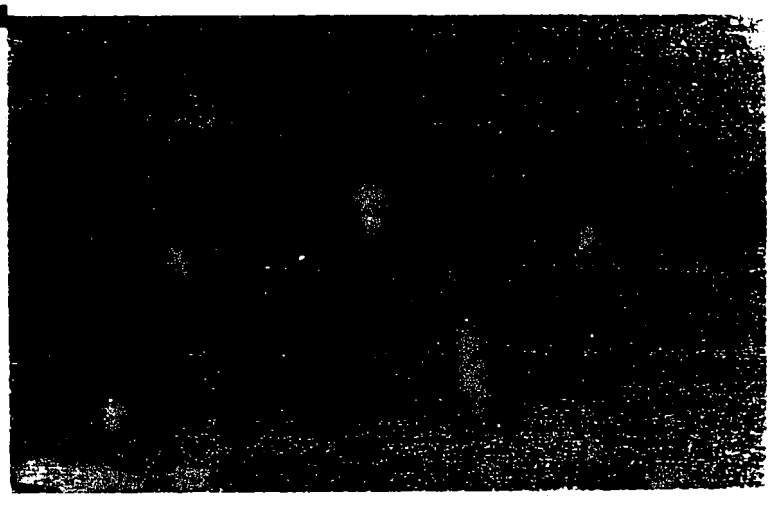
Profile for

HEPTACHLOR/HEPTACHLOR EPOXIDE

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service



ATSDR/TP-88/16

TOXICOLOGICAL PROFILE FOR HEPTACHLOR/HEPTACHLOR EPOXIDE

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Prepared by:

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Agency for Toxic Substances and Disease Registry (ATSDR)
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FOREWORD

The Superfund Amendments and Reauthorization Act 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 (also known as SARA) 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 list of the 100 most significant hazardous substances was published in the *Federal Register* on April 17, 1987.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> "(A) An examination, summary, and interpretation of available toxicological information and epidemiologic 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, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

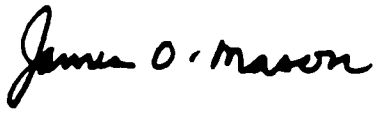
This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is 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 statement is material that presents 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. Research gaps in toxicologic and health effects information are described in the profile. Research gaps that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

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. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

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, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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1.1 WHAT ARE HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Heptachlor is a man-made compound useful for the control of termites. As a pure compound, heptachlor is a light tan solid that smells something like camphor. Heptachlor epoxide is an oxidation product of heptachlor formed by many plants and animals, including people, after exposure to heptachlor. Heptachlor is present as an impurity in the pesticide chlordane.

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

During the 1960s and 1970s, heptachlor was primarily used by farmers to kill insects in seed grains and on crops, as well as by exterminators and home owners to kill termites. During those years, people could be exposed to heptachlor, usually as its oxidation product heptachlor epoxide, through ingesting contaminated food and by the misapplication of the chemical in homes.

Since late 1978, most uses of heptachlor have been phased out so that this chemical is no longer available to the general public. In August 1987, Velsicol Chemical Company, the only U.S. producer of heptachlor, stopped selling this product. As of April 1988, heptachlor can no longer be used for the underground control of termites. People whose homes have been treated may continue to be exposed to this chemical through the air over long periods of time.

Heptachlor epoxide remains in the soil for long periods of time. One study showed that a crop grown in soil treated 15 years before with heptachlor still contained heptachlor epoxide. Exposure can, therefore, result from eating foods grown in soils treated a long time ago with heptachlor.

Heptachlor and heptachlor epoxide may also be present at numerous hazardous waste sites where workers and others on-site may be exposed. It is also possible for people off-site to be exposed from the release of heptachlor and heptachlor epoxide into the air or into neighboring bodies of water.

1.3 HOW DO HEPTACHLOR AND HEPTACHLOR EPOXIDE GET INTO MY BODY?

It is possible to breathe air containing very low levels of heptachlor over long periods of time if one's house has been treated by underground application. If the application is faulty, the level of exposure would be expected to be increased.

Another way for heptachlor and heptachlor epoxide to enter the human body is by eating foods or by drinking water or milk contaminated with the compounds. Heptachlor is converted to heptachlor epoxide in the

body. However, since heptachlor cannot be used on farm crops anymore, the risk of exposure through these routes has been considerably reduce. Residual heptachlor epoxide may still be present in soils or at hazardous waste sites from which they may be transferred to crops or food animals. If mothers have been exposed to heptachlor or heptachlor epoxide, their breast-fed babies will ingest the compound in the milk.

Heptachlor or heptachlor epoxide may enter the body by penetrating the skin. However, this route of exposure is extremely limited for the general public since heptachlor is no longer available to the consumer. Absorption through the skin is possible for those such as professional exterminators who used heptachlor to treat houses for termites, and workers at hazardous waste cleanup sites and at the manufacturing site.

1.4 HOW CAN HEPTACHLOR AND HEPTACHLOR EPOXIDE AFFECT MY HEALTH?

Heptachlor and heptachlor epoxide are clearly toxic to animals and humans. How they affect your health would depend on how much you are exposed to and for how long.

1.4.1 Brief Exposures at High Levels

Little information is available regarding human health effects from brief exposures to high levels of heptachlor. Studies with animals have shown that heptachlor and heptachlor epoxide are very toxic compounds. A level of 100 milligrams of heptachlor per cubic meter of air (mg/m^3) is considered by the National Institute for Occupational Safety and Health (NIOSH) to pose an immediate threat to life. This level of exposure could only occur in an occupational setting.

Tremors and convulsions have been reported in laboratory animals given heptachlor orally at high levels for short periods of time. Similar effects have been seen in humans exposed to some related pesticides at high levels.

1.4.2 Long-Term Exposures at Varying Levels

Little information is available with respect to health effects in humans after long-term exposure to varying levels of heptachlor. Long-term exposure to heptachlor or heptachlor epoxide may affect the liver. Studies with animals fed heptachlor or heptachlor epoxide have shown enlarged livers and damage to liver tissue, damage to kidney tissue, and increased numbers of red blood cells. Tremors and convulsions are also seen in animals in long-term exposure studies.

There is evidence that heptachlor and heptachlor epoxide are associated with infertility and improper development of offspring. Animal studies have shown that females were less likely to become pregnant when both males and females were fed heptachlor. Baby rats born to mothers fed relatively low doses of heptachlor showed a tendency to develop cataracts shortly after their eyes opened.

Heptachlor fed to animals has caused liver cancer. The U.S. Environmental Protection Agency (EPA) considers heptachlor and heptachlor epoxide to be probable human cancer-causing agents based on the results of studies with laboratory animals. The International Agency for Research on Cancer (IARC) states that there is inadequate evidence

that heptachlor causes cancer in humans, and only limited evidence that it causes cancer in animals.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO HEPTACHLOR AND HEPTACHLOR EPOXIDE?

Heptachlor epoxide, the oxidation product of heptachlor, can be measured in breast milk, body fat, or blood; however, there are insufficient data to enable correlation of concentration levels in these tissues with possible health effects.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Human data enabling correlation of levels of exposure to heptachlor or heptachlor epoxide by any route with harmful health effects were not found. Also, no information was found concerning harmful effects to laboratory animals by breathing air contaminated with heptachlor or heptachlor epoxide. The only information found, concerning harmful effects of skin contact with the compounds for animals, was that application of a solution of 195 to 250 milligrams per kilogram of body weight (mg/kg) of heptachlor to the skin of rats caused death.

Figure 1.1 shows the relationship between exposure to heptachlor or heptachlor epoxide and known health effects from eating foods or drinking liquids containing heptachlor or heptachlor epoxide. The scale on the graph represents exposure measured in milligrams of heptachlor or heptachlor epoxide per kilogram of body weight per day (mg/kg/day).

The first column, called short-term exposure, shows the known health effects from exposure to heptachlor or heptachlor epoxide for two weeks or less. The second column, long-term exposure, shows known health effects for exposures lasting over two weeks.

Levels of exposure may be calculated from cancer potency estimates from the Carcinogen Assessment Group (CAG) of the EPA that may be expected to cause a rate of 1 in 10,000 and of 1 in 10,000,000 following ingestion. It must be emphasized, however, that these calculations based on testing in animals represent the upper limit of the probable risk to man; actual risks are likely to be much lower.

	Risk	Dose
Heptachlor	1 in 10,000	0.000022 mg/kg/day
	1 in 10,000,000	0.000000022 mg/kg/day
Heptachlor epoxide	1 in 10,000	0.000011 mg/kg/day
	1 in 10,000,000	0.000000011 mg/kg/day

Since these numbers are extremely small, they have not been plotted in Fig. 1.1.

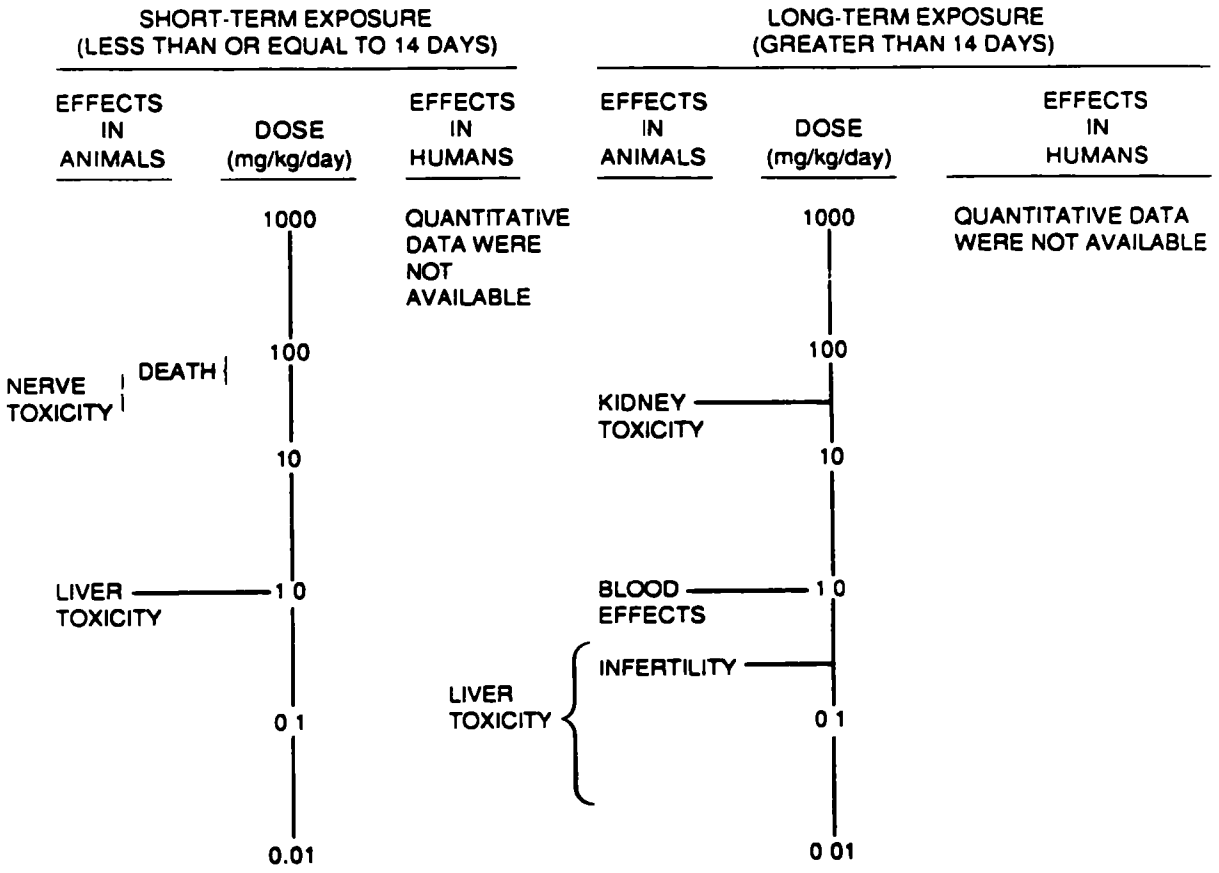


Fig. 1.1. Health effects from ingesting heptachlor / heptachlor epoxide.

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

The government has set limits on exposure of individuals to heptachlor and heptachlor epoxide from air in the workplace and from contamination of food and water.

The EPA has cancelled the registration permitting the application of heptachlor to crops or for seed treatment. The EPA has also set very low levels of less than 0.1 part of heptachlor or heptachlor epoxide per one million parts of grain or vegetable (0.1 ppm) in or on farm products.

Most heptachlor exposures now involve workers who manufacture the compound or workers at hazardous waste sites. The government has established very strict limits for exposure in the workplace. The Occupational Safety and Health Administration (OSHA) has established an occupational exposure limit for heptachlor in air of 0.5 mg/m^3. NIOSH has recommended the same exposure limit. In addition, NIOSH has recommended that workers who potentially may be exposed to heptachlor be given a preemployment physical examination as well as periodic reexaminations. These examinations should stress evaluations of the eyes, nervous system, liver, and kidneys. Since heptachlor and heptachlor epoxide have been shown to cause liver cancer in laboratory animals, any exposure to them involves some potential risk.

The EPA in 1987 published health advisories for heptachlor and heptachlor epoxide in drinking water; these advisories represent levels of protection only for noncancer toxicity.

- 10-day health advisory--10 parts heptachlor per billion parts water (ppb) based on heptachlor's ability to produce liver injury in a 10-kg child.

- Lifetime health advisory--17.5 ppb for heptachlor; 0.4 ppb for heptachlor epoxide.

The National Academy of Sciences (NAS) published a health advisory in 1977 (based on cancer risk) recommending the following limits for long-term exposure in drinking water: heptachlor, 0.0104 ppb; and heptachlor epoxide, 0.0006 ppb.

2. HEALTH EFFECTS SUMMARY

2.1 INTRODUCTION

This section summarizes and graphs data on the health effects concerning exposure to heptachlor and heptachlor epoxide. The purpose of this section is to present levels of significant exposure for heptachlor and heptachlor epoxide based on key toxicological studies, epidemiological investigations, and environmental exposure data. The information presented in this section is critically evaluated and discussed in Sect. 4, Toxicological Data, and Sect. 7, Potential for Human Exposure.

This Health Effects Summary section comprises two major parts. Levels of Significant Exposure (Sect. 2.2) presents brief narratives and graphics for key studies in a manner that provides public health officials, physicians, and other interested individuals and groups with (1) an overall perspective of the toxicology of heptachlor and heptachlor epoxide and (2) a summarized depiction of significant exposure levels associated with various adverse health effects. This section also includes information on the levels of heptachlor and heptachlor epoxide that have been monitored in human fluids and tissues and information about levels of heptachlor and heptachlor epoxide found in environmental media and their association with human exposures.

The significance of the exposure levels shown on the graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of overt clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with frank effects (Frank Effect Level, FEL). Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (Lowest-Observed-Adverse-Effect Level, LOAEL) or exposure levels below which no adverse effects (No-Observed-Adverse-Effect Level, NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels) are of interest to health professionals and citizens alike.

Adequacy of Database (Sect. 2.3) highlights the availability of key studies in the scientific literature on exposure to heptachlor and heptachlor epoxide and displays these data in three-dimensional graphs consistent with the format in Sect. 2.2. The purpose of this section is to suggest where there might be insufficient information to establish levels of significant human exposure. These areas will be considered by the Agency for Toxic Substances and Disease Registry (ATSDR), EPA, and the National Toxicology Program (NTP) of the U.S. Public Health Service in order to develop a research agenda for heptachlor and heptachlor epoxide.

2.2 LEVELS OF SIGNIFICANT EXPOSURE

2.2.1 Key Studies and Graphical Presentations

To help public health professionals address the needs of persons living or working near hazardous waste sites, the toxicology data summarized in this section are organized first by route of exposure--inhalation, ingestion, and dermal--and then by toxicological end points that are categorized into six general areas--lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, genetic toxicity, and carcinogenicity. The data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Two kinds of graphs are used to depict the data. The first type is a "thermometer" graph. It provides a graphical summary of the human and animal toxicological end points (and levels of exposure) for each exposure route for which data are available. The ordering of effects does not reflect the exposure duration or species of animal tested. The second kind of graph shows Levels of Significant Exposure (LSE) for each route and exposure duration. The points on the graph showing No-Observed-Adverse-Effect Levels (NOAELs) and Lowest-Observed-Adverse-Effect Levels (LOAELs) reflect the actual doses (levels of exposure) used in the key studies. No adjustments for exposure duration or intermittent exposure protocol were made.

Adjustments reflecting the uncertainty of extrapolating animal data to man, intraspecies variations, and differences between experimental versus actual human exposure conditions were considered when estimates of levels posing minimal risk to human health were made for noncancer end points. These minimal risk levels were derived for the most sensitive noncancer end point for each exposure duration by applying uncertainty factors. These levels are shown on the graphs as a broken line starting from the actual dose (level of exposure) and ending with a concave-curved line at its terminus. Although methods have been established to derive these minimal risk levels (Barnes et al. 1987), shortcomings exist in the techniques that reduce the confidence in the projected estimates. Also shown on the graphs under the cancer end point are low-level risks (10^{-4} to 10^{-7}) reported by EPA. In addition, the actual dose (level of exposure) associated with tumor incidence is plotted.

2.2.1.1 Inhalation

A plot of key data available for animals vs humans is not shown for the inhalation route since the only point would be the odor threshold of 0.02 ppm in humans.

Lethality. No key studies were found in the available literature. In human case reports, convulsions and death were reported following inhalation of technical-grade chlordane, a compound that is structurally similar to heptachlor and typically contains 10% of that chemical (CAG 1986).

Systemic/target organ toxicity. No key animal studies were found in the available literature. Human case reports described neurotoxic and hematologic effects following acute, intermediate, or chronic exposure to technical-grade chlordane.

Developmental toxicity. No key studies were found in the available literature. Available information on possible human developmental toxicity from exposure to heptachlor is summarized in Sect. 2.2.1.2.

Reproductive toxicity. No key studies were found in the available literature. Available information on possible human reproductive toxicity from mixed pesticide or heptachlor exposure is summarized in Sect. 2.2.1.2.

Genotoxicity. No information was found in the available literature concerning genotoxic effects in humans or animals following inhalation of heptachlor or heptachlor epoxide.

Carcinogenicity. No key animal studies were found in the available literature. Information on oncogenic effects in humans following exposures to mixtures of chemicals, including heptachlor, via unspecified routes is summarized in Sect. 2.2.1.2.

Levels of exposure can be calculated from cancer potency estimates generated by the EPA (CAG 1986) for lifetime risks of 10^{-4} to 10^{-7} for cancer from exposure by the inhalation route (plotted on Fig. 2.1). The calculations, based on testing in animals, represent the upper limit of the probable risk to man; actual risks are likely to be much lower.

	Concentration (mg/m^3)	
Risk	Heptachlor	Heptachlor epoxide
10^{-4}	7.7×10^{-5}	3.8×10^{-5}
10^{-5}	7.7×10^{-6}	3.8×10^{-6}
10^{-6}	7.7×10^{-7}	3.8×10^{-7}
10^{-7}	7.7×10^{-8}	3.8×10^{-8}

It should be noted that the EPA CAG assessment of heptachlor and heptachlor epoxide had not undergone peer review at the time this profile was prepared.

2.2.1.2 Oral

Graphical representations of key data for the oral route of exposure are shown at the end of this section for animals vs humans (Fig. 2.2) and for different durations of exposure (Fig. 2.3).

Lethality, acute. No key studies were found for humans. Key oral single-dose lethal doses in animals were as follows:

Rats--71 mg/kg, heptachlor (Podowski et al. 1979)
60 mg/kg, heptachlor epoxide (Podowski et al. 1979)

Mice--70 mg/kg, heptachlor (Gak et al. 1976)
30 mg/kg, heptachlor/heptachlor epoxide (25%:75%) (Arnold et al. 1977)

Hamsters--100 mg/kg, heptachlor (Gak et al. 1976)

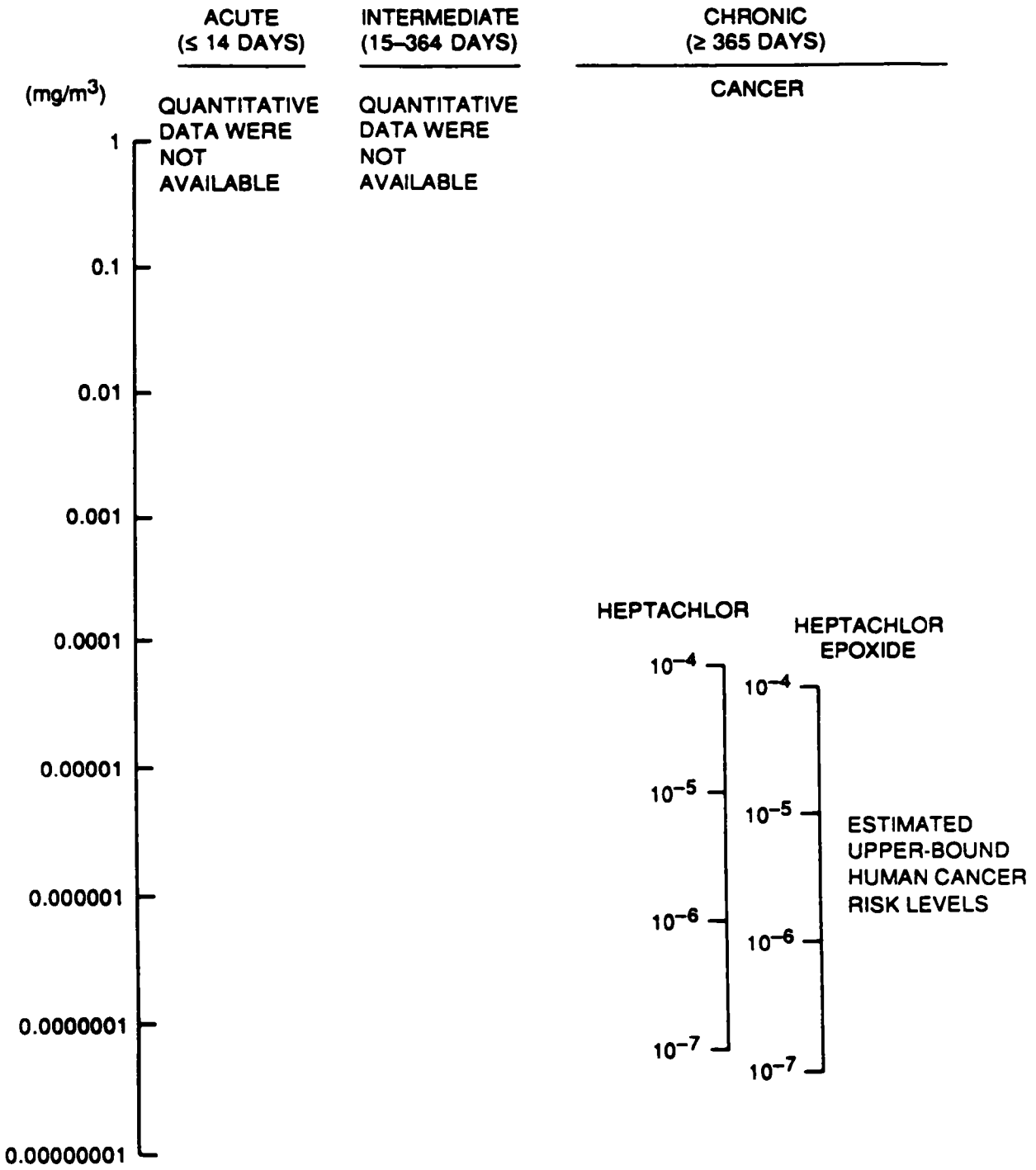


Fig. 2.1. Levels of significant exposure for heptachlor/heptachlor epoxide—inhalation.

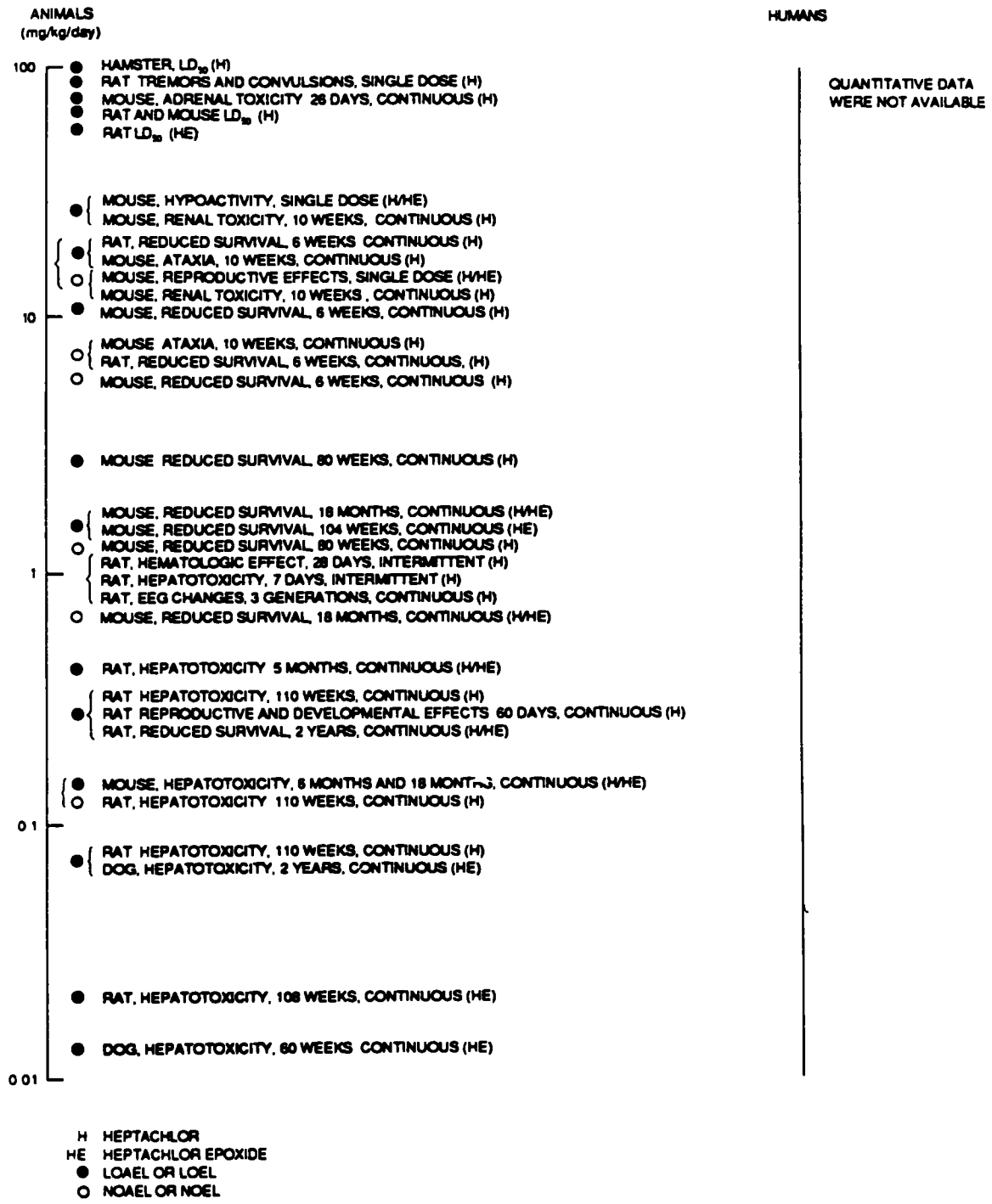


Fig. 2.2. Effects of heptachlor/heptachlor epoxide—oral exposure.

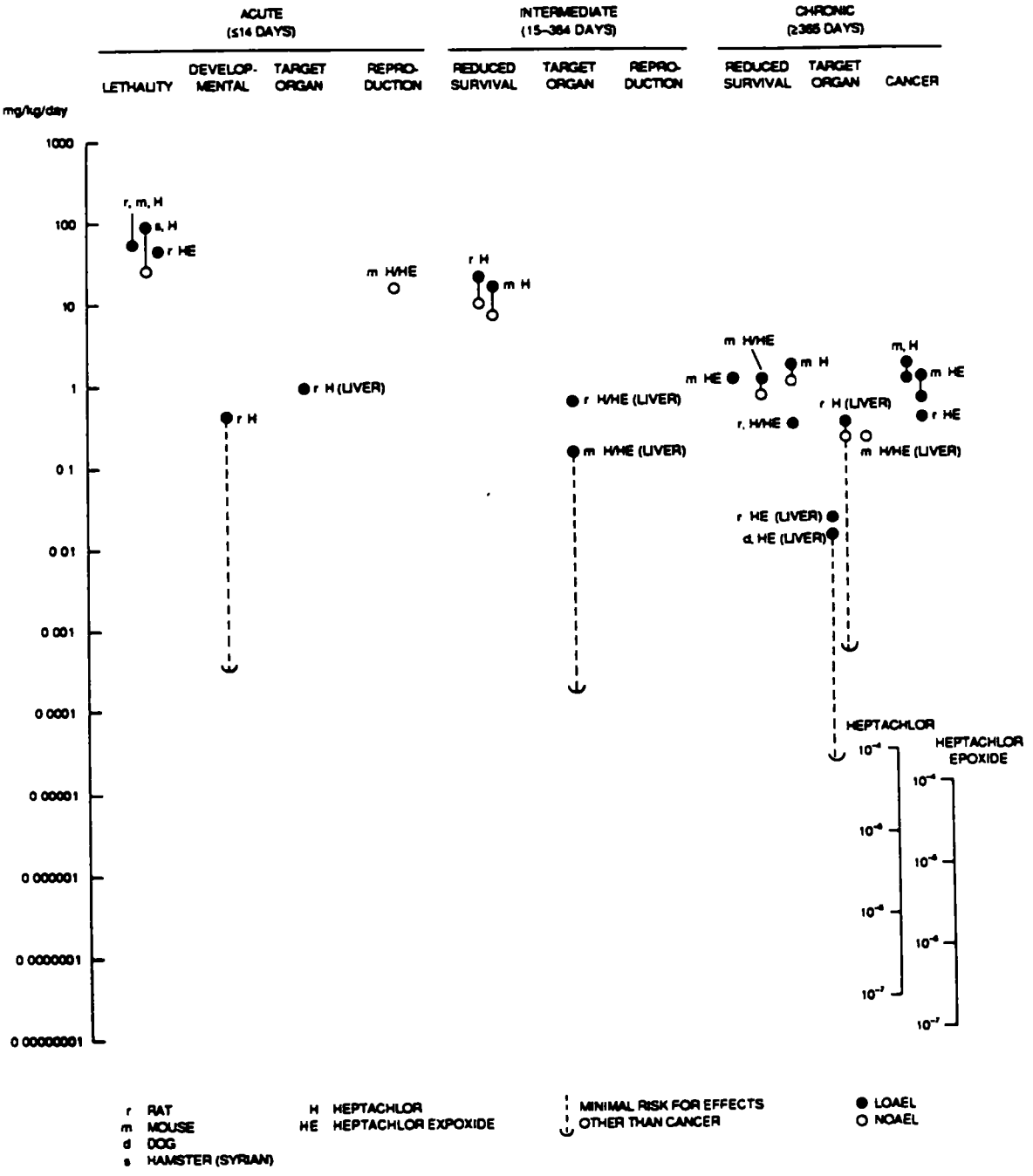


Fig. 2.3. Levels of significant exposure for heptachlor/heptachlor epoxide—oral.

Lethality, intermediate. No information was found for humans.

Increased mortality was reported in both sexes of Osborne-Mendel rats and B6C3F1 mice fed technical-grade heptachlor in the diet for 6 weeks, followed by a 2-week period of observation. The LOAEL for rats (based on data for females) was 16 mg/kg/day; the NOAEL was 8 mg/kg/day. The LOAEL for mice (based on data for males or females) was 12 mg/kg/day; the NOAEL was 6 mg/kg/day (NCI 1977).

Lethality, chronic. No information was found for humans.

Increased mortality was reported in female CD rats fed heptachlor/heptachlor epoxide (75%:25%) in the diet for up to 2 years. The LOAEL was 0.25 mg/kg/day; a NOAEL was not established (Jolley et al. 1966, as cited in Epstein 1976).

Increased mortality was reported in male and female C3H mice (combined) fed heptachlor epoxide in the diet for up to 104 weeks. The LOAEL was 1.5 mg/kg/day; a NOAEL was not established (Davis 1965, as cited in Epstein 1976).

Increased mortality was reported in both male and female Charles River CD-1 mice fed diets containing heptachlor/heptachlor epoxide (25%:75%) for up to 18 months. The LOAEL was 1.5 mg/kg/day, and the NOAEL was 0.75 mg/kg/day (IRDC 1973, as cited in Epstein 1976).

Increased mortality was reported in female, but not male, B6C3F1 mice fed diets containing technical-grade heptachlor for 80 weeks, followed by observation for 10 weeks. The LOAEL was 2.7 mg/kg/day, and the NOAEL was 1.35 mg/kg/day (NCI 1977).

Systemic/target organ toxicity, acute. No key studies for humans were found in the available literature. Case reports described neurotoxic effects in humans following their exposure (route not specified) to technical-grade chlordane, a compound structurally related to heptachlor and typically containing heptachlor at concentrations up to 10% (CAG 1986).

The liver appears to be the most sensitive target organ for the acute oral toxic effects of heptachlor/heptachlor epoxide in animals. Enan et al. (1982) reported that acute administration of heptachlor to rats in the diet induced several effects compatible with hepatic damage including increased liver weight and increased serum levels of bilirubin, alkaline phosphatase, and urea. The LOAEL was 1 mg/kg/day; a NOAEL was not established. Frank microscopic damage to the liver, including steatosis and necrosis, was reported to occur in rats at acute oral heptachlor doses of 5 to 7 mg/kg/day (Krampl 1971, Pelikan 1971).

Hypoactivity and some deaths were reported in mice given a single gavage dose of heptachlor/heptachlor epoxide (25%:75%) at levels near the LD_{50}. The LOAEL was 30 mg/kg; a NOAEL was not established (Arnold et al. 1977). Tremors and convulsions were reported in rats given the acute oral LD_{50} dose of heptachlor of 90 mg/kg (Lehman 1951).

Systemic/target organ toxicity, intermediate. No key studies for humans were found in the available literature.

The liver appears to be the most sensitive target organ for the intermediate oral toxic effects of heptachlor/heptachlor epoxide in animals. Jolley et al. (1966, as cited in Epstein 1976) reported hepatocytomegaly in rats that had been fed heptachlor/heptachlor epoxide (75%:25%) for 5 months. The LOAEL was 0.38 mg/kg/day; a NOAEL was not established. IRDC (1973, as cited in Epstein 1976) reported dose-related incidences of hepatocytomegaly and increased mean liver weights in mice that had been fed heptachlor/heptachlor epoxide (25%:75%) for 6 months. The LOAEL was 0.15 mg/kg/day; a NOAEL was not established. Frank microscopic damage to the liver, including steatosis, fibrosis, or necrosis, was reported to occur following intermediate oral exposure of rats, pigs, and sheep to heptachlor at a level of 2 or 5 mg/kg/day (Halacka et al. 1975, Pelikan 1971) and mice to heptachlor at a level of 7.5 mg/kg/day (Akay and Alp 1981).

Ataxia and whole-body tremors were reported during intermediate oral exposure of mice to heptachlor. The LOAEL was 15 mg/kg/day, and the NOAEL was 7.5 mg/kg/day (Akay and Alp 1981).

Atrophy of the adrenal cortex, including hypertrophy, heavy lipid accumulation, granulation, and cell degeneration with extensive destruction and fibrosis, was reported following administration to mice of heptachlor in the drinking water at a reported concentration of 100 ppm (80 mg/kg/day) for up to 26 days (Akay et al. 1982). The validity of the 100-ppm dose level can be questioned since the solubility of heptachlor in water is 56 mg/L or 0.056 ppm (Worthing and Walker 1983), implying either that the dose level was incorrectly reported or that heptachlor was present in suspension, thus bringing into question the uniformity of dosing. In addition, the 80-mg/kg/day dose level was calculated using the authors' stated water consumption rate of 20 cc/day/mouse Akay et al. (1982); this is in excess of the usual 4 to 7 mL/day/mouse water intake reported by Arrington (1972).

Kidney granulomas were reported following administration of heptachlor in the diet of mice for 10 weeks. The LOAEL was 30 mg/kg/day, and the NOAEL was 15 mg/kg/day (Akay and Alp 1981).

Elevated white blood cell counts were reported in rats that had been fed heptachlor at a concentration of 1 mg/kg/day, 5 days/week, for a total of 28 days (Enan et al. 1982). Spleen fibrosis and increased numbers of red and white blood cells in the spleen were reported in mice that had been fed heptachlor at a concentration of 30 mg/kg/day for 10 weeks; it was not clear whether these changes were induced by doses of 15 or 7.5 mg/kg/day (Akay and Alp 1981).

Systemic/target organ toxicity, chronic. No key studies for humans were found in the available literature. Case reports described hematologic effects in humans following exposure (route not specified) to technical-grade chlordane, which typically contains 10% heptachlor (CAG 1986). The incidence of cerebrovascular disease was significantly increased in workers engaged in the manufacture of chlordane, heptachlor, and endrin (Wang and McMahon 1979b), but was not increased in pesticide applicators and termite control operators principally exposed to chlordane and heptachlor by the inhalation, oral, and/or dermal routes (Wang and MacMahon 1979a). The observation of

cerebrovascular disease reported by Wang and MacMahon (1979b) has not been confirmed in other studies.

The liver appears to be the most sensitive target organ for the chronic oral toxic effects of heptachlor/heptachlor epoxide in animals. Increased mean liver weights and liver lesions of the "chlorinated hydrocarbon" type were reported in rats that had been fed heptachlor alone for up to 110 weeks. The LOAEL was 0.25 mg/kg/day, and the NOAEL was 0.15 mg/kg/day (Witherup 1955, as cited in Epstein 1976). Significant, dose-related increases in liver-to-body-weight ratios were reported in beagle dogs that had been administered heptachlor epoxide in the diet for 60 weeks. The LOAEL was 0.0125 mg/kg/day; a NOAEL was not established (Kettering 1958, as cited in EPA 1987c). Hepatic cell vacuolization and degeneration, hepatocytomegaly, and liver regeneration were reported in rats fed heptachlor epoxide for up to 108 weeks. The LOAEL was 0.025 mg/kg/day; a NOAEL was not established (Witherup 1959, as cited in Epstein 1976). Dose-related incidences of hepatocytomegaly and increases in mean liver weight were reported in mice that had been fed heptachlor/heptachlor epoxide (25%:75%) for up to 18 months. The LOAEL was 0.15 mg/kg/day; a NOAEL was not established (IRDC 1973, as cited in Epstein 1976).

Decreases in body-weight gain were induced by chronic oral exposure to heptachlor (rats, Witherup et al. 1955, as cited in Epstein 1976; mice, NCI 1977) and heptachlor/heptachlor epoxide (25%:75%) (mice, IRDC 1973, as cited in Epstein 1976).

Developmental toxicity. No key studies for humans were found in the available literature. However, heptachlor epoxide was found in the blood and several tissues of human stillborn infants (Curley et al. 1969). No adverse effects on human fetal development were reported following ingestion of heptachlor-contaminated cow's milk for 27 to 29 months by women of child-bearing age in Oahu, Hawaii (Le Marchand et al. 1986). Data from both studies are inadequate to determine whether reported levels of heptachlor and heptachlor epoxide are associated with any developmental effects in humans.

Green (1970) reported decreased postnatal survival in the progeny of rats that were fed heptachlor at a level of 0.25 mg/kg/day for 60 days and during gestation; no teratogenic effects were noted. The LOAEL was 0.25 mg/kg/day; a NOAEL was not established.

Reproductive toxicity. No key studies for humans were found in the available literature. Elevated levels of heptachlor epoxide, as well as elevated levels of eight of ten other organochlorine pesticides for which analytical data were available, were reported in the serum of women with premature delivery (Wassermann et al. 1982), and heptachlor epoxide has been reported in the blood and tissues of stillborn infants (Curley et al. 1969). No adverse effects on human reproduction were reported following ingestion of heptachlor-contaminated cow's milk for 27 to 29 months by women of child-bearing age in Oahu, Hawaii (Burch 1983, as cited in Le Marchand et al. 1986). These data are inadequate to provide a clear assessment of the relationship between heptachlor/heptachlor epoxide exposure and human reproductive toxicity.

In a mouse dominant lethal assay, no adverse effects on reproductive capacity were reported for male mice that had been given single oral doses of heptachlor at levels of 7.5 or 15 mg/kg. The NOAEL was 15 mg/kg; a LOAEL was not established (Arnold et al. 1977). In male and female rats fed heptachlor at a level of 0.25 mg/kg/day for 60 days prior to and during gestation, reproductive performance was unaffected in the first generation; in the second generation, however, all females receiving heptachlor at this dose failed to become pregnant. The LOAEL was 0.25 mg/kg/day; a NOAEL was not established (Green 1970).

Genotoxicity. No key studies for humans or animals were found in the available literature. The weight of evidence does not support the genotoxicity of heptachlor (Marshall et al. 1976, NTP 1987, Gentile et al. 1982, Glatt et al. 1983, Telang et al. 1982). Although there are some studies that suggest an in vitro somatic cell clastogenic effect, these findings need confirmation (NTP 1987). Evidence that heptachlor interferes with metabolic cooperation was demonstrated by independent investigators in phylogenetically different cell systems (Kurata et al. 1982, Telang et al. 1982).

Carcinogenicity. Heptachlor/heptachlor epoxide is a probable human carcinogen based on animal data, classified in Group B2 under EPA's guidelines for carcinogen risk assessment (EPA 1986g).

No key studies for humans were found in the available literature. Inconsistent oncogenic effects from human occupational or incidental exposures to heptachlor in combination with other chemicals have been reported (Infante et al. 1978, Wang and MacMahon 1979a and 1979b, Ditraglia et al. 1981, Velsicol 1981, Environmental Health Associates 1983a and 1983b, WHO 1984). These data are inadequate to establish a clear qualitative or quantitative assessment of the relationship between heptachlor exposure and human cancer risk.

Oral exposure to heptachlor/heptachlor epoxide increased the incidence of liver carcinomas in one strain of rats and three strains of mice. From geometric means for the most sensitive species tested (mice), the carcinogenic potencies are 4.5 per mg/kg/day for heptachlor and 9.1 per mg/kg/day for heptachlor epoxide. From data for the most sensitive sex and strain (female C3H mice), the carcinogenic potencies are 14.9 per mg/kg/day for heptachlor and 36.2 per mg/kg/day for heptachlor epoxide (CAG 1986).

Levels of exposure can be calculated from cancer potency estimates generated by the EPA (CAG 1986), on the basis of oral carcinogenicity data for rats and mice for lifetime upper-bound risks of 10^{-4} to 10^{-7} for cancer from exposure by the oral route (plotted on Fig. 2.3). These calculations, based on testing in animals, represent the upper limit of the probable risk to man; actual risks are likely to be much lower.

	Dose (mg/kg/day)	
Risk	Heptachlor	Heptachlor epoxide
10^{-4}	2.2×10^{-5}	1.1×10^{-5}
10^{-5}	2.2×10^{-6}	1.1×10^{-6}
10^{-6}	2.2×10^{-7}	1.1×10^{-7}
10^{-7}	2.2×10^{-8}	1.1×10^{-8}

It should be noted that the EPA CAG assessment of heptachlor and heptachlor epoxide had not undergone peer review at the time this profile was prepared.

2.2.1.3 Dermal

Plots of key data available for animals vs humans and for different durations of exposure are not shown since the only points would be the LD_{50}s of 195 mg/kg in male rats and 250 mg/kg in female rats.

Lethality. No key studies were found for humans. Key dermal LD_{50}s in animals were 195 mg/kg in male rats and 250 mg/kg in female rats (Gaines 1969).

Systemic/target organ toxicity. No key studies for humans or animals exposed to heptachlor or heptachlor epoxide via the dermal route were found in the available literature.

Developmental toxicity. No key studies for humans or animals exposed to heptachlor or heptachlor epoxide via the dermal route were found in the available literature. Available information on possible human developmental toxicity from exposure to heptachlor is summarized in Sect. 2.2.1.2.

Reproductive toxicity. No key studies for humans or animals exposed to heptachlor or heptachlor epoxide via the dermal route were found in the available literature. Available information on possible human reproductive toxicity from mixed-pesticide or heptachlor exposure is summarized in Sect. 2.2.1.2.

Genotoxicity. No information was found in the available literature concerning genotoxic effects in humans or animals following dermal exposure to heptachlor or heptachlor epoxide.

Carcinogenicity. No key studies were found in the available literature on the oncogenicity of heptachlor or heptachlor epoxide in humans or animals via the dermal route. Information on oncogenic effects in humans following exposures to mixtures of chemicals, including heptachlor, via unspecified routes is summarized in Sect. 2.2.1.2.

2.2.2 Biological Monitoring as a Measure of Exposure and Effects

Extremely sensitive analytical methods have been developed for the detection of heptachlor and heptachlor epoxide in various media (detection limits as low as 10 ng/L); these methods are summarized in Sect. 8 (Tables 8.1 and 8.2). Although most methods were developed for detecting heptachlor and heptachlor epoxide in environmental samples, the technology is readily adaptable to biological samples including breast milk, adipose tissue, and serum. These methods can be used to determine whether exposure has occurred. However, no studies were found correlating levels to which humans were exposed with actual body burdens. No specific tests for the effects of heptachlor or heptachlor epoxide were found.

2.2.3 Environmental Levels as Indicators of Exposure and Effects

2.2.3.1 Levels found in the environment

Data found concerning levels of heptachlor and heptachlor epoxide were from the 1960s and 1970s when heptachlor was actively used in agriculture. It has been shown that heptachlor epoxide can be translocated from soil to a crop 15 years after the last known application of heptachlor at a rate of 224 kg/ha (Nash and Harris 1973, as cited in WHO 1984). Talekar et al. (1983) reported the persistence of heptachlor epoxide (at a level of 0.06 ppm) in the soil throughout a 1-year observation period following application of a total of 48 kg/ha of heptachlor over a 2-year period. No data were found to indicate that heptachlor epoxide is present in present-day crops. Heptachlor has been identified at hazardous waste sites at concentrations ranging from not detected (ND) in migrating groundwater to 4,800 µg/L in sediments (EPA 1985b).

2.2.3.2 Human exposure potential

Since the cancellation of most uses of heptachlor, the potential for exposure via inhalation for farm workers has greatly diminished. In one study of houses treated for termites, the heptachlor level in the air was 1.00 ± 0.70 $\mu g/m^3$ one year after treatment (Wright and Leidy 1982), indicating that exposure to heptachlor via inhalation is possible for people whose houses have been treated with the compound for termite control.

Levels of up to 0.6 µg/L of heptachlor in drinking water have bee reported (EPA 1985a). These water data are from the period when heptachlor was used for agricultural insect control.

Heptachlor epoxide has been reported in soils, especially cropland soils, at levels up to 1.08 mg/kg (Weirsma et al. 1972a, as cited in IARC 1979). Studies have shown that heptachlor epoxide can translocate into crops 5 to 15 years after the last known application of heptachlor (Lichtenstein et al. 1970, Nash and Harris 1973, as cited in WHO 1984). Levels in foodstuff were reported for the 1970s and have been reviewed by IARC (1979), WHO (1984), and EPA (1985a). The relevance of these data to present-day residue levels of heptachlor and heptachlor epoxide in food is not clear.

No reports of human health effects as a direct consequence of exposure to heptachlor or heptachlor epoxide were found. Section 4 discusses health effects from exposure to technical-grade chlordane containing up to 10% heptachlor.

2.3 ADEQUACY OF DATABASE

2.3.1 Introduction

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each of the 100 most significant hazardous substances found at facilities on the CERCLA National Priorities List. Each profile must include the following content:

"(A) An examination, summary, and interpretation of available toxicological information and epidemiologic 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, an 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 section identifies gaps in current knowledge relevant to developing levels of significant exposure for heptachlor and heptachlor epoxide. Such gaps are identified for certain health effect end points (lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and carcinogenicity) reviewed in Sect. 2.2 of this profile in developing levels of significant exposure for heptachlor and heptachlor epoxide, and for other areas such as human biological monitoring and mechanisms of toxicity. The present section briefly summarizes the availability of existing human and animal data, identifies data gaps, and summarizes research in progress that may fill such gaps.

Specific research programs for obtaining data needed to develop levels of significant exposure for heptachlor and heptachlor epoxide will be developed by the ATSDR, NTP, and EPA in the future.

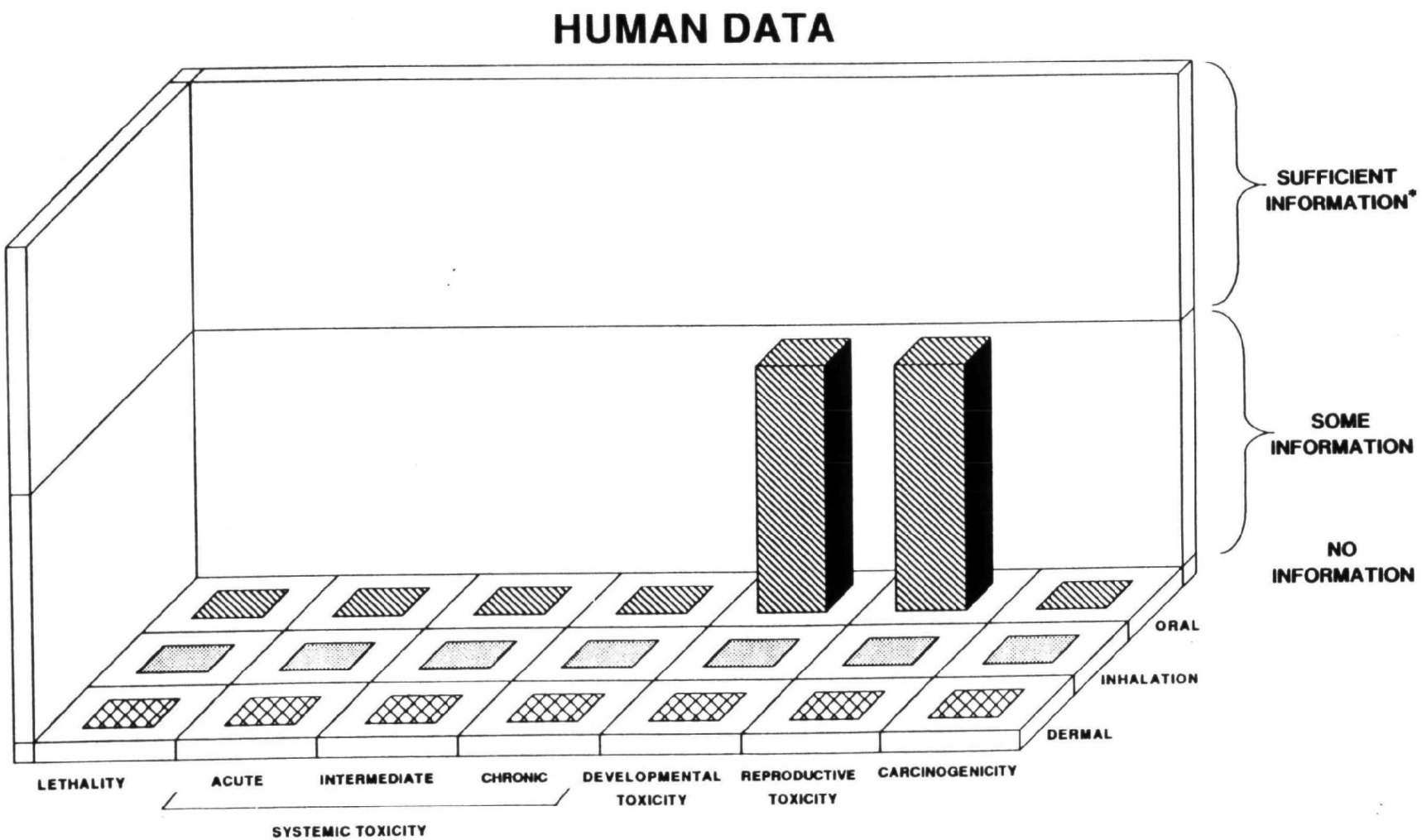
2.3.2 Health Effect End Points

2.3.2.1 Introduction and graphic summary

The following graphs summarize the availability of data for lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and carcinogenicity. The first graph (Fig. 2.4) is for human data and the second (Fig. 2.5) is for animal data.

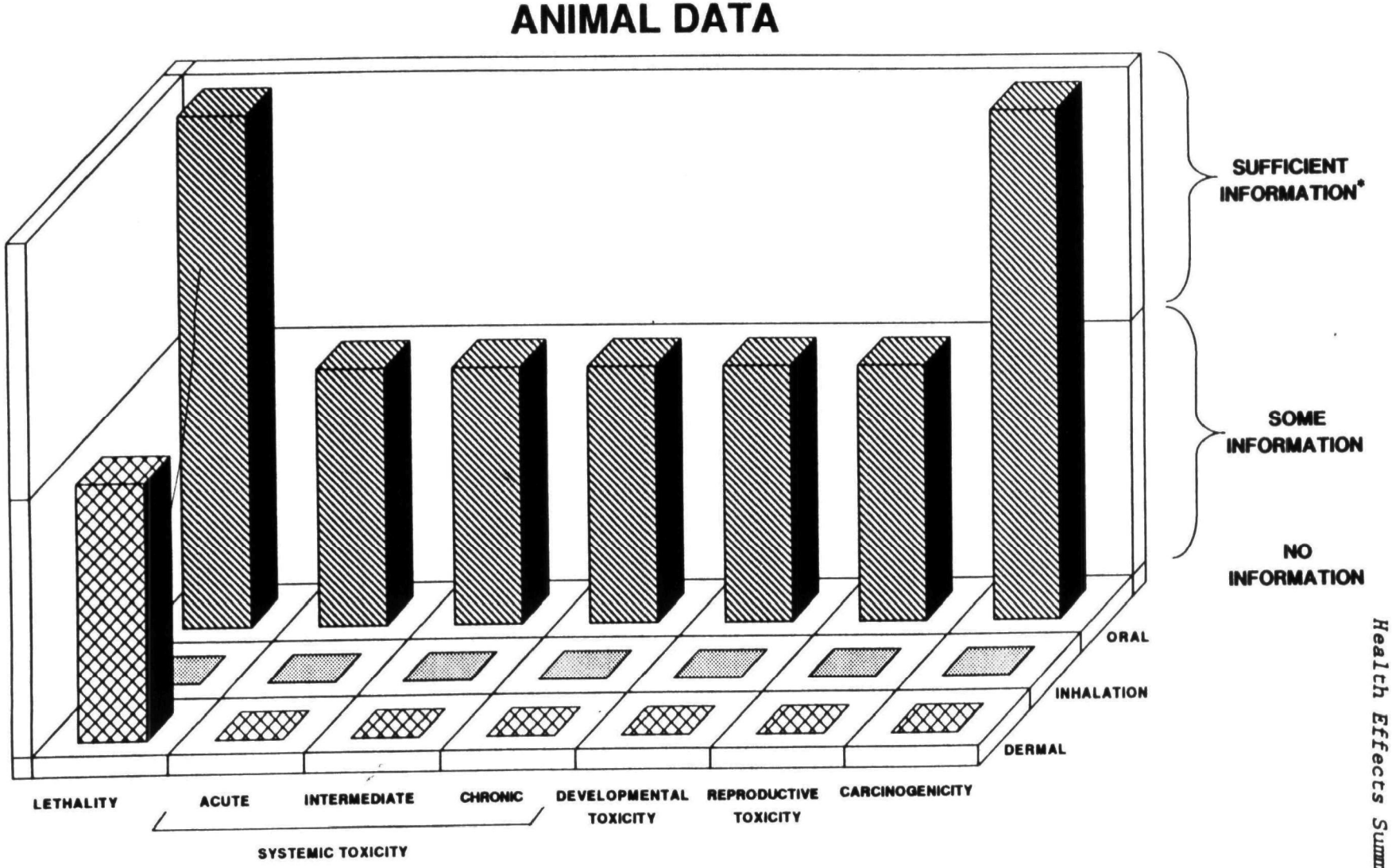
The bars of full height indicate that there are data to meet at least one of the following criteria:

1. For noncancer health end points, one or more studies are available that meet current scientific standards and are sufficient to define a range of toxicity from no-effect levels (NOAELs) to levels that cause effects (LOAELs or FELs).
2. For human carcinogenicity, a substance is classified as either a "known human carcinogen" or "probable human carcinogen" by both EPA and the International Agency for Research on Cancer (IARC) (qualitative), and the data are sufficient to derive a cancer potency factor (quantitative).



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

Fig. 2.4. Availability of information on health e[illegible]s of heptachlor/heptachlor epoxide (human data).



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

Fig. 2.5. Availability of information on health effects of heptachlor/heptachlor epoxide (animal data).

3. For animal carcinogenicity, a substance causes a statistically significant number of tumors in at least one species, and the da are sufficient to derive a cancer potency factor.
4. There are studies which show that the chemical does not cause this health effect via this exposure route.

Bars of half height indicate that "some" information for the end point exists, but does not meet any of these criteria.

The absence of a column indicates that no information exists for that end point and route.

2.3.2.2 Description of highlights of graphs

Humans. There is some evidence concerning human exposure to heptachlor and reproductive (exposure route undetermined, judged to be oral) or developmental (exposure route undetermined, judged to be oral) effects. The data in these studies were inadequate to assess whether or not human exposure to heptachlor/heptachlor epoxide can induce reproductive or developmental toxicity.

Neurotoxicity, hematotoxicity, and increased incidences of tumors of the skin, bladder, and lungs were reported following exposures of humans to mixtures of heptachlor and other chlorinated cyclodiene insecticides (primarily chlordane) or other chlorinated hydrocarbons. Because the mixed exposures preclude the determination of whether or not heptachlor was involved in the induction of these toxic effects, these studies were excluded from consideration of data adequacy. In additi the data in these studies were inadequate to provide a clear assessme of whether or not human exposure to mixtures of heptachlor and other chemicals can induce these toxic effects.

Animals. For the inhalation route, no data were available for any category of toxicity. For the oral route, adequate data were available for lethality and carcinogenicity, and some data were available for developmental and reproductive toxicity and for systemic/target organ toxicity of all durations of exposure. For the dermal route, some data were available for lethality, but no data were available for any other category of toxicity.

For systemic effects other than hepatotoxicity (neurotoxicity, adrenal toxicity, renal toxicity, and hematologic effects), the database is grossly inadequate.

2.3.2.3 Summary of relevant ongoing research

A Special Data Call-in (EPA 1986f) for termiticides by the EPA requires registrants to provide the following chemical-specific toxicology studies to support a more comprehensive risk assessment of each termiticide:

- General metabolism studies, one in rats and one in mice, giving special consideration to pharmacokinetics
- Battery of acute toxicity studies

- Subchronic inhalation study--rats (1 year), guinea pigs or rats (2 weeks)
- Chronic feeding--nonrodents and rats (heptachlor epoxide); nonrodents (heptachlor)
- Oncogenicity--rats (heptachlor epoxide)
- Mutagenicity studies
- Teratogenicity--rats and rabbits
- Optic tissue pathology--rats

The status of these data requirements for heptachlor follows:

The metabolism data required from the registrant have also been submitted, reviewed, and accepted. The mutagenicity data requirements have not been fully satisfied, and additional mutagenicity studies are being requested. The registrant submitted a subchronic inhalation study that was invalid because chlordane was used rather than heptachlor; moreover, the lowest dose tested in the study was 20 times higher than the National Academy of Science (NAS) airborne guideline of 0.005 mg/m^3, the lowest dose level requested by the Data Call-in. An inhalation study for heptachlor is required (EPA 1986f).

Public Health Service research grants have been awarded to the following investigators for studies on heptachlor/heptachlor epoxide (CRISP database 1987): (1) F. Matsumura to study effects on calcium-regulating processes in the nervous system, liver, and heart of rodents, guinea pigs, and some invertebrate species; (2) J.E. Casida to study effects on the brains (neurotransmitter receptors, cholinergic receptors) of rats, chickens, fish, insects, and humans; and (3) D.E. Moreland to study mechanisms of action in rats, insects, and sheep with respect to bioenergetics, biological transport, oxidative phosphorylation, and membrane permeability.

A request for proposals concerning heptachlor has been issued (Science 1987) indicating the following areas of research interest:

- Definition of exposure and exposed populations. Establishment of a registry (in Hawaii).
- Body burdens of heptachlor and other chlorinated hydrocarbon pesticides (in Hawaii).
- Epidemiological evaluation of heptachlor exposure to define current and anticipated risk (in Hawaii).
- Metabolism of heptachlor and related substances. Biological effects on heptachlor.
- Clinical management, surveillance, and treatment of exposed persons (in Hawaii).

2.3.3 Other Information Needed for Human Health Assessment

2.3.3.1 Pharmacokinetics and mechanisms of action

No information was found for the following:

- Absorption of heptachlor or heptachlor epoxide from the respiratory tract,
- Quantitative data concerning dermal absorption of heptachlor or heptachlor epoxide,
- Distribution of heptachlor or heptachlor epoxide following inhalation exposure,
- Distribution of heptachlor or heptachlor epoxide following dermal exposure,
- Metabolism of heptachlor or heptachlor epoxide following inhalation exposure,
- Excretion of heptachlor or heptachlor epoxide by humans following ingestion,
- Excretion of heptachlor or heptachlor epoxide following dermal exposure.

2.3.3.2 Monitoring of human biological samples

Analytical methods are available to determine if a person has been exposed to heptachlor or heptachlor epoxide (see Sect. 8, Table 8 2) These methods do not, however, differentiate between routes of exposure. No information was found to correlate levels of heptachlor epoxide in tissue with either level or duration of exposure.

No information was found to indicate that there is any ongoing research to correlate levels of heptachlor epoxide in the body with level or duration of exposure.

2.3.3.3 Environmental considerations

Numerous analytical methods are available for the determination of heptachlor and heptachlor epoxide in environmental samples (see Sect. 8, Table 8.1).

Data were not found for levels of heptachlor or heptachlor epoxide in soil or foodstuff from agricultural lands treated with heptachlor since the cancellation of agricultural uses of heptachlor.

Available data indicate that heptachlor is converted to heptachlor epoxide in the environment. The data also indicate that heptachlor epoxide is persistent in the environment. The environmental fate and transport characteristics of heptachlor epoxide have been determined.

No data on interactions of heptachlor or heptachlor epoxide with other chemicals in the environment were found. In vivo, there are limited data to indicate that heptachlor acts as a promoter of carcinogenesis.

As part of a Special Data Call-in for termiticides, the EPA has requested the following studies concerning environmental levels of heptachlor (EPA 1986f):

- Hydrolysis,
- Aerobic and anaerobic soil metabolism,
- Aerobic aquatic metabolism,
- Leaching and adsorption/desorption,
- Soil dissipation: field study,
- Photodegradation in water,
- Special monitoring study of heptachlor residues entering surface water from sanitary sewers, sumps, and drainage tiles from home foundations known to have been properly treated with heptachlor,
- Applicator exposure,
- Indoor air exposure,
- Avian acute oral toxicity,
- All product chemistry.

3. CHEMICAL AND PHYSICAL INFORMATION

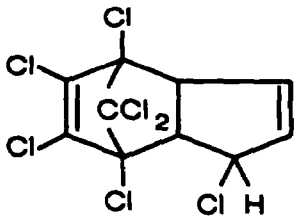
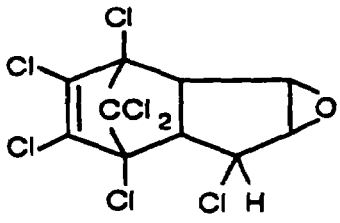
3.1 CHEMICAL IDENTITY

The chemical formulae, structures, synonyms, and identification numbers for heptachlor and heptachlor epoxide are listed in Table 3.1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Physical and chemical properties of heptachlor and heptachlor epoxide are given in Table 3.2.

Table 3.1. Chemical identity of heptachlor and heptachlor epoxide

Chemical name	Heptachlor	Heptachlor epoxide
Synonyms	1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene, heptachlorodicyclopentadiene	1,4,5,6,7,8,8-Heptachloro-2,3-epoxy-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene, epoxyheptachlor
Trade names	Velsicol 104® Drinox®	Velsicol 53-CS-17®
Chemical formula	$C_{10}H_5Cl_7$	$C_{10}H_5Cl_7O$
Wiswesser line notation	L C555 A DU IUTJ AG AG BG FG HG IG JG	T D3 C555 A EO JUTJ AG AG BG GG IG JG KG
Chemical structure		
Identification Numbers		
CAS Registry No.	76-44-8	1024-57-3
NIOSH RTECS No.:	PC0700000	PB9450000
EPA Hazardous Waste No.	P059	NA[a]
OHM-TADS No.	7216526	NA
DOT/UN/NA/IMCO Shipping Nos.	UN2762, UN2995, UN2996, UN2761, NA3761	NA
STCC No.	49 606 30	NA
Hazardous Substances Data Bank No.	554	6182
National Cancer Institute No.	10875-C	NA

[a]NA = Not available.

Table 3.2. Physical and chemical properties of heptachlor and heptachlor epoxide

Property	Heptachlor	Heptachlor epoxide
Molecular weight	373.5	389.4
Physical state	Crystalline solid (pure), waxy solid (technical-grade product) (Worthing and Walker 1983)	Solid
Color	Light tan (Sittig 1985)	NA[a]
Odor/odor threshold	Camphorlike (Sittig 1985) Odor threshold in water: 0 02 mg/kg (Vereschueren 1983)	NA
Melting point	95–96°C (pure) 46–74°C (technical-grade product) (Worthing and Walker 1983)	160–161.5°C (IARC 1979)
Boiling point	135–145°C @ 1.5 torr (IARC 1979)	
Autoignition temperature	NA	NA
Solubility in water	56 mg/L @ 25–29°C (Worthing and Walker 1983)	Insoluble (IARC 1979), 0.35 ppm (Hayes 1982)
Organic solvents	1.65 kg/L cyclohexanone, 6.25 g/L ethanol, 263 g/L deodorized kerosene,1.41 kg/L xylene @ 20–30°C (Worthing and Walker 1983)	NA
Density	1.57–1.59 (Verschueren 1983)	NA
Log partition coefficient(s)	Hexane/water· 5.05 (Hansch and Leo 1979)	Hexane/water: 4.60 (Hansch and Leo 1979)

Table 3.2 (continued)

Property	Heptachlor	Heptachlor epoxide
Vapor pressure	3.0×10^{-4} torr @ 25°C (Windholz 1983)	NA
Henry's law constant	NA	NA
Refractive index	NA	NA
Flash point	NA	NA
Flammability limits	NA	NA
Conversion factors	1 mg/L = 65.1 ppm and 1 ppm = 15.35 mg/m^3 at 25°C and 760 torr (CAG 1986)	1 mg/L = 62.5 ppm and 1 ppm = 15.9 mg/m^3 at 25°C and 760 torr (CAG 1986)
Other	Stable to light, moisture, air and at temperatures ≤261°C, not readily dehydrochlorinated, susceptible to epoxidation (Worthing and Walker 1983)	NA

[a]NA = Not available.

4. TOXICOLOGICAL DATA

The toxicity of heptachlor and heptachlor epoxide in animals has been reviewed in Anonymous (1986), CAG (1986), Eisler (1968), IARC (1979), NRC (1982), EPA (1985a and 1987c), and WHO (1984). When not provided elsewhere, conversions of parts per million test compound in diet to milligram test compound per kilogram body weight per day (abbreviated mg/kg/day) were made using the table of Lehman (1959).

4.1 OVERVIEW OF TOXICOLOGICAL DATA

Though limited, data suggest that heptachlor is readily absorbed from the gastrointestinal tract and may be absorbed from the skin. No information was found on absorption via the lungs. A large portion of the absorbed heptachlor is slowly eliminated, primarily via the bile duct into the feces. Heptachlor is readily oxidized to heptachlor epoxide in mammals. Unchanged heptachlor has been detected in human milk. Heptachlor epoxide has been detected in human milk, several human tissues, blood, and amniotic fluid. No relationship has been established between the metabolism and the toxic effects of heptachlor or heptachlor epoxide.

Acute lethality data were available for animals exposed via the oral and dermal routes. Heptachlor/heptachlor epoxide may be classified as very toxic via the oral route on the basis of acute animal data. Intermediate or chronic oral exposure to these compounds also induced mortality in animals. Heptachlor may be classified as very toxic to extremely toxic via the dermal route on the basis of acute lethality data in animals. In human case reports, convulsions and death were reported following inhalation of technical-grade chlordane, which typically contains 10% heptachlor.

On the basis of animal data, hepatotoxicity may be the most sensitive systemic/target organ end point for heptachlor/heptachlor epoxide; signs of toxicity in animals following short- or long-term oral exposure include histologic evidence of severe liver damage, increased liver weight, and increased levels of serum components 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/heptachlor epoxide.

Neurotoxic signs, including hypoactivity, tremors and convulsions, ataxia, and changes in EEG patterns have been induced in animals by acute, intermediate, or chronic oral intake of heptachlor/heptachlor epoxide. Studies in rat brain suggest that the neurotoxic effects of heptachlor/heptachlor epoxide may involve, in part (1) interference with nerve action or release of neurotransmitters as the result of inhibition of either Na^+-K^+ ATPase or Ca^{2+}-Mg^{2+} ATPase activity or (2) inhibition of the function of the receptor for γ-aminobutyric acid (GABA). 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 typically contains 10% heptachlor. 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 exposed to chlordane and heptachlor by unspecified routes.

Additional systemic/target organ toxicities observed in animals during long-term oral exposures include renal toxicity, adrenotoxicity, and hematologic effects. Intermediate and chronic inhalation exposure of humans to mixtures of heptachlor with chlordane and other chemicals has been associated with pancytopenia, leukemia, and aplastic, hemolytic, and megaloblastic anemias.

Heptachlor epoxide was found in the blood and several tissues of human stillborn infants. No adverse effects on human fetal development were reported following ingestion of heptachlor-contaminated cow's milk for 27 to 29 months by women of child-bearing age in Oahu, Hawaii. These data are inadequate to provide a clear assessment of the relationship between heptachlor/heptachlor epoxide exposure and human developmental toxicity. Cataracts and decreased postnatal survival were reported in the progeny of rats fed diets containing heptachlor. No developmental toxicity data were available for animals for other routes of exposure.

Elevated levels of heptachlor epoxide, as well as elevated leve' of eight of ten other organochlorine pesticides for which analytical data were available, were reported in the serum of women with premature delivery, and heptachlor epoxide has been reported in the blood and tissues of stillborn infants. No adverse effects on human reproduction (no decrease in fertility, no increase in fetal or neonatal deaths) were reported following ingestion of heptachlor-contaminated cow's milk for 27 to 29 months by women of child-bearing age in Oahu, Hawaii. These data are inadequate to provide a clear assessment of the relationship between heptachlor/heptachlor epoxide exposure and human reproductive toxicity. Male and female mice that received heptachlor in the diet for 10 weeks were unable to produce a new generation. Decreased pregnancy rates were reported following oral administration of heptachlor to male and female rats for two generations. In male and female rats fed heptachlor, heptachlor epoxide, or a mixture of the two for three generations, the number of resorbed fetuses increased and fertility decreased with succeeding generations. No reproductive toxicity data were available for animals for other routes of exposure.

Heptachlor and heptachlor epoxide, with or without a metabolic activation system, tested negative in well-conducted microbial gene mutation assays, and heptachlor was not mutagenic in an epithelial cell line (ARL) derived from rat liver. Heptachlor, with metabolic activation, was clastogenic in Chinese hamster ovary (CHO) cells, but neither heptachlor nor heptachlor epoxide was clastogenic in male mouse germinal cells in a dominant lethal assay. With the exception of a single positive in vitro sister chromatid exchange (SCE) assay with heptachlor in CHO cells (with or without metabolic activation), the

results of DNA repair assays suggest that heptachlor is unlikely to elicit DNA repair mechanisms unless the cell has been preinitiated. Heptachlor appears to be a promoter of hepatocarcinogenesis in mice. Consistent with this finding, low concentrations of heptachlor inhibited metabolic cooperation in Chinese hamster cells and rat liver cells, a property common to many known promoters. 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 genotoxic.

The ability of heptachlor to act as an inhibitor of intercellular communication may also be a component in the mechanism of systemic/target organ, developmental, and reproductive toxicities, although this mechanism of action has not been verified experimentally.

Available epidemiological studies on heptachlor are considered to be inadequate to establish a clear qualitative or quantitative assessment of the relationship between heptachlor exposure and human risk of developing cancer. Chronic oral exposure to heptachlor/ heptachlor epoxide increased the incidence of liver carcinomas in CFN rats and C3H, CD-1, and B6C3F1 mice. Heptachlor/heptachlor epoxide is classified as a probable human carcinogen, Group B2, under EPA's guidelines for carcinogen risk assessment.

4.2 TOXICOKINETICS

4.2.1 Overview

Though limited, data suggest that heptachlor is readily absorbed from the gastrointestinal tract and may be absorbed through the skin. A large portion of the absorbed heptachlor is slowly eliminated, primarily via the bile duct into the feces.

Heptachlor is readily oxidized to heptachlor epoxide in mammals. Heptachlor epoxide has been detected in various tissues of rats and dogs, with the highest levels found in fat. The accumulation of heptachlor epoxide in fat is dose dependent, and female rats accumulate more than males.

Heptachlor epoxide has been detected in several human tissues, blood, milk, and amniotic fluid at concentrations of <1 ppm. Unchanged heptachlor was also detected in human milk samples.

4.2.2 Absorption

4.2.2.1 Inhalation

Human. No information was found.

Animal. One group of 20 rabbits (10 males, 10 female; strain not reported) was housed outdoors in an area of high pesticide use; an equal-sized group was housed inside a building in an area of low pesticide use. The groups were on study for 3 months. The heptachlor epoxide level in adipose tissue of the outdoor group was 0.039 ± 0.002 ppm; the level in the control group (indoor) was 0.016 ± 0.001 ppm. The

calculated average respiratory intake of heptachlor epoxide was 0.002 ppm. The calculated average respiratory intake of heptachlor epoxide w 0.002 μg/day (Arthur et al. 1975).

4.2.2.2 Oral

Human. Members of farm families who consumed raw dairy products from cattle fed heptachlor-contaminated feed had significantly ($P < 0.01$) elevated serum levels of heptachlor metabolites (Stehr-Green et al. 1986). Heptachlor epoxide levels in the cow's milk ranged up to 89.2 ppm (fat basis); mean levels in human serum were 0.81 ± 0.94 ppb for heptachlor epoxide, 0.70 ± 0.75 ppb for oxychlordane, and 0.79 ± 0.60 ppb for *trans*-nonachlor.

Animal. Heptachlor is absorbed from the gastrointestinal tract as indicated by the presence of heptachlor and/or its metabolites in the urine (feces) and tissues of animals dosed orally, but quantitative data are not available. Only 6% of the radioactivity from a dose of ^{14}C-labeled heptachlor was found in the urine while 60% was found in the feces of male rats 10 days after dosing (Tashiro and Matsumura 1978). Thus, the available data strongly indicate that a large percentage is absorbed from the gastrointestinal tract and eliminated via the bile into the feces. Approximately 60% of the radioactivity eliminated in the feces was present in metabolites of heptachlor (Tashiro and Matsumura 1978).

4.2.2.3 Dermal

Human. No information was found.

Animal. Heptachlor is absorbed through the skin following topical application as indicated by its dermal toxicity to rats (LD_{50} = 195-250 mg/kg, Gaines 1969), but quantitative data are not available.

4.2.3 Distribution

4.2.3.1 Inhalation

Human. No information was found.

Animal. No information was found.

4.2.3.2 Oral

Human. The routes of exposure leading to detectable levels of heptachlor and heptachlor epoxide in humans are not known for certain. Since the majority of data are from the period when heptachlor was widely used in agriculture, making ingestion of heptachlor likely, human tissue levels are presented in this section. Other routes of exposure may have contributed to the overall body burden of heptachlor/heptachlor epoxide. Data are insufficient to determine whether or not the observed levels of heptachlor and heptachlor epoxide were associated with any toxic effects.

Heptachlor epoxide has been detected in human tissues, blood, milk, and amniotic fluid at various concentrations. Zavon et al. (1969) reported levels of heptachlor epoxide in the range of not detected (N

to 0.563 ppm in fat of deceased infants. Curley et al. (1969) reported heptachlor epoxide levels in the liver (0.03-1.67 ppm), kidneys (0.19-1.14 ppm), and adrenals (0.46-1.00 ppm) of deceased infants. Heptachlor epoxide levels in extracted lipids from mothers and newborn infants were adipose tissue (0.2856 ± 0.3109 ppm), maternal blood (0.2798 ± 0.4626 ppm), uterine muscle (0.4895 ± 0.5086 ppm), fetal blood (0.9959 ± 0.9458 ppm), placenta (0.5000 ± 0.3950 ppm), and amniotic fluid (0.6730 ± 1.1645 ppm) (Polishuk et al. 1977b). These data provide evidence of transplacental transfer to the fetus.

Heptachlor was detected by Jonsson et al. (1977) in 3 of 51 human milk samples at an average concentration of 0.019 ppm. Heptachlor epoxide was detected in 12 of the 51 samples at an average concentration of 0.0027 ppm. Other investigators have reported the presence of heptachlor epoxide in human milk at concentrations ranging from ND to 0.46 ppm (Kroger 1972, Polishuk et al. 1977a, Strassman and Kutz 1977, Savage et al. 1981, Takahashi 1981, Takei et al. 1983).

Unchanged heptachlor was not detected (detection limit = 0.06 ppm) in adipose tissue (Barquet et al. 1981). Heptachlor epoxide has been detected in adipose tissue at levels ranging from <0.0001 ppm to 1.12 ppm (Radomski et al. 1968, Burns 1974, Wassermann et al. 1974, Greer et al. 1980, Barquet et al. 1981), in tissue at 1-32 ppb (highest in bone marrow and liver) (Klemmer et al. 1977), in liver and brain at trace to 0.05 ppm (detection limit not reported) (Radomski et al. 1968), in blood at 0-9.9 ppb (detection limit not reported) (Mossing et al. 1985), and in whole plasma at 0.0136 ± 0.0057 ppm (Polishuk et al. 1977a).

Animal. Radomski and Davidow (1953) studied the pharmacokinetics of heptachlor in rats. When rats were fed diets containing heptachlor for 2 months or more the highest levels of heptachlor epoxide were found in the fat with markedly lower levels in liver, kidneys, and muscles; none was detected in the brain. Levels in all tissues were higher in females than in males.

The rate of heptachlor epoxide accumulation in and elimination from body fat was determined in male and female rats by Radomski and Davidow (1953). Rats were placed on diets containing heptachlor for 12 weeks then placed on untreated diets for 12 more weeks. In males, the heptachlor epoxide level reached a maximum plateau at approximately 2 to 8 weeks; thereafter the levels decreased, and, by the end of week 6 postdosing, the heptachlor epoxide level was below the detection limit. In females, the heptachlor epoxide level in fat was much higher than in males by 2 weeks and throughout the remainder of the study. By the end of week 8 postdosing, the heptachlor epoxide level in the fat was below the detection limit.

4.2.3.3 Dermal

Human. No information was found.

Animal. No information was found.

4.3 TOXICITY

4.3.1 Lethality and Decreased Longevity

4.3.1.1 Overview

Inhalation. No key studies on increased mortality in humans or animals following inhalation exposure of any duration to heptachlor/heptachlor epoxide were found in the literature. In human case reports, convulsions and death were reported following inhalation of technical-grade chlordane, which typically contains 10% heptachlor.

Oral. Heptachlor/heptachlor epoxide may be classified as very toxic (Toxicity Category II) via the oral route on the basis of acute oral LD50s in rats of 71 mg/kg for heptachlor and 60 mg/kg for heptachlor epoxide.

Studies in rodents and dogs have shown that heptachlor, heptachlor epoxide, or a mixture of these compounds may induce increased mortality in animals following intermediate or chronic oral exposures.

No data describing increased mortality in humans following oral exposures of any duration to heptachlor/heptachlor epoxide were found in the literature.

Dermal. Heptachlor may be classified as very toxic (Toxicity Category II) to extremely toxic (Toxicity Category I) via the dermal route on the basis of acute dermal LD50 in rats of 195 mg/kg in males and 250 mg/kg in females. Data were not available for classifying the acute dermal lethality of heptachlor epoxide in animals or for assessing the acute, intermediate, or chronic dermal lethality of heptachlor/heptachlor epoxide in humans.

4.3.1.2 Inhalation

Human. No key studies describing increased mortality in humans following inhalation exposure of any duration were found in the literature.

Animal. No data describing increased mortality in animals following inhalation exposure of any duration were found in the literature.

4.3.1.3 Oral

Human. No data describing increased mortality in humans following oral exposure of any duration were found in the literature.

Animal, acute. Acute oral LD50s for heptachlor in rodents (rats, mice, hamsters, and guinea pigs) and rabbits were in the range of 40 to 162 mg/kg (Ben-Dyke et al. 1970, Eisler 1968, Gaines 1969, Gak et al. 1976, Lehman 1951, RTECS 1983-84, Sperling et al. 1972, Sun 1972, Podowski et al. 1979).

Acute oral LD50s for heptachlor epoxide in rodents (rats and mice) and rabbits were in the range 39 to 144 mg/kg (Eisler 1968, RTECS 19[illegible] 84, Sperling et al. 1972, Podowski et al. 1979).

Data from key studies, defined as peer-reviewed studies that report the lowest oral LD_{50} for each species, are shown in Table 4.1.

Animal, intermediate. Increased mortality was reported following intermediate oral intake of heptachlor by rats (NCI 1977), mice (NCI 1977), and dogs (Lehman 1952).

Groups of 10 Osborne-Mendel rats (5/sex) and 10 B6C3F1 mice (5/sex) were fed technical-grade heptachlor (73% heptachlor; 22% *trans*-chlordane; 5% nonachlor) for 6 weeks, followed by a 2-week period of observation. Dietary concentrations were 20, 40, 80, 160, and 320 ppm (NCI 1977).

Two of five male rats died at the 320-ppm level; no deaths were reported at 160 ppm or at lower levels. The LOAEL for male rats was 320 ppm (32 mg/kg/day), and the NOAEL was 160 ppm (16 mg/kg/day). Five of five females rats died at the 320-ppm level, and four of five died at the 160-ppm level; no deaths were reported at 80-ppm or lower levels. The LOAEL in female rats was 160 ppm (16 mg/kg/day), and the NOAEL was 80 ppm (8 mg/kg/day).

All male mice died at the 80-ppm level; no deaths were reported at levels of 40 or 20 ppm. Data were not reported for levels of 160 and 320 ppm. The LOAEL for male mice was 80 ppm (12 mg/kg/day), and the NOAEL was 40 ppm (6 mg/kg/day). Two of five female mice died at the 80-ppm level; no deaths were reported at levels of 40 or 20 ppm. Data were not reported for levels of 160 and 320 ppm. The LOAEL for female mice was 80 ppm (12 mg/kg/day), and the NOAEL was 40 ppm (6 mg/kg/day).

Animal, chronic. Increased mortality was reported following chronic oral intake of heptachlor by rats and mice (NCI 1977), heptachlor epoxide by mice (Davis 1965, as cited in Epstein 1976), heptachlor/heptachlor epoxide (75%:25%) by rats (Jolley et al. 1966, as cited in Epstein 1976), and heptachlor/heptachlor epoxide (75%:25%) by mice (IRDC 1973, as cited in Epstein 1976).

Groups of 20 to 24 female CD rats were fed diets containing 5, 7.5, 10, or 12.5 ppm heptachlor/heptachlor epoxide (75%:25%) for up to 2 years. Prior to mixing, heptachlor was 99.9% pure, and heptachlor epoxide was 96.0% pure. Forty-seven females served as controls. Mortality was increased in all test groups: control, 21%; 5 ppm, 39%; 7.5 ppm, 25%; 10 ppm, 43%; and 12.5 ppm, 50%. The LOAEL was 5 ppm (0.25 mg/kg/day); a NOAEL was not established (Jolley et al. 1966, as cited in Epstein 1976).

Groups of 100 male and 100 female C3H mice were fed diets containing 0 or 10 ppm heptachlor epoxide (purity not indicated) for up to 104 weeks. Survival data were reported for males and females combined. Mortality was increased in the test group. Excluding the 18 control mice sacrificed for transplant studies, survival at 104 weeks was 34% in controls and 9.5% in animals that received heptachlor epoxide. The LOAEL was 10 ppm (1.5 mg/kg/day); a NOAEL was not established (Davis 1965, as cited in Epstein 1976).

Groups of 100 male and 100 female Charles River CD-1 mice were fed diets containing 0, 1, 5, or 10 ppm heptachlor/heptachlor epoxide (25%:75%) for up to 18 months; 10 males and 10 females from each group

Table 4.1. Lowest reported LD_{50} for heptachlor and heptachlor epoxide for various species

Species	Sex/strain	Chemical	LD_{50} (mg/kg)	References
Rats	Male/Charles River-derived	Heptachlor	71	Podowski et al. 1979
Rats	Male/Charles River-derived	Heptachlor epoxide	60	Podowski et al. 1979
Mice	ND/ND[a]	Heptachlor	70	Gak et al. 1976
Hamsters	ND/golden	Heptachlor	100	Gak et al. 1976

[a]ND, no data.

were killed at 6 months. Based on the adjusted numbers of mice at risk after the 6-months sacrifice, survival was similar in the control, 1-ppm, and 5-ppm groups (51 to 66%) but was reduced in 10-ppm test group to 29% in males and 30% in females. The LOAEL was 10 ppm (1.5 mg/kg/day), and the NOAEL was 5 ppm (0.75 mg/kg/day) (IRDC 1973, as cited in Epstein 1976).

Groups of 50 male and 50 female B6C3F1 mice were fed diets containing technical-grade heptachlor (73% heptachlor, 22% *trans*-chlordane, 5% nonachlor) for up to 80 weeks at time-weighted average (TWA) concentrations of 6.1 or 13.8 ppm for males and 9 or 18 ppm 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 statistically significant ($P = 0.02$) trend for increased mortality, due mainly to the effect of the high dose. Data from the survival curves indicate that the LOAEL in females was 18 ppm (2.7 mg/kg/day), and the NOAEL was 9 ppm (1.35 mg/kg/day) (NCI 1977).

4.3.1.4 Dermal

Human. No data describing inereased mortality in humans following dermal exposure of any duration were found in the literature.

Animal, acute. Acute dermal LD50s for heptachlor were 195 and 250 mg/kg (in xylene) in male and female Sherman rats, respectively (Gaines 1969), 119 mg/kg (vehicle not specified) in rats of unidentified sex and strain (RTECS 1983-84), and approximately 2,000 mg/kg (dry powder) in rabbits (sex and strain not indicated) (Eisler 1968); data were not found for heptachlor epoxide.

A key study of acute lethality is one that is peer reviewed and reports the lowest LD50 for a given species.

Gaines (1969) reported acute dermal LD50s for heptachlor (technical grade, purity not indicated) of 195 mg/kg in male and 250 mg/kg in female Sherman rats. Xylene was the solvent.

The mechanism for induction of lethality from acute exposure to heptachlor/heptachlor epoxide may involve the abilities of these compounds to (1) interfere with nerve action or release of neurotransmitters as the result of inhibition of the activities of Na^+-K^+ ATPase (Folmar 1978, Yamaguchi et al. 1980) or Ca^{2+}-Mg^{2+} ATPase (Yamaguchi et al. 1980) and (2) inhibit the function of the receptor for γ-aminobutyric acid, as discussed further under the section on neurotoxicity (see Sect. 4.3.2.3) (Abalis et al. 1985, 1986; Matsumura and Ghiasuddin 1983; Lawrence and Casida 1984; Bloomquist and Soderlund 1985; Cole and Casida 1986).

With intermediate or chronic exposures to heptachlor/heptachlor epoxide, death may be mediated by systemic toxicity, particularly hepatotoxicity; in the case of chronic exposures, death may also be related to the presence of hepatic tumors.

4.3.2 Systemic/Target Organ Toxicity

4.3.2.1 Overview

Animal data on the systemic/target organ toxicity of heptachlor/heptachlor epoxide were available only for the oral route.

Evaluation of the existing toxicological database for heptachlor/heptachlor epoxide suggests that hepatotoxicity may be the most sensitive noncancer end point of toxicity for these substances in animals.

Neurotoxic signs have been reported during short- and long-term oral exposure of animals to heptachlor/heptachlor epoxide. In human case reports, 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 typically contains 10% heptachlor. 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 exposed to chlordane and heptachlor by unspecified routes.

Additional effects observed in animals during long-term exposures include renal toxicity, adrenotoxicity, hematologic effects, and decreased body weight gain. Intermediate and chronic inhalation exposure of humans to mixtures of heptachlor with chlordane and other chemicals has been associated with pancytopenia, leukemia, and aplastic, hemolytic, and megaloblastic anemias.

4.3.2.2 Hepatotoxicity

Overview. Hepatotoxic effects of the short- and long-term oral administration of heptachlor/heptachlor epoxide to animals included histologic changes (necrosis, steatosis, hepatocytomegaly, or increased numbers of lysosomes), increased liver weight, and increases in the levels of serum components that are indicative of hepatic damage (e.g., alkaline phosphatase, bilirubin, cholesterol, and glutamic-pyruvic transaminase). Studies were available only for the oral route.

Inhalation, human. No data describing hepatotoxicity in humans following inhalation exposure of any duration were found in the literature.

Inhalation, animal. No data describing hepatotoxicity in animals following inhalation exposure of any duration were found in the literature.

Oral, human. No key studies describing hepatotoxicity in humans following oral exposure of any duration were found in the literature.

In 45 individuals exposed for approximately 2 months to contaminated raw milk products from cattle fed heptachlor-contaminated feed, 23 to 31% had significantly ($P < 0.01$) 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 control cohort (Stehr-Green et al. 1986). Exposure measurements were

reported; inadequacies of analysis limit the use of these data (Frumkin et al. 1987).

Oral, animal (acute). Adverse hepatic effects from acute oral exposure to heptachlor have been demonstrated in rats. Microscopic effects included liver necrosis (Krampl 1971), cell vacuolization (Krampl 1971), and liver steatosis (Pelikan 1971). Other effects compatible with hepatic damage from heptachlor include increased relative liver weight (Pelikan 1971, Enan et al. 1982) and elevated serum levels of aldolase (Krampl 1971), glutamic-pyruvic transaminase (Krampl 1971), bilirubin (Enan et al. 1982), alkaline phosphatase (Enan et al. 1982), and cholesterol (Enan et al. 1982).

Other liver effects from acute oral exposure of rats to heptachlor, such as reduced liver glycogen, increases in gluconeogenic enzymes, elevated blood sugar, and increases in microsomal drug-metabolizing enzymes, have been reported (Enan et al. 1982, Gillett and Chan 1968, Kacew and Singhal 1973, Den Tonkelaar and Van Esch 1974), but their relevance to liver toxicity is uncertain.

The investigation of Enan et al. (1982) was selected by EPA (1985a and 1987c) for derivation of a 10-day health advisory for heptachlor. A group of 15 female white rats (strain not indicated) was fed heptachlor (96%) 5 days per week for 4 weeks at a concentration of 10 ppm in the diet (equivalent to 1 mg/kg/day; EPA 1985a and 1987c, conversion assumptions not given). Four animals were killed after receiving 1, 7, or 28 daily doses. Controls were fed a diet containing corn oil, the solvent used for addition of test compound to diet. Effects compatible with hepatic damage from acute oral intake of heptachlor included increased relative liver weight (7 days) and elevated serum bilirubin (1, 7, and 28 days), alkaline phosphatase (1 and 7 days), and blood urea (7 days). The liver was not examined histologically. The LOAEL was 1 mg/kg/day; a NOAEL was not established.

Oral, animal (intermediate). Adverse hepatic effects from intermediate oral exposure to heptachlor or a mixture of heptachlor and heptachlor epoxide have been demonstrated in rats, mice, pigs, and sheep. Microscopic effects are shown in Table 4.2.

The following effects of intermediate oral exposure were also compatible with hepatic damage: an increase in liver LDH5 (least anodic isoenzyme of lactic dehydrogenase) in pigs treated with heptachlor (Halacka et al. 1974); elevated serum bilirubin, blood urea, serum cholesterol, serum alkaline phosphatase, and relative liver weight in rats treated with heptachlor (Enan et al. 1982); enlarged livers and increased relative liver weight in rats treated with heptachlor (Pelikan 1971); and increased liver weight in mice treated with heptachlor/heptachlor epoxide (25%:75%) (IRDC 1973, as cited in Epstein 1976).

Other liver effects from intermediate oral exposure of animals to heptachlor or heptachlor epoxide, such as reduced liver glycogen (heptachlor in pigs, Dvorak and Halacka 1975; rats, Enan et al. 1982), increased blood glucose (heptachlor in rats, Enan et al. 1982), increases in microsomal drug-metabolizing enzymes (heptachlor and heptachlor epoxide in rats, Kinoshita and Kempf 1970), and increased

Table 4.2. Microscopic hepatic effects of intermediate oral exposure to heptachlor/heptachlor epoxide

Compound(s)	Microscopic findings	Species	References
Heptachlor	Liver necrosis	Mice	Akay and Alp 1981
Heptachlor	Liver necrosis	Rats, pigs, sheep	Halacka et al. 1975
Heptachlor	Liver fibrosis	Mice	Akay and Alp 1981
Heptachlor	Liver steatosis	Rats, mice	Pelikan 1971, Akay and Alp 1981
Heptachlor	Increased number of lysosomes in hepatocytes	Pigs	Halacka et al. 1974
Heptachlor	Nuclear irregularities	Mice	Akay and Alp 1981
Heptachlor/ heptachlor epoxide (75%:25%)	Centrilobular hepatocytomegaly	Rats	Jolley et al. 1966, as cited in Epstein 1976

agranular endoplasmic reticulum (heptachlor in pigs, Dvorak and Halacka 1975) and dose-related changes in biochemical values related to liver function (heptachlor epoxide in dogs, IRDC 1971, as cited in EPA 1985a), have been reported, but their relevance to liver toxicity is uncertain.

Five female CD rats, an interim sacrifice group in a 24-month study, were fed a diet containing 7.5 ppm heptachlor/heptachlor epoxide (75%:25%) for 5 months. Prior to mixing, heptachlor was 99.9% pure, and heptachlor epoxide was 96.0% pure. Seven females served as controls. Hepatocytomegaly in excess of control levels was reported in the test group (incidence and severity not given). The LOAEL was 7.5 ppm, or 0.38 mg/kg/day; a NOAEL was not established (Jolley et al. 1966, as cited in Epstein 1976).

Groups of 100 male and 100 female Charles River CD-1 mice were fed diets containing 0, 1, 5, or 10 ppm heptachlor/heptachlor epoxide (25%:75%, purities not specified) for 18 months. At the 6-month interim sacrifice of 10 males and 10 females, dose-related incidences of hepatocytomegaly (data not given) were reported in all treated males and in 5- and 10-ppm females. Mean liver weights were increased in 5- and 10-ppm males and in all treated females. The LOAEL was 1 ppm (0.15 mg/kg/day); a NOAEL was not established (IRDC 1973, as cited in Epstein 1976).

Oral, animal (chronic). Adverse hepatic effects of chronic oral exposure to heptachlor, heptachlor epoxide, or a mixture of the two compounds have been demonstrated in rats, mice, and dogs. Microscopic effects are shown in Table 4.3.

Other effects compatible with hepatic damage from chronic oral exposure to heptachlor or heptachlor epoxide include increased liver weight in rats exposed to heptachlor (Witherup et al. 1955, as cited in Epstein 1976) or heptachlor epoxide (Witherup et al. 1959, as cited in Epstein 1976), dose-related changes in biochemical values related to liver function in dogs exposed to heptachlor epoxide (IRDC 1971, as cited in EPA 1985a), increased relative liver weight in dogs exposed to heptachlor epoxide (Kettering 1958, as cited in EPA 1987c), and increased liver weight in mice exposed to heptachlor/heptachlor epoxide (25%:75%) (IRDC 1973, as cited in Epstein 1976).

The investigation of Witherup et al. (1955) was selected by EPA (1985a and 1987c) for derivation of a lifetime health advisory for heptachlor. Heptachlor of unspecified purity was administered in the diet to groups of 20 male and 20 female CF rats at concentrations of 1.5, 3, 5, 7, or 10 ppm for up to 110 weeks. Liver lesions characteristic of chlorinated hydrocarbons (i.e., hepatocellular swelling, homogeneity of the cytoplasm, and peripheral arrangements of the cytoplasmic granules of cells in the central zone of liver lobules) were increased in males and females of the 7- and 10-ppm groups. Mean liver weights were increased in males in the 5-, 7-, and 10-ppm groups. On the latter basis, EPA reported the LOEL to be 5 ppm (0.25 mg/kg/day) and the NOEL to be 3 ppm (0.15 mg/kg/day).

EPA (1987c) selected a Kettering Laboratory study (Kettering 1958) for derivation of a lifetime health advisory for heptachlor epoxide. Groups of three female and two male beagle dogs were administered diets

Table 4.3. Microscopic hepatic effects of chronic oral exposure to heptachlor/heptachlor epoxide

Compound(s)	Microscopic findings	Species	References
Heptachlor	Hepatic cell vacuolization	Rats	Witherup et al. 1959, as cited in Epstein 1976
Heptachlor	Hepatic vein thrombosis	Mice	Reuber 1977
Heptachlor epoxide	Hepatic vein thrombosis	Mice	Reuber 1977
Heptachlor epoxide	Microscopic changes in liver (NOS)	Dogs	IRDC 1971, as cited in EPA 1985a
Heptachlor/ heptachlor epoxide (25%:75%)	Hepatocytomegaly (mostly centrilobular)	Mice	IRDC 1973, as cited in Epstein 1976
Heptachlor/ heptachlor epoxide (75%:25%)	Centrilobular hepatocytomegaly	Rats	Jolley et al. 1966, as cited in Epstein 1976

containing 0, 0.5, 2.5, 5, or 7.5 ppm of heptachlor epoxide (purity not given) for 60 weeks. Relative mean liver weights were significantly increased (significance level not given) in treated animals compared with controls, and the increases were dose related. The LOEL was 0.5 ppm (0.0125 mg/kg/day); a NOEL was not established.

Witherup et al. (1959, as cited in Epstein 1976) fed heptachlor epoxide (purity not indicated) in the diet to groups of 25 male and 25 female CFN rats at concentrations of 0.5, 2.5, 5, 7.5, or 10 ppm for up to 108 weeks. Hepatic cell vacuolization, which was centrilobular at low doses and irregular at higher doses, was reported in all test groups (incidences not given). Degeneration, hepatocytomegaly, and regeneration were also reported (incidences not given). The LOAEL was 0.5 ppm (0.025 mg/kg/day); a NOAEL was not established.

IRDC (1973, as cited in Epstein 1976) administered heptachlor/heptachlor epoxide (25%:75%) of unspecified purity at concentrations of 0, 1, 5, or 10 ppm in the diet to groups of 100 male and 100 female Charles River CD-1 mice for up to 18 months; 10 males and 10 females from each group were killed at 6 months. Dose-related incidences of hepatocytomegaly (data not given), particularly involving centrilobular cells, were reported in males and females of all test groups. A dose-related incidence of nodular hyperplasia of the liver was reported for the 5- and 10-ppm test groups. Mean liver weights were significantly increased by 13% ($P < 0.05$) in females dosed at 1 ppm, by 33% ($P < 0.01$) at 5 ppm, and by 89% ($P < 0.01$) at 10 ppm, and in males by 38% ($P < 0.01$) at 5 ppm and by 169% ($P < 0.01$) at 10 ppm. The LOAEL was 1 ppm (0.15 mg/kg/day); a NOAEL was not established.

Dermal, human. No data describing hepatotoxicity in humans following dermal exposure of any duration were found in the literature.

Dermal, animal. No data describing hepatotoxicity in animals following dermal exposure of any duration were found in the literature.

General discussion. Oral exposures to heptachlor/heptachlor epoxide of any duration induced hepatotoxicity in rodents, as evidenced by microscopic changes, increases in liver weight, and changes in serum parameters indicative of liver damage. Although no direct evidence is available, it is possible that the ability of heptachlor to inhibit intercellular communication, as shown by in vitro evidence (see Sect. 4.3.5, Genotoxicity), may be involved in the mechanism of hepatotoxicity; also, the inhibition of intercellular communication and the induction of toxic effects in the liver may play roles in the hepatocarcinogenic process.

Suppression of body weight gain has often been reported in conjunction with the induction of hepatotoxicity by intermediate or chronic oral exposure to heptachlor/heptachlor epoxide. NOAELs/LOAELs for the suppression of body weight gain by oral intake of these compounds are given in Table 4.4.

4.3.2.3 Neurologic effects

Overview. Neurotoxic signs, including hypoactivity, tremors and convulsions, ataxia, and changes in EEG patterns have been induced in

Table 4.4. NOAELs and LOAELs for suppression of body weight gain by oral intake of heptachlor/heptachlor epoxide[a]

Species	Strain/sex	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	Chemical, duration	References
Rats	Sprague-Dawley/M	1	NE	H,I	Shain et al. 1977
Mice	O.ASA/M,F	7.5	NE	H,I	Akay and Alp 1981
Pigs	NA/ND	5	2	H,I	Halacka et al. 1974
Rats	CF/M	0.075	NE	H,C	Witherup et al. 1955, as cited in Epstein 1976
Rats	Osborne-Mendel/M	3.9[b]	1.9	H,C	NCI 1977
Rats	Osborne-Mendel/F	2.6[b]	1.3	H,C	NCI 1977
Mice	CD-1/F	1.5	0.75	H/HE (25%:75%), C	IRDC 1973, as cited in Epstein 1976

[a]Abbreviations: NE, not established; ND, no data; NA, not applicable; H, heptachlor; HE, heptachlor epoxide; F, female; M, male; I, intermediate; C, chronic.

[b]Dose levels represent time-weighted averages.

animals by acute, intermediate, or chronic oral intake of heptachlor/heptachlor epoxide.

In human case reports, 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 typically contains 10% heptachlor. 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 exposed to chlordane and heptachlor by unspecified routes.

Inhalation, human. No key studies describing neurologic effects in humans following inhalation exposure to heptachlor were found in the literature.

Human case reports which described acute neurological effects were reported following exposure to technical-grade chlordane, which typically contains 10% heptachlor (CAG 1986, EPA 1985a, EPA 1987c). These effects included irritability, salivation, lethargy, dizziness, labored respiration, muscle tremors, and convulsions. Reported dose levels ranged from 10 to 104 mg/kg body weight (EPA 1985a). In all of these cases, the effects observed cannot be attributed to heptachlor alone.

In a study of 16,126 pesticide applicators and termite control operators principally exposed to chlordane and heptachlor by unspecified routes, cerebrovascular disease was found to be significantly ($P < 0.05$) decreased in termite control operators (Wang and MacMahon 1979a). Incidence did not increase with increased estimated exposure. However, incidence of cerebrovascular disease was found to be significantly ($P < 0.05$) increased (17 cases) when compared to expected incidence (9.3 cases) among 1,403 workers engaged in the manufacture of chlordane, heptachlor, and endrin (Wang and MacMahon 1979b). This increased incidence of cerebrovascular disease was not correlated to length of exposure or latency and was reported to occur only after termination of employment (EPA 1985a). Methodological deficiencies limit the usefulness of these data; quantitative exposure (concentration and duration) data were not reported, the workers were exposed to multiple chemicals, and there was no control for confounding factors. The increased incidence of cerebrovascular disease reported by Wang and MacMahon (1979b) was not found in a subsequent study of heptachlor and chlordane-manufacturing workers (Ditraglia et al. 1981).

Inhalation, animal. No data describing neurologic effects in animals following inhalation exposure of any duration were found in the literature.

Oral, human. No key studies describing neurologic effects in humans following oral exposure to heptachlor were found in the literature. The occurrence of cerebrovascular disease in workers exposed to mixtures of heptachlor with chlordane and endrin is discussed under the inhalation route (Sect. 4.3.2.3).

Oral, animal (acute). Hypoactivity and some deaths (incidences not given) were reported in CD-1 male mice given a single gavage dose of heptachlor/heptachlor epoxide (25%:75%, w/w) at levels of 30 to 100

mg/kg, values near the LD50. Prior to mixing, the purity of the heptachlor was 73%; the purity of the heptachlor epoxide was not giver The LOAEL was 30 mg/kg; a NOAEL was not established (Arnold et al. 1977).

Tremors and convulsions (incidences not given) were reported in rats (sex and strain not indicated) given the acute oral LD50 dose (90 mg/kg) of heptachlor (purity not indicated). Neurotoxic signs appeared 30 to 60 min after dosing and lasted 2 days (Lehman 1951).

Oral, animal (intermediate). Heptachlor (purity not indicated) was fed to groups of at least 10 female and 5 male O.ASA F15 mice for 10 weeks at concentrations of 50, 100, or 200 ppm in the diet. Controls received diet without heptachlor. At 100 ppm, ataxia was reported in half the females, and whole-body tremors were observed in some (incidence not given). No neurotoxic signs were observed at 50 ppm, and no information was given on effects at 200 ppm. The LOAEL was 100 ppm (15 mg/kg/day), and the NOAEL was 50 ppm (7.5 mg/kg/day) (Akay and Alp 1981).

Oral, animal (chronic). Statistically significant changes in EEG patterns ($P < 0.05$) were reported in female Wistar rats administered heptachlor in the diet at levels of 1 or 5 mg/kg/day for three generations. The LOAEL was 1 mg/kg/day; a NOAEL was not established (Formanek et al. 1976).

Dermal, human. No key studies describing neurologic effects in humans following dermal exposure to heptachlor were found in the literature. The occurrence of cerebrovascular disease in workers exposed to mixtures of heptachlor with chlordane and endrin is discussed unde the inhalation route (Sect. 4.3.2.3).

Dermal, animal. No data describing neurologic effects in animals following dermal exposure of any duration were found in the literature.

General discussion. Investigations of heptachlor/heptachlor epoxide effects in rat brain suggest that the neurotoxic effects of these compounds may, in part, involve the following two processes: (1) interference with nerve action or release of neurotransmitters as the result of inhibition of the activities of Na^+-K^+ ATPase (Folmar 1978; Yamaguchi et al. 1980) or Ca^{2+}-Mg^{2+} ATPase (Yamaguchi et al. 1980) and (2) inhibition of the function of the receptor for γ-aminobutyric acid (GABA) (Abalis et al. 1985 and 1986, Matsumura and Ghiasuddin 1983). Heptachlor, heptachlor epoxide, and other cyclodiene insecticides bind to the picrotoxin binding site of the GABA receptor in mammalian brain synaptosomes or membrane vesicles (Matsumura and Ghiasuddin 1983, Abalis et al. 1985, Lawrence and Casida 1984) and inhibit GABA-stimulated chloride uptake by the GABA receptor-chloride ionophore complex in the central nervous system (Abalis et al. 1986, Bloomquist and Soderlund 1985, Gant et al. 1987). The convulsant activity and toxicity of the chlorinated cyclodiene insecticides (including heptachlor and heptachlor epoxide) are closely related to their potency as inhibitors of the in vitro or in vivo binding of t-butylbicyclo-phosphorothionate (TBPS) to the picrotoxinin binding site of the GABA receptor (Cole and Casida 1986, Lawrence and Casida 1984).

4.3.2.4 Adrenotoxicity

Overview. Microscopic changes in the cortex of the adrenal gland were reported following intermediate oral exposure of mice to heptachlor. These changes were observed in one study but have not been confirmed.

Inhalation, human. No data describing adrenotoxicity in humans following inhalation exposure of any duration were found in the literature.

Inhalation, animal. No data describing adrenotoxicity in animals following inhalation exposure of any duration were found in the literature.

Oral, human. No data describing adrenotoxicity in humans following oral exposure of any duration were found in the literature.

Oral, animal. Ten female albino mice (strain not indicated) were given heptachlor (89% purity) at a dose level of 100 ppm (80-mg/kg/day) in the drinking water for up to 26 days. Six untreated females served as controls. The adrenal glands from all treated animals showed cortical atrophy. After 11 days of treatment, slight hypertrophy was reported in the zona glomerulosa; after 26 days of treatment, cortical cells showed hypertrophy, heavy lipid accumulation, granulation, and cell degeneration with extensive destruction and fibrosis (Akay et al. 1982). The validity of the 100-ppm dose level can be questioned since the solubility of heptachlor in water is 56 mg/L or 0.056 ppm (Worthing and Walker 1983), implying either that the dose level was incorrectly reported or that the heptachlor was present in suspension, thus bringing into question the uniformity of dosing. In addition, the 80-mg/kg/day dose level was calculated using the authors' stated water consumption rate of 20 cm^3/day/mouse (Akay et al. 1982); this is in excess of the usual 4 to 7 mL/day/mouse water intake reported by Arrington (1972).

Dermal, human. No data describing adrenotoxicity in humans following dermal exposure of any duration were found in the literature.

Dermal, animal. No data describing adrenotoxicity in animals following dermal exposure of any duration were found in the literature.

General discussion. The induction of adrenal toxicity by heptachlor, reported in a single study, has not been confirmed by other investigators. No information was found on the mechanism of action.

4.3.2.5 Renal toxicity

Overview. Kidney granulomas were reported in mice following intermediate oral exposure to heptachlor. This effect was observed in one study but has not been confirmed.

Inhalation, human. No data describing renal toxicity in humans following inhalation exposure of any duration were found in the literature.

Inhalation, animal. No data describing renal toxicity in animals following inhalation exposure of any duration were found in the literature.

Oral, human. No data describing renal toxicity in humans follow' oral exposure of any duration were found in the literature.

Oral, animal. Heptachlor (purity not indicated) was fed to groups of at least 10 female and 5 male O.ASA F15 mice for 10 weeks at concentrations of 50, 100, or 200 ppm in the diet. Controls received diet without heptachlor. The kidneys of the mice receiving 200 ppm heptachlor had granulomas containing mononuclear cells, histiocytes, and eosinophilic granulocytes (incidences not given). The LOAEL was 200 ppm (30 mg/kg/day), and the NOAEL was 100 ppm (15 mg/kg/day) (Akay and Alp 1981).

Dermal, human. No data describing renal toxicity in humans following dermal exposure of any duration were found in the literature.

Dermal, animal. No data describing renal toxicity in animals following dermal exposure of any duration were found in the literature.

General discussion. The induction of renal toxicity by heptachlor, reported in a single study, has not been confirmed by other investigators. No information was found on the mechanism of action.

4.3.2.6 Hematologic effects

Overview. Spleen fibrosis and increased numbers of leukocytes in the blood and spleen and erythrocytes in the spleen were reported following intermediate oral exposure of rodents to heptachlor. These effects were observed at the high dose; data were insufficient to determine if they were seen at lower doses.

Inhalation, human. No key studies describing hematologic effect. in humans following inhalation exposure to heptachlor were found in the literature.

Intermediate and chronic multichemical exposure of humans by inhalation of heptachlor, chlordane, and other chemicals has been associated with several hematologic effects (CAG 1986, EPA 1985a). These include aplastic anemia, hemolytic anemia, megaloblastic anemia, pancytopenia, and leukemia (Infante et al. 1978, EPA 1985a). Quantification of exposures was not reported. A separate case-control study suggests that there is no increased risk of aplastic anemia to people in pesticide-exposed occupations (Wang and Grufferman 1981). Again, quantification of exposure was not reported.

Inhalation, animal. No data describing hematologic effects in animals following inhalation exposure of any duration were found in the literature.

Oral, human. No key studies describing hematologic effects in humans following oral exposure to heptachlor were found in the literature. Information concerning exposure to undetermined concentrations of multiple chemicals is discussed under the inhalation route (Sect. 4.3.2.6).

Oral, animal (intermediate). Administration of heptachlor (96%) at a concentration of 1 mg/kg/day in the diet 5 days/week for a total of 28 doses induced a significant ($P < 0.05$) elevation (1.7-fold) of the wh blood cell count in rats (Enan et al. 1982).

Heptachlor (purity not indicated) was fed to groups of at least 10 female and 5 male O.ASA F_{15} mice for 10 weeks at concentrations of 50, 100, or 200 ppm in the diet. Controls received diet without heptachlor. Spleen fibrosis and increased numbers of red blood cells (RBCs) and eosinophilic white blood cells (WBCs) in the spleen were induced at 200 ppm; it was not clear whether increased spleen RBCs and WBCs were induced by the two lower-dose levels (Akay and Alp 1981).

Dermal, human. No key studies describing hematologic effects in humans following dermal exposure to heptachlor were found in the literature. Information concerning exposure to undetermined concentrations of multiple chemicals is discussed under the inhalation route (Sect. 4.3.2.6).

Dermal, animal. No data describing hematologic effects in animals following dermal exposure were found in the literature.

General discussion. In rodents, spleen fibrosis was induced by oral exposure to a high dose of heptachlor; the induction of hematologic effects was minimal at lower doses. No information was found on the mechanism of action.

4.3.3 Developmental Toxicity

4.3.3.1 Overview

Heptachlor epoxide has been found in tissues of stillborn infants. A study was conducted of women of child-bearing age who ingested heptachlor-contaminated milk; however, the resulting data were considered inadequate to establish a relationship between exposure and human developmental toxicity.

Cataracts and decreased postnatal survival were reported in the progeny of rats fed diets containing heptachlor. These effects are included as an indication of the kinds of developmental effects reported in the literature; data were insufficient to further evaluate these studies. No data were available for other routes of exposure in animals.

4.3.3.2 Inhalation

Human. No key studies describing human developmental toxicity following inhalation exposure to heptachlor were found in the literature. However, transplacental transfer of heptachlor epoxide and possible concentration in fetal tissues have been indicated. Heptachlor epoxide concentrations in fetal blood (0.9959 ppm) have been found to exceed concentrations in maternal blood (0.2798 ppm) (Polishuk et al. 1977b). In addition, heptachlor epoxide has been reported in stillborn infant brain, adrenal, lung, heart, liver, kidney, spleen, and adipose tissues (Curley et al. 1969). Data concerning route, duration, and extent of exposure were not provided.

Animal. No information was found.

4.3.3.3 Oral

Human. No key studies describing human developmental toxicity following oral exposure to heptachlor were found in the literature.

Le Marchand et al. (1986) reported no adverse effects on human fetal development following ingestion of milk containing heptachlor for 27 29 months among women of child-bearing age in Oahu, Hawaii. Milk fat levels of heptachlor measured in Hawaii during this time, which ranged from 0.12 to 5.00 ppm, were compared with EPA's "worst case" estimates on record of 0.10 to 1.20 ppm. Burch (1983, as cited in Le Marchand et al. 1986) reported no increase in fetal or neonatal deaths or incidence of low-birth-weight infants in this study cohort. Twenty-two of the 23 major congenital malformations evaluated were found to be decreased in the study population when compared with control cohorts. One 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, data for this malformation were not available prior to study initiation. It was therefore not possible to compare the incidence of this anomaly prior to exposure with the incidence during exposure. The inadequacies of this study were (1) milk fat residue levels of heptachlor were not reported for Oahu specifically, and (2) milk fat residue levels of heptachlor were not measured in the control population.

Transplacental transfer of heptachlor epoxide following exposure via an unidentified route is discussed under the inhalation route (Sect. 4.3.3.2).

Animal. Cataracts were observed in progeny of rats fed 6.9 mg/kg/day of heptachlor for 3 months prior to mating (FAO/WHO 1967, as cited in WHO 1984). Mestitzova (1967) reported that rats fed an "appl' dose" of 6 mg/kg heptachlor produced progeny in which increased mortality and cataracts were noted shortly after eye opening. This stu. was included as an indication of the kinds of developmental effects that have been observed; data were insufficient to further evaluate these studies.

Three unpublished three-generation studies with rats yielded inconsistent results. In one study (Witherup et al. 1955, as cited in WHO 1984), intermediate dose levels of heptachlor or heptachlor epoxide increased postnatal mortality, but the highest dose had no effect. In another study (Witherup et al. 1976b, as cited in WHO 1984), increased postnatal mortality in rats was seen at the highest dose only in the second generation. In a third study (Witherup et al. 1976a, as cited in WHO 1984), results for rats receiving a mixture of heptachlor and heptachlor epoxide were not considered by the investigators to be compound related.

Eisler (1968) reported two three-generation studies in rats. The animals (male and female) were fed either a mixture of heptachlor and its epoxide (ratio not specified) at 0.3, 3, or 7 ppm, or heptachlor at 0.3, 3, 6, or 10 ppm. Over 7,000 rats were examined in the two studies; no anatomical anomalies were observed. F_3 pups had no histological changes in their viscera. The mixture, fed during lactation, did not retard postnatal development. No other results were reported.

Male and female Sprague-Dawley rats (number not reported) were fed diets containing 5 ppm (0.25 mg/kg/day) heptachlor (purity not report for 60 days prior to and during gestation (Green 1970). Postnatal survival in the F_1 progeny was reduced. Only 19/122 offspring of trea

rats survived 21 days postpartum compared to 179/288 offspring of controls. The LOAEL was 0.25 mg/kg/day; a NOAEL was not established.

4.3.3.4 Dermal

Human. No key studies describing human developmental toxicity following dermal exposure to heptachlor were found in the literature. Transplacental transfer of heptachlor epoxide following exposure via an unidentified route is discussed under the inhalation route (Sect. 4.3.3.2).

Animal. No information was found.

4.3.3.5 General discussion

Although no direct evidence is available, it is possible that the ability of heptachlor to inhibit intercellular communication, as shown by in vitro evidence (see Sect. 4.5, Genotoxicity), may be involved in the mechanism of developmental toxicity.

4.3.4 Reproductive Toxicity

4.3.4.1 Overview

Heptachlor epoxide has been found in tissues of stillborn infants. A study was conducted of women of child-bearing age who ingested heptachlor-contaminated milk. The resulting data from both were considered inadequate to establish a relationship between exposure and human reproductive toxicity.

Male and female mice that received heptachlor in the diet for 10 weeks were unable to produce a new generation. Decreased pregnancy rates were reported following oral administration of heptachlor to male and female rats for two generations. In male and female rats fed heptachlor, heptachlor epoxide, or a mixture of the two for three generations, the number of resorbed fetuses increased and fertility decreased with succeeding generations. No reproductive toxicity data were available for other routes of exposure for animals.

4.3.4.2 Inhalation

Human. No key studies describing adverse reproductive effects in humans following inhalation exposure to heptachlor were found in the literature. Wassermann et al. (1982) detected significantly higher levels of heptachlor epoxide in the serum of a group of women with premature delivery than in the serum of a control group with normal delivery. However, serum levels of eight of the ten organochlorine pesticides for which analytical data were obtained were all significantly higher in the premature delivery group; route, duration, and level of exposure were 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 (Curley et al. 1969).

Animal. No information was found.

4.3.4.3 Oral

Human. No key studies describing adverse reproductive effects in humans following oral exposure to heptachlor were found in the literature. Burch (1983, as cited in Le Marchand et al. 1986) reported no adverse effects on human reproduction (no decrease in fertility, no increase in fetal or neonatal deaths) among women of child-bearing age following ingestion of heptachlor-containing milk for 27 to 29 months. It was not established, however, that the levels of heptachlor ingested by the "exposed" group were higher than the levels ingested by the control group. Other information concerning possible reproductive effects from heptachlor exposure via unspecified routes are presented under the inhalation route (Sect. 4.3.4.2).

Animal. Epstein et al. (1972) administered heptachlor or its epoxide to male mice that were then bred to untreated females; preimplantation losses and resorptions were within control limits.

Male and female mice that received 50, 100, or 200 ppm (7.5, 15, or 30 mg/kg/day, respectively) heptachlor in the diet for 10 weeks were unable to produce a new generation (Akay and Alp 1981). No microscopic alterations were found in ovaries or testes. This study was included as an indication of the kinds of reproductive effects that have been observed. Failure of mice to produce offspring following dosing with heptachlor has not been confirmed.

In two three-generation studies with rats (male and female) fed diets containing either heptachlor, heptachlor epoxide, or a mixture the two, the number of resorbed fetuses increased and fertility decreased with succeeding generations, in some cases to zero (Cerey and Ruttkay-Nedecka 1971, Ruttkay-Nedecka et al. 1972). The results reported by these authors have not been confirmed.

In a dominant lethal assay, 8 male CD-1 mice received single oral doses of 7.5 or 15 mg/kg heptachlor/heptachlor epoxide (25%:75%) and were bred with three untreated females each week for 6 weeks (Arnold et al. 1977). No adverse effects on reproductive capacity were reported. The NOAEL was 15 mg/kg; a LOAEL was not established.

Male and female Sprague-Dawley rats (number not reported) were fed a diet containing 5 ppm (0.25 mg/kg/day) heptachlor (purity not reported) for 60 days and then during gestation (Green 1970). Females killed on gestation day 21 showed no significant reproductive effects. In a second phase of the study, however, rats receiving 5 ppm (0.25 mg/kg/day) for two generations showed decreased pregnancy rates. In the first generation, 18/25 heptachlor-treated females (compared to 30/32 controls) became pregnant. In the second generation, none of 12 females receiving heptachlor became pregnant. The LOAEL was 0.25 mg/kg/day; a NOAEL was not established.

4.3.4.4 Dermal

Human. No key studies describing adverse reproductive effects in humans following dermal exposure to heptachlor were found in the literature. Information concerning possible reproductive effects fro.

heptachlor exposure via unspecified routes is presented under the inhalation route (Sect. 4.3.4.2).

Animal. No information was found.

4.3.4.5 General discussion

When male mice were fed diets containing heptachlor or heptachlor epoxide in a dominant lethal study, no effects on reproduction were noted. On the other hand, when both sexes of mice or rats were fed diets containing either heptachlor or heptachlor epoxide in multigeneration studies, resorptions were increased relative to controls and fertility was markedly decreased, in some instances to zero. These results seem to indicate that heptachlor or heptachlor epoxide has the greatest effect upon the female reproductive tract and/or upon the fetuses residing therein. No studies were found where only female rodents were dosed.

4.3.5 Genotoxicity

4.3.5.1 Overview

Heptachlor and heptachlor epoxide, with or without metabolic activation, tested negative in well-conducted microbial gene mutation assays, and heptachlor was not mutagenic in an epithelial cell line (ARL) derived from rat liver. Heptachlor, with metabolic activation, was clastogenic in Chinese hamster ovary (CHO) cells, but neither heptachlor nor heptachlor epoxide induced a dominant lethal effect in male mouse germinal cells. Heptachlor (with or without metabolic activation) was positive in an in vitro CHO cell SCE assay. The results of unscheduled DNA synthesis (UDS) assays with heptachlor were negative (primary hepatocytes from mouse, rat, or hamster) except when preinitiated cells (virally transformed human cell line) were used as the target. Heptachlor inhibited metabolic cooperation in Chinese hamster lung cells and rat liver epithelial cells.

4.3.5.2 Review of data

Tables 4.5 and 4.6 summarize the findings of relevant genetic toxicology assays with heptachlor or heptachlor epoxide. Only those studies considered acceptable by today's criteria or those reporting a positive response are included.

These studies are categorized into gene mutation (Category 1), chromosome aberrations (Category 2), other mutagenic mechanisms (Category 3), and epigenetic mechanisms (Category 4).

Gene mutation (Category 1). Heptachlor and heptachlor epoxide, with or without activation, tested negative in well-conducted gene mutation assays. Inconclusive evidence for a mutagenic effect (single dose only, weak response, questionable control values) was reported for heptachlor in two strains of *Salmonella* (TA98 and TA100) following activation with S-9 fractions from Arochlor 1254-induced rats and one strain (TA1535) following activation with a 1S fraction from maize (*Zea mays* inbred B37, Gentile et al. 1982).

Table 4.5. Genotoxicity of heptachlor and heptachlor epoxide (in vitro)

End point	Compound	Species	Result with activation/ without activation	References
Gene mutation	Heptachlor	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1536, TA1537, TA1538	−/−	Marshall et al 1976, NTP 1987
	Heptachlor (technical grade)	*S. typhimurium* strains TA98, TA100, TA1535	+/−	Gentile et al 1982
	Heptachlor epoxide	*S typhimurium* strains TA98, TA100, TA1535, TA1536, TA1537, TA1538	−/−	Marshall et al 1976, Glatt et al. 1983
	Heptachlor (technical grade)	*Zea mays*	+	Gentile et al. 1982
	Heptachlor	Adult rat liver (ARL) epithelial cells	−/NA[a]	Telang et al. 1982
Chromosomal aberrations (somatic cells)	Heptachlor	Chinese hamster ovary (CHO) cells	+/−	NTP 1987
Sister chromatid exchange	Heptachlor	CHO cells	+/+	NTP 1987
Unscheduled DNA synthesis	Heptachlor	Mouse, rat, hamster primary hepatocytes	−	Maslansky and Williams 1981, Probst et al 1981
	Heptachlor	SV-40 transformed human fibroblasts (VA-4)	+/− (significant at 2 doses; $P < 0.05$	Ahmed et al 1977
	Heptachlor epoxide	SV-40 transformed human fibroblasts (VA-4)	+/− (significant at 3 doses; $P < 0.05$	Ahmed et al 1977
Gap junction inhibition	Heptachlor	Chinese hamster V79 ($6TG^S$ and $6TG^R$)	+ (Dose related)	Kurata et al. 1982
	Heptachlor	ARL ($HGPRT^+$ and $HGPRT^-$)	+ (Dose related)	Telang et al 1982

[a]NA = Not applicable.

Table 4.6. Genotoxicity of heptachlor and heptachlor epoxide (in vivo)

End point	Compound	Species	Route	Result	References
Dominant lethal assay	Heptachlor	Swiss mice	Oral	–	Epstein et al. 1972
			ip[a]	–	
	Heptachlor/heptachlor epoxide (25% 75%)	CD-1 mice	Oral	–	Arnold et al. 1977
			ip	–	
	Heptachlor epoxide	Swiss mice	Oral	–	Epstein et al 1972
			ip	–	

[a] ip = intraperitoneal.

Qualitative results presented by Gentile et al. (1982) indicated that commercial-grade heptachlor caused a significant increase ($P < 0.05$) in back mutations in *Zea mays*, leading to the conclusion that heptachlor is presumptively mutagenic to corn.

Telang et al. (1982) demonstrated that heptachlor, assayed up to a cytotoxic dose was not mutagenic in a mammalian liver cell system (rat liver epithelial cells obtained from F344 rats, ARL) derived from the only organ in which heptachlor induces tumors in vivo.

Structural chromosome aberrations (Category 2). The in vitro CHO cell assay performed by NTP (1987) indicated that S-9-activated heptachlor was clastogenic. No in vivo somatic cell assay has been published. The dominant lethal assay results presented in Table 4.2 show that neither heptachlor nor heptachlor epoxide is clastogenic in male germinal cells (Epstein et al. 1972, Arnold et al. 1977).

Other mutagenic mechanisms (Category 3). NTP (1987) reported nonactivated and S-9-activated heptachlor increased the frequency of sister chromatid exchange in CHO cells. Heptachlor did not induce UDS in primary hepatocytes from mouse, rat, or hamster (Maslansky and Williams 1981, Probst et al. 1981). In contrast, both heptachlor and heptachlor epoxide induced significant dose-related increased UDS in a virally transformed human cell line (Ahmed et al. 1977). These assays were seriously compromised by technical deficiencies and have not been confirmed.

Epigenetic effects (Category 4). Heptachlor induced inhibition of gap junctional intercellular communication (metabolic cooperation) between Chinese hamster V79 6-thioguanine-sensitive ($6TG^S$) cells and 6-thioguanine-resistant ($6TG^r$) cells (Kurata et al. 1982). The effect was dose related (2.5 to 10 mg/mL) and included a cytotoxic level. Telang et al. (1982) evaluated heptachlor at the same end point but used a different mammalian cell line--rat liver epithelial cells. Heptachlor, assayed up to a cytotoxic dose, was positive, and the effect was clearly dose related. Of note was the demonstration of assay specificity to detect only agents which interfere with cell-to-cell communication (epigenetic) in contrast to chemicals which induce a genotoxic effect. Four doses of the lipophilic procarcinogen/promutagen benzo[a]pyrene, up to a cytotoxic dose, caused no interference with cell-to-cell communication. The findings of Kurata et al. and Telang et al. are of singular importance because they demonstrated that heptachlor interfered with gap junction-mediated communication between contiguous cells in two phylogenetically different mammalian cell lines. Moreover, this constitutes independent confirmation of an alternative mechanism of action for heptachlor.

General discussion. No compelling evidence of a mutagenic effect in relevant biological systems was uncovered. Clastogenic activity in mammalian somatic cells (in vitro) was observed but should be independently verified before reaching a definitive conclusion. There was no evidence of a clastogenic effect in male mouse germinal cells. The results of DNA repair assays have been negative except for one assay using SV-40 transformed human cells; however, this study is considered to be equivocal. A single SCE study reported positive results, but it requires confirmation.

4.3.6 Carcinogenicity

4.3.6.1 Overview

Chronic oral exposure to heptachlor increased the incidence of liver carcinomas in C3H and B6C3F1 mice. Chronic oral exposure to heptachlor epoxide increased the incidence of liver carcinomas in CFN rats and C3H, CD-1, and B6C3F1 mice.

Available epidemiological studies on heptachlor are considered to be inadequate to establish a clear qualitative or quantitative assessment of the relationship between heptachlor exposure and the risk of developing cancer in humans. Summaries and reviews of the animal and epidemiological studies can be found in CAG (1986), Reuber (1978), and WHO (1984).

Heptachlor/heptachlor epoxide is classified as a probable human carcinogen, Group B2, under the EPA's guidelines for carcinogen risk assessment. The EPA CAG assessment of heptachlor and heptachlor epoxide had not undergone peer review at the time this profile was prepared.

4.3.6.2 Inhalation

Human. No key studies describing carcinogenic effects in humans following exposure to heptachlor by inhalation were found in the literature.

Evidence has shown that inhalation and skin absorption are the principal routes of heptachlor exposure for the industrial worker. However, secondary exposures for these individuals may occur through ingestion (NCI 1977).

In a study of 16,126 pesticide applicators and termite control operators principally exposed to chlordane and heptachlor, cancer of the skin and bladder was increased (but $P > 0.05$) in both groups (Wang and MacMahon 1979a). Apparent increases were noted in cancer of the lung among pesticide applicators only. This study provides inadequate evidence of the carcinogenicity of heptachlor because of methodological deficiencies. Quantitative exposure (concentration and duration) data were not reported; multiple chemical exposures were studied; 42 deaths were classified without death certificates; no individual follow-up was conducted; and there was no control of confounding factors. A follow-up of this study in 1982 indicated that cancer of the bladder was slightly increased among termite control operators, whereas cancers of the lung and skin were slightly increased among pesticide applicators; these increases were not significant (WHO 1984). Termite control operators were assumed to have had a greater exposure to heptachlor and chlordane.

In a study of 1,403 workers engaged in the manufacture of chlordane, heptachlor, and endrin, lung cancer incidence appeared to be increased for the entire study cohort, but significantly ($P < 0.01$) increased for workers less than 35 years of age at occupation initiation and less than 50 years of age at the time of observation (Wang and MacMahon 1979b, CAG 1986). Twelve mortalities from lung cancer were observed. One death from liver cancer was reported. The increased incidences of skin and bladder cancer among pesticide applicators of the former study (Wang and MacMahon 1979a) were not reflected in this study

cohort. Methodological deficiencies included a lack of quantitative exposure data, mixed exposures, small cohort size, and the inclusion of workers with little potential for exposure (office workers). This latter factor may have underestimated the cancer incidence of the manufacturing workers.

Ditraglia et al. (1981) conducted a study of 2,100 manufacturing workers from four pesticide plants, one of which produced heptachlor, endrin, and other chemical products. At this plant, no statistically significant increases were observed, although the incidences of intestinal, bladder, urinary, and respiratory cancer appeared elevated. The lack of quantitative exposure data, mixed exposures, small cohort size, no adjustment of confounding variables, and inclusion of minimally exposed workers in the study cohort limit the usefulness of these data (CAG 1986).

In a study of 783 workers engaged in the manufacture of heptachlor and chlordane in 1976-1977, and a subsequent follow-up in 1980-1981, no increase in cancer incidence or mortality from cancer was reported (Velsicol 1981). An industrial hygiene survey indicated a heptachlor concentration in the plant atmosphere of 0.025 to 0.202 mg/m^3 (Netzel 1981). As in previous studies, the lack of individual quantitative exposure data for the study cohort, mixed exposures, limited follow-up, and no adjustment of confounding variables limit the usefulness of these data.

In a study of 3,496 chemical workers involved in the manufacture of agricultural chemical products including heptachlor, no evidence of increased cancer risk was found (Environmental Health Associates 1983a, 1983b).

Animal. No data describing carcinogenicity in animals following inhalation exposure of any duration were found in the literature.

4.3.6.3 Oral

Human. Epidemiological studies of carcinogenicity from occupational exposure to mixtures of chlordane, heptachlor, and other chemicals are described under inhalation (Sect. 4.3.6.2).

Animal. Heptachlor/heptachlor epoxide increased the incidence of liver carcinomas in CFN rats and C3H, CD-1, and B6C3F1 mice. EPA's CAG (CAG 1986) presented summaries of the nine data sets (Tables 4.7-4.15) that showed significant increases in the incidence of hepatocellular carcinomas in treated groups compared with controls.

4.3.6.4 Dermal

Human. Epidemiological studies of carcinogenicity from occupational exposure to mixtures of chlordane, heptachlor, and other chemicals are described under inhalation (Sect. 4.3.6.2).

Animal. No data describing carcinogenicity in animals following dermal exposure of any duration were found in the literature.

Table 4.7. Cancer data sheet for derivation of potency of heptachlor from hepatocellular carcinomas in female mice—I

Compound	Heptachlor
Species, strain, sex	Mouse, C3H, female
Body weight	0.030 kg (assumed)
Length of experiment	24 months
Length of exposure	24 months
Tumor site and type	Liver carcinoma
Route, vehicle	Oral, diet
Human potency (q_1^*)	14.9 per mg/kg/day

Experimental animal dose (ppm)	Average animal dose (mg/kg/day)	Equivalent human dose (mg/kg/day)	Tumor incidence (No. responding/ No. examined)
0	0.00	0.000	2/54
10	1.43[a]	0.108	57/78

[a]Lowest exposure level associated with increased tumors in experimental animals.

Source: Davis 1965, as diagnosed by Reuber 1977b. Extracted from CAG 1986.

Table 4.8. Cancer data sheet for derivation of potency of heptachlor from hepatocellular carcinomas in male mice—I

Compound	Heptachlor
Species, strain, sex	Mouse, C3H, male
Body weight	0.030 kg (assumed)
Length of experiment	24 months
Length of exposure	24 months
Tumor site and type	Liver carcinoma
Route, vehicle	Oral, diet
Human potency (q_1^*)	12.4 per mg/kg/day

Experimental animal dose (ppm)	Average animal dose (mg/kg/day)	Equivalent human dose (mg/kg/day)	Tumor incidence (No. responding/ No. examined)
0	0.00	0.000	22/78
10	1.43[a]	0.108	64/87

[a]Lowest exposure level associated with increased tumors in experimental animals.

Source: Davis 1965, as diagnosed by Reuber 1977b. Extracted from CAG 1986.

Table 4.9. Cancer data sheet for derivation of potency of heptachlor from hepatocellular carcinomas in female mice—II

Compound	Technical-grade heptachlor
Species, strain, sex	Mouse, $B6C3F_1$, male
Body weight	0.030 kg (assumed)
Length of experiment	90 months
Length of exposure	80 months
Tumor site and type	Liver, carcinoma
Route, vehicle	Oral, diet
Human potency (q_1^*)	0.83 per mg/kg/day

Experimental animal dose (ppm)	Average animal dose (mg/kg/day)	Equivalent human dose (mg/kg/day)	Tumor incidence (No. responding/ No. examined)
0	0.00	0.000	2/10
18.0	2.34[a]	0.18	30/42

[a]Lowest exposure level associated with increased tumors in experimental animals.

Source: NCI 1977b. Extracted from CAG 1986.

Table 4.10. Cancer data sheet for derivation of potency of heptachlor from hepatocellular carcinomas in male mice—II

Compound	Technical-grade heptachlor
Species, strain, sex	Mouse, $B6C3F_1$, male
Body weight	0.030 kg (assumed)
Length of experiment	90 months
Length of exposure	80 months
Tumor site and type	Liver, carcinoma
Route, vehicle	Oral, diet
Human potency (q_1^*)	2.79 per mg/kg/day

Experimental animal dose (ppm)	Average animal dose (mg/kg/day)	Equivalent human dose (mg/kg/day)	Tumor incidence (No. responding/ No. examined)
0	0	0	5/19
6.1	0.79	0.063	11/46
13.8	1.79[a]	0.14	34/47

[a]Lowest exposure level associated with increased tumors in experimental animals.

Source: NCI 1977b. Extracted from CAG 1986.

Table 4.11. Cancer data sheet for derivation of potency of heptachlor epoxide from hepatocellular carcinomas in female mice

Compound	Heptachlor epoxide
Species, strain, sex	Mouse, C3H, female
Body weight	0.030 kg (assumed)
Length of experiment	24 months
Length of exposure	24 months
Tumor site and type	Liver carcinoma
Route, vehicle	Oral, diet
Human potency (q_1^*)	36.2 per mg/kg/day

Experimental animal dose (ppm)	Average animal dose (mg/kg/day)	Equivalent human dose (mg/kg/day)	Tumor incidence (No. responding/ No. examined)
0	0.00	0.000	2/54
10.0	1.43[a]	0.108	77/81

[a]Lowest exposure level associated with increased tumors in experimental animals.

Source: Davis 1965, as diagnosed by Reuber 1977b. Extracted from CAG 1986.

Table 4.12. Cancer data sheet for derivation of potency of heptachlor epoxide from hepatocellular carcinomas in male mice

Compound	Heptachlor epoxide
Species, strain, sex	Mouse, C3H, male
Body weight	0.030 kg (assumed)
Length of experiment	24 months
Length of exposure	24 months
Tumor site and type	Liver carcinoma
Route, vehicle	Oral, diet
Human potency (q_1^*)	27.7 per mg/kg/day

Experimental animal dose (ppm)	Average animal dose (mg/kg/day)	Equivalent human dose (mg/kg/day)	Tumor incidence (No. responding/ No. examined)
0	0.00	0.000	22/78
10	1.43[a]	0.108	73/79

[a]Lowest exposure level associated with increased tumors in experimental animals.

Source: Davis 1965, as diagnosed by Reuber 1977b. Extracted from CAG 1986.

Table 4.13. Cancer data sheet for derivation of potency of heptachlor epoxide from hepatic carcinomas in female mice—I

Compound	25.75 mixture of heptachlor/heptachlor epoxide
Species, strain, sex	Mouse, CD-1, female
Body weight	0.030 kg (assumed)
Length of experiment	19 months
Length of exposure	18 months
Tumor site and type	Liver, carcinoma
Route, vehicle	Oral, diet
Human potency (q_1^*)	1.04 per mg/kg/day

Experimental animal dose (ppm)	Average animal dose (mg/kg/day)	Equivalent human dose (mg/kg/day)	Tumor incidence (No. responding/ No. examined)
0	0	0	6/76
1	0.13	0.01	1/70
5	0.65	0 052	6/65
10	1.30[a]	0 10	30/57

[a]Lowest exposure level associated with increased tumors in experimental animals.

Source: IRDC 1973b, as reevaluated by Reuber. Extracted from CAG 1986.

Table 4.14. Cancer data sheet for derivation of potency of heptachlor epoxide from hepatic carcinomas in male mice

Compound	25.75 mixture of heptachlor/heptachlor epoxide
Species, strain, sex	Mouse, CD-1, male
Body weight	0.030 kg (assumed)
Length of experiment	19 months
Length of exposure	18 months
Tumor site and type	Liver, carcinoma
Route, vehicle	Oral, diet
Human potency (q_1^*)	6.48 per mg/kg/day

Experimental animal dose (ppm)	Average animal dose (mg/kg/day)	Equivalent human dose (mg/kg/day)	Tumor incidence (No. responding/ No. examined)
0	0	0	0/62
1	0.13	0.010	2/68
5	0.65[a]	0.052	18/68
10	1.30	0.10	52/80

[a]Lowest exposure level associated with increased tumors in experimental animals.

Source: IRDC 1973b, as reevaluated by Reuber. Extracted from CAG 1986.

Table 4.15. Cancer data sheet for derivation of potency of heptachlor epoxide from hepatic carcinomas in female mice—II

Compound	Heptachlor epoxide
Species, strain, sex	Rat, CFN, female
Body weight	0.350 kg (assumed)
Length of experiment	108 weeks
Length of exposure	108 weeks
Tumor site and type	Liver, carcinoma
Route, vehicle	Oral, diet
Human potency (q_1^*)	5.76 per mg/kg/day

Experimental animal dose (ppm)	Average animal dose (mg/kg/day)	Equivalent human dose (mg/kg/day)	Tumor incidence (No. responding/ No. examined)
0	0	0	0/17
0.5	0.025	0.0043	3/22
2.5	0.125	0.021	3/18
5.0	0.250[a]	0.043	7/22
7.5	0.375	0.064	3/21
10.0	0.500	0.085	5/19

[a]Lowest exposure level associated with increased tumors in experimental animals.

Source: Witherup et al. 1959, as reevaluated by Reuber. Extracted from CAG 1986.

4.3.6.5 General discussion

Low concentrations of heptachlor have been shown to inhibit metabolic cooperation in Chinese hamster cells (Kurata et al. 1982) and rat liver cells (Telang et al. 1982) in vitro, a property common to many known promoters. It is postulated, therefore, that heptachlor may act through an epigenetic rather than a genotoxic mechanism. Data exist that demonstrate a correlation between interference with metabolic cooperation and tumor promotion. The assumption that heptachlor may possess promoter activity is further supported by the action of the test material on preinitiated virally transformed cells and by the evidence from in vivo studies indicating that heptachlor is a promoter of hepatocarcinogenesis in mice (Williams and Numoto 1984). The multistage concept of carcinogenesis was first formalized by Friedewald and Rous (1944), who coined the now classic terms "initiation" and "promotion" to denote, respectively (1) the production of potentially tumorigenic cells by limited exposure to a carcinogen, and (2) the completion of the neoplastic transformation as the result of subsequent treatment with appropriate agents that are not intrinsically carcinogenic. Complete carcinogens are considered to be those compounds that are capable of both initiation and promotion.

4.4 INTERACTIONS WITH OTHER CHEMICALS

Williams and Numoto (1984) reported that heptachlor (purity 97.6%), when administered in the diet at 5 or 10 ppm for 25 weeks, promoted the development of hepatocellular foci and hepatocellular neoplasms in male B6C3F1 mice previously initiated with 20 ppm diethylnitrosamine given the drinking water for 14 weeks.

5. MANUFACTURE, IMPORT, USE, AND DISPOSAL

5.1 OVERVIEW

One company manufactured heptachlor in the United States; however, as of August 1987, this company voluntarily stopped selling chlordane and heptachlor. No information was found concerning the importation of heptachlor. Heptachlor epoxide is not produced commercially in the United States; no importation data were found. Methods of disposal include high-temperature incineration and burial in a hazardous waste landfill.

5.2 PRODUCTION

5.2.1 Manufacturing Process

Heptachlor is prepared 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 h. The chlordene starting material is prepared by the Diels-Alder condensation of hexachlorocyclopentadiene with cyclopentadiene (Sittig 1980).

Heptachlor epoxide is an oxidation product of heptachlor; it is not produced commercially in the United States (IARC 1979).

5.2.2 Volume

Heptachlor and heptachlor epoxide were not reported in the public portion of the Toxic Substances Control Act Chemical Substance Inventory (TSCA Inventory) (EPA 1987a). Since the chemicals are used solely as pesticides, reporting in the TSCA Inventory is not required.

The *Chemical Economics Handbook* (CEH) reported the production of 2.0 million pounds of heptachlor for the year 1974, 1.3 million pounds for 1978, 0.4 million pounds for 1980, and 0.1 million pounds for 1982 (CEH 1984). Sales of chlordane and heptachlor in the United States were voluntarily stopped by the sole U.S. producer in August 1987 (The Washington Post 1987).

The U.S. International Trade Commission (USITC) did not report the domestic production volume of heptachlor separately for the years 1981 through 1985 (USITC 1982a, 1983a, 1984a, 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.

5.2.3 Producers

The following company was listed as a producer of heptachlor in the United States:

Farley Northwest Industries, Inc., subsidiary Velsicol Chemical Corp., Memphis, Tennessee	(SRI International 1986, USITC 1986)

5.3 IMPORT

The USITC did not report separate import data for heptachlor for the years 1981, 1982, and 1983 (USITC 1982b, 1983b, 1984b). The U.S. Department of Commerce did not report separate importation data for heptachlor for the years 1983, 1984, and 1985 (USDOC 1984-1986).

No information was found on the importation of heptachlor epoxide.

5.4 USE

The only registered uses for heptachlor in the United States are for subterranean termite control by methods other than pressure rodding (EPA 1987d, 1987e), the dipping of roots or tops of nonfood plants for insect control (Windholz 1983), and treatment of power and telephone pedestals for fire ant control (EPA 1986f).

5.5 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 s for primary combustion and at 3,200°F for 1.0 s for secondary combustion, with adequate scrubbing of incinerator exhaust and disposal of ash (Sittig 1985).

6. ENVIRONMENTAL FATE

6.1 OVERVIEW

Heptachlor and heptachlor epoxide are persistent in the environment, with half-lives in soil of 2 and 14 years, respectively. Heptachlor epoxide has been found in food crops grown in soils last treated with heptachlor 15 years before. Both heptachlor and heptachlor epoxide have been shown to bioconcentrate in aquatic organisms, especially in fish and mollusks.

6.2 RELEASES TO THE ENVIRONMENT

Information on point source and nonpoint source releases of heptachlor and heptachlor epoxide was not found. However, based on the registered use of heptachlor as an insecticide for non-pressure-injected subterranean termite control and for the dipping of roots and tops of ornamental (nonfood) plants, it may be assumed that heptachlor could be released to the environment.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Release of heptachlor to the environment from its use as an insecticide or from disposal will result in its transport into surface waters and/or soils. A computer fate model, developed using heptachlor released to water, predicts that it will partition from water into sediment and then into aquatic biota (Simon and Parker 1984).

The evidence suggests that heptachlor may be found in the atmosphere. Taylor et al. (1976, as cited in WHO 1984) found that 90% of the heptachlor applied to moist, bare soil volatilized within 2 to 3 days following its application.

While transport through the water column is likely for heptachlor (Simon and Parker 1984), its penetration into groundwater will probably be insignificant (Tzapko et al. 1967, as cited in WHO 1984).

Information on transport and compartmentalization of heptachlor epoxide was not found.

6.3.2 Transformation and Degradation

The degradation of heptachlor and heptachlor epoxide has been well studied, as reviewed by WHO (1984) and EPA (1985a). Heptachlor may be subject to oxidation and biodegradation in the environment (EPA 1985a, Simon and Parker 1984, Lichtenstein et al. 1970, Eichelberger and Lichtenberg 1971, Petrasak et al. 1983).

Heptachlor epoxide is not very susceptible to biodegradation, photolysis, oxidation, or hydrolysis in the environment (Mabey et al. 1981, as cited in EPA 1985a; Callahan et al. 1979, as cited in EPA 1985a). The resistance to degradation may account for an estimated half-life of 2 years in soil and the persistence of heptachlor epoxide in a field for up to 14 years after the last application of heptachlor (Vrochinsky 1980, as cited in WHO 1984).

Lichtenstein et al. (1970) found that potatoes grown in soil that had been treated with heptachlor at 5 lb/5-in. acre for 5 consecutive years contained 0.002 ppm heptachlor, 0.054 ppm heptachlor epoxide, 0.015 ppm γ-chlordane, 0.004 ppm α-chlordane, and 0.002 ppm nonachlor 5 years after the last heptachlor application.

Soybeans, grown in soil treated 15 years previously with heptachlor at 224 kg/ha, contained no heptachlor residues but did have residues of heptachlor epoxide ranging from 0.067 to 0.237 mg/kg (Nash and Harris 1973, as cited in WHO 1984). Talekar et al. (1983) reported the persistence of heptachlor epoxide at a level of 0.06 ppm in the soil throughout a 1-year observation period following application of a total of 48 kg/ha of heptachlor over a 2-year period.

6.3.3 Bioconcentration

Geyer et al. (1982) found that exposure of the mussel (*Mytilus edulis*) for 4 days to heptachlor epoxide at 1.95 mg/L resulted in a bioconcentration factor (BCF) of 1,700 (log BCF = 3.23). Hawker and Connell (1986) determined the log BCFs for heptachlor and heptachlor epoxide in several mollusks: heptachlor had a log BCF of 3.41 for the soft clam (*Mya arenaria*) and 3.93 for the oyster (*Crassotrea virginica*); heptachlor epoxide had a log BCF of 3.23 for the mussel (*Mytilus edulis*) and 2.93 for the oyster.

Bioconcentration factors have also been determined for fish: in the pinfish (*Lagodon rhomboides*) the log BCF was 3.71 for heptachlor and 3.46 for heptachlor epoxide, and in the sheepshead minnow (*Cyprinodon variegatus*) the log BCFs were 4.33 and 3.65 for heptachlor and heptachlor epoxide, respectively (Zaroogian et al. 1985).

7. POTENTIAL FOR HUMAN EXPOSURE

7.1 OVERVIEW

Data concerning potential human exposure to heptachlor and heptachlor epoxide are from the era when heptachlor was actively used as an agricultural insecticide. More recent data were not available The exposure data, especially exposure from residues in foods, combined with environmental persistence data indicate that human exposure to heptachlor or heptachlor epoxide could occur if food crops were inadvertently grown in a contaminated site. Since the discontinuation of the use of heptachlor on agricultural products, exposure is more likely to occur from the inhalation of vapors or direct contact with residual heptachlor from improper residential pesticide application and the accidental contamination of dairy and meat products.

7.2 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

7.2.1 Air

Little data are available on concentrations of heptachlor and heptachlor epoxide in air after the use of heptachlor as an agricultural pesticide was restricted. However, during its period of maximum usage, heptachlor was found in ambient air in the United States at a mean concentration of approximately 0.5 ng/m^3 (Peirano 1980, as cited in WHO 1984). A survey of 16 states between 1970 and 1972 detected heptachlor in 42% of 2,479 air samples with a mean concentration of 1.0 ng/m^3 in positive samples; the maximum concentration found was 27.8 ng/m^3 in Tennessee (Kutz et al. 1976, as cited in EPA 1985a).

Three houses in North Carolina were treated with a termiticide containing both chlordane (0.5%) and heptachlor (0.25%). Immediately after treatment, the average atmospheric heptachlor level was 1.41 ± 0.64 $\mu g/m^3$. At 12 months posttreatment, the heptachlor level in the air was 1.00 ± 0.70 $\mu g/m^3$ (Wright and Leidy 1982).

An air monitoring study in houses treated with heptachlor has been conducted; however, at the time this report was prepared, data were not available for release to the public by EPA (Jaquith 1987).

7.2.2 Water

Heptachlor and heptachlor epoxide have been found in ambient waters at concentrations ranging from 0.001 $\mu g/L$ to 0.5 $\mu g/L$ (IJC 1983, STORET 1987). A range of drinking water concentrations for heptachlor, based on regional surveys conducted in the 1970s, was reported as 0.005 to 0.6 $\mu g/L$ (EPA 1985a).

7.2.3 Soil

During the years that heptachlor was used as an agricultural pesticide, substantial levels of it and of heptachlor epoxide were present in soil, particularly in soil used for crops. In 1969, heptachlor was detected in 68 of 1,729 cropland soils at levels of 0.01 to 0.97 mg/kg; however, it was not detected in noncrop soils (Wiersma et al. 1972a, as cited in IARC 1979). In the same survey, heptachlor epoxide was found in 139 of the 1,729 cropland soil samples at concentrations of 0.01 to 1.08 mg/kg and in 2 of 199 noncropland soil samples at 0.01 mg/kg. In a study of corn belt region soils of the United States, heptachlor was found in 5.7% of samples, and heptachlor epoxide was found in 8% of samples at concentrations of 0.01 to 0.84 mg/kg and 0.01 to 0.31 mg/kg, respectively (Carey et al. 1973, as cited in IARC 1979). Heptachlor has also been detected in urban environments; in 1969, the soil of seven of eight cities surveyed had heptachlor levels of 0.01 to 0.53 mg/kg (Wiersma et al. 1972b, as cited in IARC 1979).

Heptachlor and heptachlor epoxide have been detected in sediments from streams and rivers at concentrations ranging from 0.1 µg/kg to 100 µg/kg (STORET 1987).

Heptachlor has been identified in soils (up to 38 µg/L) and sediments (up to 4,800 µg/L) from Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) hazardous waste sites (EPA 1985b).

7.2.4 Other

Heptachlor and heptachlor epoxide have been identified in foodstuffs, although the data are almost exclusively from studies conducted prior to 1980 when heptachlor was still being used as an agricultural pesticide. Both IARC (1979) and WHO (1984) present reviews of heptachlor and heptachlor epoxide levels in foods. The Total Diet Study, conducted by the Food and Drug Administration (FDA) between 1972 and 1973, found no heptachlor in any of the foods tested (Johnson and Manske 1976, as cited in IARC 1979). A study of 20 U.S. cities two years later (1974-75) found heptachlor epoxide in 3 of 12 food classes examined at levels of 0.6 to 3.0 µg/kg (Peirano 1980, as cited in WHO 1984). Market basket surveys in 30 cities found similar results: heptachlor epoxide was present at up to 2 µg/kg in 21 samples of dairy products and in 24 samples of meat, fish, and poultry; 1 sample of potatoes had trace levels of the compound (Johnson and Manske 1976, as cited in IARC 1979).

7.3 OCCUPATIONAL EXPOSURES

An industrial hygiene survey conducted at a plant manufacturing heptachlor detected the compound at levels of 0.025 to 0.202 mg/m^3 in workplace air; breathing-zone samples were not taken (Netzel 1981).

Because use of heptachlor is limited to underground termite and fire ant control and ornamental plant applications, much of the widespread occupational exposure to the compound has been eliminated. The *Quarterly Hazard Summary Report* (NIOSH 1980) estimated 566,911

workers in 119 occupations were exposed to heptachlor in generic formulations based on a 1972 to 1974 survey. Since that time, heptachlor use has been drastically reduced. Given the current restrictions on heptachlor use, occupational exposure can still be expected for exterminators, ornamental plant pesticide applicators, and waste-site cleanup personnel. Documentation of exposure levels encountered in these occupations was not found.

7.4 POPULATIONS AT HIGH RISK

FDA comparisons for fiscal years (FY) 1977 and 1979 (FDA 1980a,b, 1982a,b, as cited in EPA 1985a) of estimated dietary intake of heptachlor epoxide by geographic region indicate that toddlers and infants from the north central region of the United States are at greater risk of heptachlor epoxide exposure than those in other sections of the country. In FY 1979, average infant intake was approximately 0.021 μg/kg/day, whereas north central infant intake was 0.041 μg/kg/day. Toddlers across the United States ingested an average of 0.018 μg/kg/day, in comparison to 0.051 μg/kg/day ingested by north central toddlers. Similar results were reported for FY 1977. It should be noted that these estimates are for a period when heptachlor was widely used for agricultural insect control.

Jensen (1983, as cited in WHO 1984) reported that the concentrations of fat-soluble contaminants in breast milk are expected to be considerably higher than in whole blood since the blood flow to the breast is much more rapid than the rate of milk secretion. Infant exposure to heptachlor from human milk may be significant. Heptachlor epoxide was found in the breast milk of 63% of 1,436 nursing women sampled in 1980 (mean concentration in milkfat 91.4 ppb) (Savage et al. 1981). Fifty-four nursing mothers studied in Hawaii (1979-1980) exhibited heptachlor epoxide in their milk, with a mean concentration in milkfat of 0.036 ppm (Takei et al. 1983).

A possibly significant area of exposure risk involves people, especially military personnel (NRC 1982), whose homes have been treated with heptachlor for termite control. Given its volatility, it may be possible for the compound to reach significant atmospheric concentrations in the home.

8. ANALYTICAL METHODS

8.1 ENVIRONMENTAL MEDIA

Analytical methods for the detection of heptachlor and heptachlor epoxide in environmental media, including air, soil, water, food, and solid waste are presented in Table 8.1.

8.2 BIOLOGICAL SAMPLES

Analytical methods for the detection of heptachlor and heptachlor epoxide in biological samples are shown in Table 8.2.

8.3 GENERAL DISCUSSION

Sample preparation steps vary, but, in general, involve a gross extraction of a heptachlor-containing fraction (usually lipids for biological samples) and a single- or multistep cleanup. The clean-up steps chosen depend to a large extent on the lipid content of the sample.

The method of detection and quantification of heptachlor and heptachlor epoxide in environmental and biological samples is gas chromatography (GC) with either electron capture (EC) or mass spectrometry (MS) detection.

Table 8.1. Analytical methods for heptachlor and heptachlor epoxide in environmental media

Sample type	Extraction/cleanup[a]	Detection[a]	Limit of detection[a]	References
Air				
Ambient (NIOSH method S287)	Adsorb on Chromosorb 102, desorb with toluene	GC/ECD	0.1 $\mu g/m^3$	NIOSH 1979
Water				
Rural potable	Extract (hexane), CC	GC/ECD	10 ng/L	Sandhu et al 1978
Soil				
Sediments and sewage sludge	Centrifuge, extract solid (acetone), liquid/liquid partition, transfer into trimethylpentane, treat to remove sulfur, isolate in trimethylpentane.	GC/ECD	1-10 $\mu g/kg$	Jensen et al 1977
Soil	Add acetone, extract (petroleum ether or hexane), filter, wash (water) to remove acetone, CC	GC/ECD	1 $\mu g/kg$	Harris and Sans 1971
Soil	Extract (hexane-isopropanol), filter, wash (water) to remove isopropanol, filter, dry	GC/ECD	10 $\mu g/kg$	Wiersma et al 1972a,b
Soil	Extract (acetone-hexane), add benzene to extract, evaporate to dryness, dissolve in hexane, CC	GC/ECD	NR	Townsend and Specht 1975
Soil	Wet sample, extract (hexane-isopropanol), filter, wash (water) to remove isopropanol, dry	GC/ECD	10 $\mu g/kg$	Carey et al 1973
Food				
Fruits, vegetables, dairy products, vegetable oils	Extract (acetonitrile), dilute (water), extract (petroleum ether), CC	GC/ECD, thermionic detection	NR	Horwitz 1975

Table 8.1 (continued)

Sample type	Extraction/cleanup[a]	Detection[a]	Limit of detection[a]	References
Food (continued)				
Fish, crabs, shellfish	Extract (hexane-acetone), dry filter, wash filtrate (water), distill, CC	GC/ECD	4 μg/kg	Albright et al 1975
Molasses	Dilute (water), add hexane, shake, add isopropanol, shake, wash (water), separate hexane layer, dry, filter	GC/ECD	10 g/kg	Yang et al 1976
Crops	Blend with water-acetonitrile, decant, separate liquid, concentrate, extract (hexane), liquid/liquid partition, transfer to hexane, CC	GC/ECD	10 μg/kg	Carey et al 1973
Corn fodder	Extract (hexane)	TLC/oscillo-polarography on TLC plate	20 μg/kg	Kosmatyi and Bublik (1974)
Fats	Dissolve (methylene chloride-hexane), GPC	GC/EC	NR	Hopper 1982
Waste Samples				
Solid waste (EPA Method 8080)	Extract with appropriate solvent, transfer to hexane, cleanup on Florisil	GC/EC	0 003 μg/L (heptachlor) 0 083 mg/L (heptachlor epoxide)	EPA 1986e
Solid waste (EPA Method 8250)	Extract with appropriate solvent	CCGC/MS	1.9 μg/L (heptachlor) 2.2 μg/L (heptachlor epoxide)	EPA 1986e

[a]GC/ECD - gas chromatography/electron capture detection, CC - column chromatography, TLC - thin-layer chromatography, CCGC/MS - capillary column gas chromatography/mass spectrometry, GPC - gel permeation chromatography, NR - not reported

Source Adapted from IARC 1979

Table 8.2. Analytical methods for heptachlor and heptachlor epoxide in biological samples

Sample type	Extraction/cleanup[a]	Detection[a]	Limit of detection[a]	References
Biological				
Adipose tissue	Extract (hexane), re-extract (petroleum ether, chloroform-methanol, acetonitrile or acetone-hexane), dry, dissolve (hexane), CC	GC/ECD and TLC	10 ppb	Clausen et al 1974, EPA 1980
Wildlife tissues	Grind with sodium sulfate, extract (ethyl ether-petroleum ether) in Soxhlet, CC	GC/ECD	5 μg/kg	White 1976
Blood serum	Extract (chloroform-methanol), filter, add solvent, dissolve (petroleum ether), CC	GC/ECD, TLC	1 ppb	Polishuk et al. 1977a, EPA 1980
Plant tissues	Blend in acetonitrile, extract (hexane), wash (water), evaporate to dryness, dissolve (hexane), CC	GC/ECD	NR	Townsend and Specht 1975

[a]GC/ECD - gas chromatography/electron capture detection, CC - column chromatography; TLC - thin-layer chromatography; NR - not reported.

Source Adapted from IARC (1979)

9. REGULATORY AND ADVISORY STATUS

9.1 INTERNATIONAL

The World Health Organization (WHO) has recommended an acceptable daily intake of heptachlor plus heptachlor epoxide in food of 0 to 0.5 mg/kg body weight (WHO 1984). WHO has also recommended a guideline concentration of 0.1 mg/L in drinking water (EPA 1987c).

9.2 NATIONAL

9.2.1 Regulations

The Occupational Safety and Health Administration (OSHA) has established an 8-h time-weighted average (TWA) permissible exposure limit for heptachlor of 0.5 mg/m^3 with the notation "skin" (OSHA 1985).

Cancellation of most uses of heptachlor was announced in the *Federal Register* (EPA 1978) in 1978. Uses that were cancelled and their effective dates of cancellation are:

- Field corn treatment--August 1, 1980;
- Seed treatment--September 1, 1982 (barley, oats, wheat, and rye corn), July 1, 1983 (sorghum);
- Citrus--Florida--December 31, 1979;
- Pineapples--December 31, 1982;
- Narcissus bulbs--December 31, 1980.

Heptachlor and heptachlor epoxide are not regulated by EPA under the Clean Air Act. Heptachlor is regulated as a hazardous substance under Section 311 of the Federal Water Pollution Control Act (Clean Water Act), with a reportable quantity of 1 lb (0.454 kg) for discharges into publicly owned treatment works (EPA 1986a). Heptachlor and metabolites are listed under Section 307 of the Federal Water Pollution Control Act as toxic pollutants (EPA 1986d).

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 formulating, ink formulating, gum and wood, pesticides, and carbon black.

Tolerances for residues of heptachlor and heptachlor epoxide in or on various raw agricultural commodities were set at 0, 0.01, 0.02, or

0.1 ppm under Section 408 of the Pesticide Residue Amendment to the Federal Food, Drug, and Cosmetic Act as administered by the EPA (EPA 1986b). In 1985 the EPA proposed a rule to revoke the tolerances for heptachlor and heptachlor epoxide and replace them with an action level of 0.02 ppm based on the detection limits for heptachlor/heptachlor epoxide using the FDA multiresidue analytical method (EPA 1985c). Heptachlor is listed under RCRA as an acute hazardous waste (Waste No. P059), and heptachlor and heptachlor epoxide are listed as RCRA Appendix VIII hazardous constituents (EPA 1986c).

Heptachlor and heptachlor epoxide are regulated as hazardous substances under CERCLA, with a reportable quantity of 1 lb (0.454 kg) for releases of each from vessels and facilities (EPA 1986c).

The EPA initiated a Label Improvement Program (LIP) to reduce the potential risk from pesticide application in 1981. For heptachlor, the label changes included specific precautions concerning application near domestic water supplies, near heating ducts, and around structures with subfloor crawl spaces. The label must also warn against yearly retreatment (EPA 1986f).

As a result of a risk/benefit review of the chlorinated cyclodiene pesticides (including heptachlor), the EPA issued a Special Data Call-in for the termiticides requiring the following information to be submitted (EPA 1986f).

- A one-year indoor air monitoring study in homes of various construction types that were treated for subterranean termite control in accordance with label instructions as revised by EPA's termiticide LIP;
- General metabolism studies, one in rats and one in mice, giving special consideration to pharmacokinetics;
- Five short-term mutagenicity (gene mutation) assays;
- A subchronic inhalation study in rats to assess the potential toxic response from the inhalation route of exposure.

Based on the results of the first indoor air monitoring study, a settlement agreement was reached between EPA and Velsicol. Under the terms of that agreement, registration of heptachlor as a termiticide was canceled pending the results of a new air monitoring study. In addition, certain application methods (e.g., pressure injection) may not be used. If other application methods can be developed, and if the subsequent air monitoring study provides adequate data to determine that human health risks are sufficiently low, then the registration for use as a termiticide will be reinstated. Otherwise, the cancellation will stand (EPA 1988b).

No other federal regulations relating to heptachlor and heptachlor epoxide were found.

9.2.2 Advisory Guidance

The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted an 8-h TWA threshold limit value (TLV) for exposu to heptachlor of 0.5 mg/m^3 (ACGIH 1986b). The ACGIH recommendation

includes a "skin" notation to indicate the potential for absorption of the compound by the cutaneous route, including via mucous membranes and eyes, either by airborne or direct contact. This TWA limit was considered to be sufficiently low to prevent systemic poisoning (ACGIH 1986a).

The National Institute for Occupational Safety and Health (NIOSH) has recommended a permissible exposure limit for heptachlor of 0.5 mg/m^3, and has recommended the designation of 100 mg/m^3 as the airborne concentration immediately dangerous to life or health (NIOSH/OSHA 1978). In addition, NIOSH has recommended that workers who potentially may be exposed to heptachlor be given a preemployment physical examination as well as periodic reexaminations. These examinations should stress evaluations of the eyes, nervous system, liver, and kidneys (NIOSH/OSHA 1981).

The ACGIH has not adopted a TWA-TLV for heptachlor epoxide, and NIOSH has not recommended a permissible exposure limit for the compound.

The Office of Drinking Water of the EPA has issued the following health advisories for heptachlor and heptachlor epoxide in drinking water (EPA 1987c); these levels represent protection only for noncancer toxicity end points:

- One day: insufficient data to establish;
- Ten day: 10 μg/L;
- Longer term: insufficient data to establish;
- Lifetime: 17.5 μg/L (heptachlor), 0.4 μg/L (heptachlor epoxide).

The National Academy of Sciences has issued a health advisory level for chronic exposure to heptachlor (0.0104 ppb) and heptachlor epoxide (0.0006 ppb) from drinking water (EPA 1987c).

The EPA has established a National Ambient Water Quality Criterion for heptachlor of 0.28 ppb, and has proposed maximum contaminant level goals for heptachlor and heptachlor epoxide of 0 in drinking water; the concentration in drinking water, with an upper-bound lifetime cancer risk of 10^{-6}, was calculated as 0.0104 μg/L for heptachlor and 0.00065 μg/L for heptachlor epoxide (EPA 1985b).

9.2.3 Data Analysis

9.2.3.1 Reference doses (RfDs)

The EPA has calculated a reference dose (RfD) for heptachlor of 0.0005 mg/kg/day (EPA 1987c) based on a study with CF rats fed various dose levels of heptachlor (Witherup et al. 1955, as cited in Epstein 1976); see Sect. 4.2.2.3.

The EPA has calculated an RfD for heptachlor epoxide of 0.000013 mg/kg/day (EPA 1987c) based on a study in dogs (Kettering 1958, as cited in EPA 1987c); see Sect. 4.2.2.3.

9.2.3.2 Carcinogenic potency

q_1*. EPA has calculated carcinogenic potency (q_1*) values for heptachlor and heptachlor epoxide. The methodology used by the EPA for calculating the q_1*s is described by Anderson et al. (1983). The details of the derivation of q_1* values for heptachlor and heptachlor epoxide are given by CAG (1986).

Briefly, oral exposure to heptachlor/heptachlor epoxide increased the incidence of liver carcinomas in one strain of rats and three strains of mice. From geometric means of cancer potencies calculated for studies for the most sensitive species tested (mice), the q_1*s are 4.5 per mg/kg/day for heptachlor and 9.1 per mg/kg/day for heptachlor epoxide. From data for the most sensitive sex and strain (female C3H mice), the q_1*s are 14.9 per mg/kg/day for heptachlor and 36.2 per mg/kg/day for heptachlor epoxide (CAG 1986).

IARC (1979) classified heptachlor as Group 3: inadequate evidence of carcinogenicity in humans and limited evidence of carcinogenicity in animals. The IARC (1979) position on heptachlor epoxide is that there is limited evidence that it is carcinogenic in experimental animals.

The EPA has classified heptachlor/heptachlor epoxide as a Group B2 carcinogen based on animal studies: probable human carcinogen. This classification is for compounds for which there is inadequate evidence from human studies and sufficient evidence from animal studies (EPA 1986g).

Methods used by other agencies. No information was found.

9.3 STATE

9.3.1 Regulations

The State of California has established Applied Action Levels (AALs) for drinking water for heptachlor (0.02 ppb) and heptachlor epoxide (0.10 ppb) (EPA 1987b).

Use of heptachlor has been banned by Minnesota, Massachusetts, and New York (P&TC News 1987).

9.3.2 Advisory Guidance

No information was found.

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11. GLOSSARY

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

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 time period.

Carcinogen--A chemical capable of inducing cancer.

Ceiling value (CL)--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.

Frank Effect Level (FEL)--That level of exposure which produces a statistically or biologically significant increase in frequency or severity of unmistakable adverse effects, such as irreversible functional impairment or mortality, in an exposed population when compared with its appropriate control.

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.

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.

Key Study--An animal or human toxicological study that best illustrates the nature of the adverse effects produced and the doses associated with those effects.

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 have caused death in humans or animals.

Lethal Dose(50) (LD_{50})--The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

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

Lowest-Observed-Effect Level (LOEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of 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 chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) 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 a chemical.

No-Observed-Adverse-Effect Level (NOAEL)--That dose of chemical at which there are 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.

No-Observed-Effect Level (NOEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of effects seen between the exposed population and its appropriate control.

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

q_1^*--The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ 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 RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)--The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb 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-h 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 effe 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 8-h workday or 40-h workweek.

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 humans, (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: PEER REVIEW

A peer review panel was assembled for heptachlor/heptachlor epoxide. The pannel consisted of the following members: Dr. Sheldon D. Murphey, University of Washington; Dr. Michael J. Norvell, M. J. Norvell Assoc., Inc.; and Dr. Jean Scholler, Scholler Assoc., Inc. These experts collectively have knowledge of heptachlor/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 the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has 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 their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.