania-Philadelphia	(1 year)	0.18 $\mu g/m^3$	
Pennsylvania-Philadelphia	(Annual)	0.18 $\mu g/m^3$	
South Carolina	(24-hour)	2.50 $\mu g/m^3$	
Texas	(30 minutes)	5.00 $\mu g/m^3$	
Texas	(Annual)	0.50 $\mu g/m^3$	
Virginia	(24-hour)	8.30 $\mu g/m^3$	
Kentucky	Significant Emission Levels of Toxic Air Pollutants	1.276×10^{-4} pounds/hour	NREPC 1986 (401 KAR 63.022)
Wisconsin	Hazardous Air Contaminants with Acceptable Ambient Concentrations:		CELDS 1990a
	Emission points <25 ft	0.0408 pounds/hour	
	Emission points ≥25 ft	0.1704 pounds/hour	

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
b. Water:			
	Drinking water quality guidelines and standards		FSTRAC 1988
Arizona		0.50 µg/L	
California		0.02 µg/L	
Illinois		0.1 µg/L	
Kansas		0.104 µg/L	
Maine		0.23 µg/L	
Minnesota		0.1 µg/L	
Alabama	Toxic Pollutant Criteria for Aquatic Life:		CELDS 1990b
	Freshwater		
	Acute	0.52 µg/L	
	Chronic	0.0038 µg/L	
	Marine		
	Acute	0.053 µg/L	
	Chronic	0.0036 µg/L	
Arkansas	Surface Water Quality Standards		CELDS 1990a
	Chronic (24-hour average)	0.0038 µg/L	
	Acute	0.52 µg/L	
California	Applied Action Levels for drinking water	0.02 ppb	EPA 1987f
California	Toxic materials limitations objectives for protection of human health (30-day average)	0.72 ng/L	CELDS 1990b
Florida	Class I surface water for use as potable water; shall not exceed	0.001 µg/L	CELDS 1990a
Florida	Class II water criteria	0.001 µg/L	CELDS 1990a
Florida	Unregulated contaminant subject to community water systems monitoring	Yes	CELDS 1990a
Illinois	MCL in drinking water	0.0001 mg/L	CELDS 1990a
Illinois	Public and food processing water supply standards	0.0001 mg/L	IEPA 1988

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
Indiana	Water Quality Criteria		CELDS 1990b
	Acute aquatic (maximum)	0.26 mg/L	
	continuous criterion concentration for human health (4-day average):		
	Outside mixing zone	0.0028 mg/L	
	Point of water intake	0.0028 mg/L	
Nevada	Water Quality Criteria for Agricultural Water Uses		CELDS 1990a
	Irrigation	<0.0001 mg/L	
	Watering of livestock	<0.00052 mg/L	
Nevada	Water Quality Criteria for Aquatic Use		CELDS 1990a
	Acute	<0.00052 mg/L	
	Chronic (24-hour average)	<0.0000038 mg/L	
	Propagation of wildlife	<0.0001 mg/L	
	Municipal or domestic water supply	<0.0001 mg/L	
New York	Allowable concentration limits for Class GA waters	Not detectable	CELDS 1990a
New York	Effluent standards: MACs into saturated or unsaturated zones	Not detectable	CELDS 1990a
North Carolina	Water quality standards for salt and fresh water	0.004 μg/L	CELDS 1990a
North Dakota	Water Quality Standards for Class I streams		CELDS 1990a
	Chronic	0.004 μg/L	
	Acute	0.52 μg/L	
Ohio	Permissible concentration in		CELDS 1990a
	Public water supply	0.00028 μg/L	
	Aquatic life habitats	0.001 μg/L	
Oklahoma	Pesticide criteria in the water column for the protection of fish and wildlife propagation	0.50 mg/L	CELDS 1990a
Oklahoma	Pesticide alert levels in fish tissues	0.3 mg/kg	CELDS 1990a

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
Puerto Rico	Maximum Allowable Concentration	0.001 µg/L	CELDS 1990a
Virginia	Chronic criteria for protection of aquatic life		CELDS 1990a
	Freshwater	0.0038 µg/L	
	Saltwater	0.0036 µg/L	
Virginia	Groundwater Monitoring Parameter	Yes	CELDS 1990b
Virginia	Statewide groundwater standard	0.001 µg/L	CELDS 1990a
Washington, DC	Water Quality Standards		CELDS 1990a
	Class C waters protected for aquatic life, waterfowl, shore birds, and water-oriented wildlife	0.0038 mg/L	
	Class D waters protected for use as a raw water source for public water supply	0.0003 mg/L[f]	
Wisconsin	Human Cancer Criteria		DNR 1987
	Public water supply:		
	Warm water sport fish communities	1.4 ng/L	
	Cold water communities	0.41 ng/L	
	Great Lakes communities	0.42 ng/L	
	Non-Water Supply:		
	Warm water sport fish communities	1.4 ng/L	
	Cold water communities	0.42 ng/L	
	Warm water forage and limited forage fish communities and limited aquatic life	16,000 ng/L	
c. Food:			
Illinois	FDA Action Levels	0.3 ppm	IEPA 1988
d. Other:			
	Permitted use of heptachlor banned		CELDS 1990a
Minnesota		Yes	
New York		Yes	
	Sale and use of heptachlor is prohibited		CELDS 1990a
New Hampshire		Yes	
New Jersey		Yes	
South Carolina		Yes	

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
	Designated as a restricted pesticide		CELDS 1990a
Alabama		Yes	
Hawaii		Yes	
New Mexico		Yes	
Florida	Persistant pesticides may not be applied in a broadcast manner	Yes	CELDS 1990a
Connecticut	Heptachlor used only to control subterranean termites	Yes	CELDS 1990a
Kentucky	Defined as a hazardous waste	Yes	NREPC 1988 (401 KAR 31:040)
Maine	Heptachlor is a limited use insecticide	Yes	CELDS 1990a
Michigan	Restricted use pesticide; may not be distributed without a license	Yes	CELDS 1990a
Ohio	Heptachlor banned except for use in subterranean termite control	Yes	CELDS 1990a
Wisconsin	Defined as "limited use pesticide," permit required for use	Yes	WAC 1988
Wisconsin	Designated as a toxic pollutant	Yes	CELDS 1990a

[a]Group 3: not classifiable as to human carcinogenicity
[b]Suspected human carcinogen
[c]Heptachlor has not been assigned a lifetime health advisory because of its carcinogenic potential.
[d]Because of its carcinogenic potential, the EPA-recommended concentration for heptachlor in ambient water is zero. However, because attainment of this level may not be possible, levels that correspond to upper-bound incremental lifetime cancer risks of 10^{-5}, 10^{-6}, and 10^{-7} are estimated.
[e]Group B2: possible human carcinogen
[f]A risk factor of 10^{-6} is associated with the criterion. The preferred level is zero.

ACGIH = American Conference of Governmental Industrial Hygienists; ADI = Acceptable Daily Intake; BAT = Best Available Technology; Ca = agent recommended by NIOSH to be treated as a potential occupational carcinogen; DWEL = Drinking Water Equivalent Level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health Level; MAC = Maximum Allowable Concentration; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NA = Not applicable; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; NSPS = New Source Performance Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; PSES = Pretreatment Standards for Existing Sources; PSNS = Pretreatment Standards for New Sources; RfC = Reference Concentration; RfD = Reference Dose; RMCL = Recommended Maximum Contaminant Level; TLV = Threshold Limit Value; TWA = Time-Weighted Average; WHO = World Health Organization

TABLE 7-2. Regulations and Guidelines Applicable to Heptachlor Epoxide

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC 1979
WHO	ADI in food	0.5 μg/kg/day	WHO 1984
WHO	Drinking Water Guidance Level based on a carcinogenic end point	0.1 μg/L	WHO 1984
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA (skin)	None	OSHA 1989b (29 CFR 1910.1000); OSHA 1989a
b. Water:			
EPA ODW	RMCL in drinking water (proposed)	0.2 μg/L	EPA 1989b (40 CFR 141, 142, 143); EPA 1989a
EPA OWRS	Excluded from Subcategory 1-Organic Pesticide Chemicals Manufacturing Regulations	Yes	EPA 1978c (40 CFR 455); EPA 1985d
	Pesticides regulated by NSPS, PSES, and PSNS when formulated and packaged	Yes	EPA 1978c (40 CFR 455); EPA 1985d
c. Other:			
EPA	RfD (oral)	1.30×10^{-5} mg/kg/day	IRIS 1990
EPA OERR	Reportable quantity (CERCLA Statuatory RQ)	1 pound	EPA 1985a (40 CFR 302); EPA 1985b
EPA OSW	Designated as a toxic pollutant under Section 307(a)(1) of the Federal Water Pollution Control Act	Yes	EPA 1979a (40 CFR 401.15); EPA 1979b
	Listing as a hazardous constituent	Yes	EPA 1988b (40 CFR 261, Appendix VIII); EPA 1988c
	Groundwater Monitoring Requirement	Yes	EPA 1987a (40 CFR 264, Appendix IX); EPA 1987c
Guidelines:			
a. Air:			
ACGIH	TLV TWA	None	ACGIH 1990
	Proposed	0.05 mg/m^3	
	Carcinogen category (proposed)	A2[b]	ACGIH 1990
EPA	RfC (inhalation)	None	IRIS 1990
NIOSH	IDLH	None	NIOSH 1985

TABLE 7-2 (Continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
b. Water:			
EPA ODW	MCLG	0.00	EPA 1989b (40 CFR 141, 142): EPA 1989a
EPA OWRS	Health Advisories		EPA 1990a
	1-day (recommended)(child)	0.010 mg/L	
	10-day (child)	None[c]	
	Longer-term (child)	0.00015 mg/L	IRIS 1990
	Longer-term (recommended)(adult)	0.0005 mg/L	IRIS 1990
	Lifetime	None[d]	
	DWEL	0.00044 mg/L	
	Ambient Water Quality Criteria for Protection of Human Health[d]		EPA 1980d
	Ingesting water and organisms:		
	10^{-5}	2.78 ng/L	
	10^{-6}	0.28 ng/L	
	10^{-7}	0.028 ng/L	
	Ingesting organisms only:		
	10^{-5}	2.85 ng/L	
	10^{-6}	0.29 ng/L	
	10^{-7}	0.029 ng/L	
	Water Quality Standards for Protection of Aquatic Life		EPA 1980d
	Concentration should never exceed:		
	Saltwater	0.053 µg/L	
	Freshwater	0.52 µg/L	
	24-hour average:		
	Saltwater	0.0036 g/L	
	Freshwater	0.0038 µg/L	
c. Food:			
FDA	Action level for edible fish and shellfish	0.3 ppm	FDA 1989a, 1989b
	Action level for raw food crops	0.01 ppm	FDA 1989b
	Recommended action level for fat from meat	0.2 ppm	FDA 1989b
NAS	ADI	0-0.0005 mg/kg	HSDB 1990
d. Other:			
EPA	RfD (oral)	1.30×10^{-5} mg/kg/day	IRIS 1990
	Carcinogen classification	B2[e]	IRIS 1990
	Unit risk (air)	2.6×10^{-3} $(\mu g/m^3)^{-1}$	IRIS 1990
	Unit risk (water)	2.6×10^{-4} $(\mu g/L)^{-1}$	IRIS 1990
	q_1^* (oral)	9.1 mg/kg/day	IRIS 1990
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable Ambient Air Concentrations		NATICH 1991
Maryland		0.00	

TABLE 7-2 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
b. Water:			
	Drinking water quality guidelines and standards		FSTRAC 1988
California		0.10 μg/L	
Illinois		0.1 μg/L	
Kansas		0.006 μg/L	
Minnesota		0.006 μg/L	
California	Applied Action Levels for drinking water	0.10 ppb	EPA 1987f
Illinois	MCL in drinking water	0.0001 mg/L	CELDS 1990a
Illinois	Public and food processing water supply standards	0.0001 mg/L	IEPA 1988
New York	Allowable concentration limits for Class GA waters	Not detectable	CELDS 1990a
New York	Effluent standards: MACs into saturated or unsaturated zones	Not detectable	CELDS 1989
North Carolina	Water quality standards for fresh water	0.004 mg/L	CELDS 1990b
Ohio	Permissible concentration in:		CELDS 1990a
	Public water supply	0.1 μg/L	
	Aquatic life habitats	Not available	
Virginia	Groundwater Monitoring Parameter	Yes	CELDS 1990b
Virginia	Statewide groundwater standard	0.001 μg/L	CELDS 1990a
c. Food:			
Illinois	FDA Action Levels	0.3 ppm	IEPA 1988
d. Other:			
Wisconsin	Designated as a toxic pollutant	Yes	CELDS 1990a

[a]Group 3: not classifiable as to human carcinogenicity
[b]Suspected human carcinogen
[c]No data are available from which to derive a 1- or 10-day Health Advisory for heptachlor epoxide.
[d]Heptachlor epoxide has not been assigned a lifetime health advisory because of its carcinogenic potential.
[e]Group B2: possible human Carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; ADI = Acceptable Daily Intake; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; DWEL = Drinking Water Equivalent Level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health Level; MAC = Maximum Allowable Concentration; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; NSPS = New Source Performance Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; PSES = Pretreatment Standards for Existing Sources; PSNS = Pretreatment Standards for New Sources; RfC = Reference Concentration; RfD = Reference Dose; RMCL = Recommended Maximum Contaminant Level; RQ = Reportable Quantity; TLV = Threshold Limit Value; TWA = Time-Weighted Average; WHO = World Health Organization

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coellicient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect *on* the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration($_{LO}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration($_{50}$) (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose ($_{LO}$) (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to ave caused death in humans or animals.

Lethal Dose ($_{50}$) (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.
Lethal Time ($_{50}$)(LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually @L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RtDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal S-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended *to* account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The <answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summ,arize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, 'and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l 'and Figure 2- 1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhdation, oral, and dermal (LSE Table 2-1,2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes.

2) Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days): and chronic (365 days or more) are presented within each route of exposure. In this example. an inhalation study of intermediate duration exposure is reported.

APPENDIX A

3) Health Effect The major categories of health effects included in LSE tables and figures are death. systemic, immunological, neurological, developmental, reproductive. and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but c'anccr. Systemic effects are further defined in the"System" column of the LSE table.

4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example. the study represented by key number I8 has been used to define a NOAEL 'and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

5) Species The test species, whether animal or human, are identified in this column.

6) Exposure Frequency/Duration The duration of the study and the weekly 'and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18). rats were exposed to [substance x] via inhaIation for 13 weeks, 5 days per week, for 6 hours per day.

7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other"refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive <an intermediate exposure, inhalation MRL of 0.005 ppm (see foomote "b").

9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects fast appear and the gradation of effects with increasing dose, A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

10) Reference The complete reference citation is given in Chapter 8 of the profile.

11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the foomotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

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LEGEND

See LSE Figure 2-1

LSE figures _graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

13) Exposure Duration The same exposure periods appear as in the LSE table. In this example. health effects observed within the intermediate and chronic exposure periods ‘are illustrated.

14) Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appe.ar in the LSE table.

15) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale “y” axis. Inhalation exposure is reported in mg/m’ or ppm and oral exposure is reported in mg/k&lay.

16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalationexposure MRL is based As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote “b” in the LSE table).

17) CEL Key number 38r is one of three studies for which C‘ancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA’s Human Health Assessment Group’s upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5	6	7	8	9		10
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer						11	
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

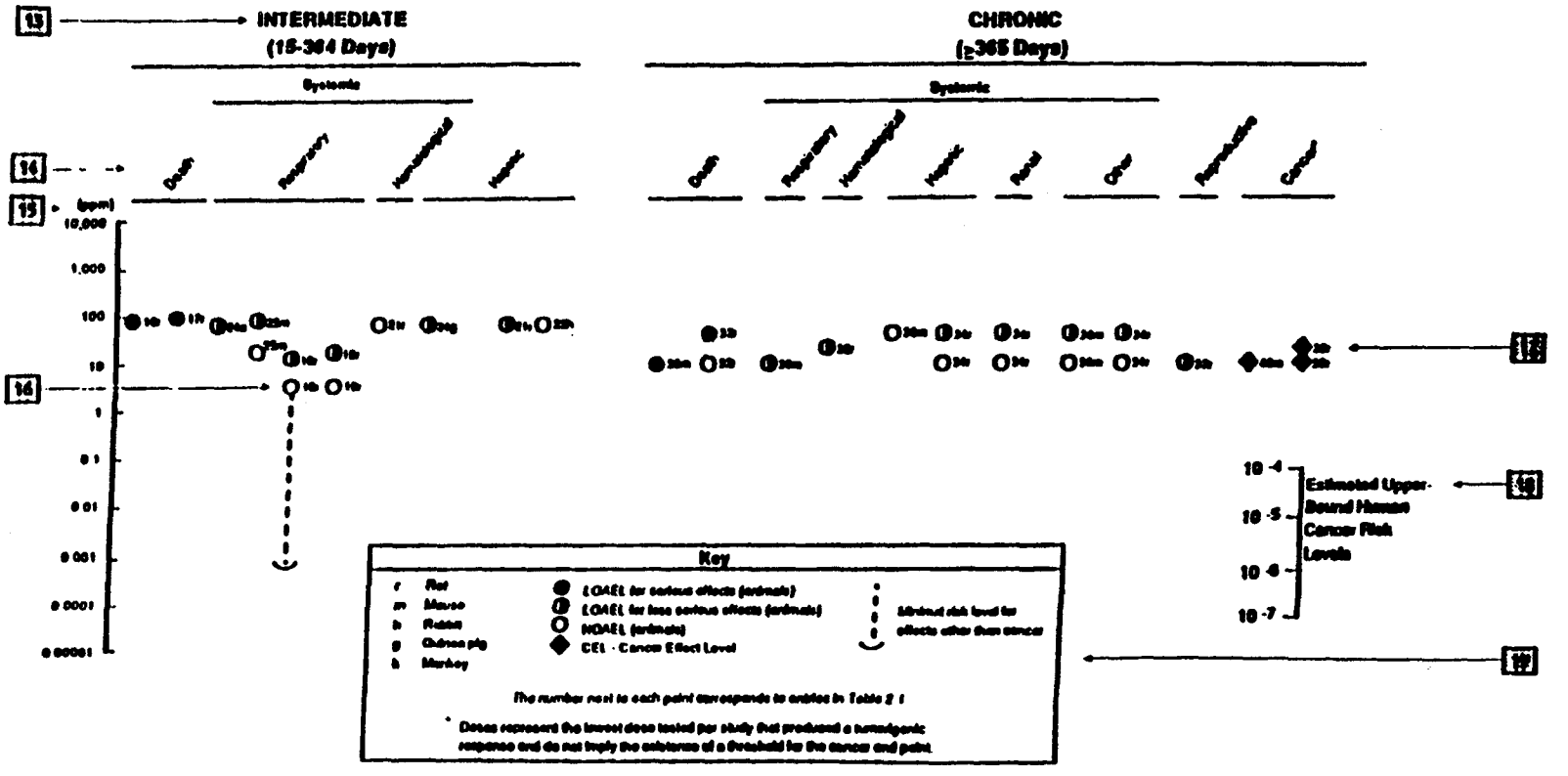

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary biased on evaluations of existing toxicological. epidemiological, ‘and toxicokinetic information. This summary is designed to present interpretive,weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans. especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inh,alation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parent&al routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated. when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, Marls were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. IdeaBy, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not me‘ant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based Section 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Chemicals” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

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To derive an MRL. ATSDR generally selects the end point which, in its best judgement. represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g.. systemic, neurological. And developmental). In order to compare NOAELs ‘and LOAELs for specific end points, all inhalation exposure levels rue adjusted for 24hr exposures and all intermittent exposures for inhalation ‘and oraJ routes of intermediate and chronic duration are adjusted for continous exposure (i.e.. 7 days/week). If the information and reliable qtuantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that dots not exceed any adverse effect levels. The NOAJZL is the most suitable end point for deriving an MRL. When a NOAEL is not available. a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for inter-species vruiability (extrapolation from animals to hum‘ans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter

LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
$>$	greater than
$\geq$	greater than or equal to
$=$	equal to
$<$	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for heptachlor and heptachlor epoxide. The panel consisted of the following members: Dr. Brent Burton, Associate Professor of Emergency Medicine, Oregon Poison Center, Oregon Health Sciences University, Portland, Oregon; Dr. Finis Cavender, Associate Professor and Academic Development Director, Abilene Christian University, Abilene, Texas; Dr. Sam Kacew, Professor of Pharmacology, University of Ottawa, Ottawa, Ontario; Dr. Peter Lacouture, Associate Director, Clinical Research, The Purdue Frederick Company, Norwalk, Connecticut; Dr. Fumio Matsumura, Associate Director, Toxic Substances Program, Institute of Toxicology and Environmental Health, University of California, Davis, California; Dr. Frederick Oehme, Director, Comparative Toxicology Laboratories, Kansas State University, Manhattan, Kansas; and Dr. Jack Radomski, Private Consultant, Jonesport, Maine. These experts collectively have knowledge of heptachlor and heptachlor epoxide's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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