Public Health Goal for Heptachlor and Heptachlor Epoxide In Drinking Water

Prepared by

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Pesticide and Environmental Toxicology Section
Anna M. Fan, Ph.D., Chief

Deputy Director for Scientific Affairs
George V. Alexeeff, Ph.D.

February 1999

LIST OF CONTRIBUTORS

PHG PROJECT MANAGEMENT	REPORT PREPARATION	SUPPORT
Project Director Anna Fan, Ph.D.	***Author*** Joseph Brown, Ph.D.	***Administrative Support*** Edna Hernandez Coordinator Juliet Rafol Genevieve Vivar
Workgroup Leaders Joseph Brown, Ph.D. Robert Howd, Ph.D. Lubow Jowa, Ph.D. David Morry, Ph.D. Rajpal Tomar, Ph.D.	***Primary Reviewer*** Jim Collins, Ph.D.	***Library Support*** Charleen Kubota, M.L.S. Mary Ann Mahoney, M.L.I.S. Valerie Walter
Public Workshop Rajpal Tomar, Ph.D. Coordinator Judy Polakoff, M.S. Juliet Rafol	***Secondary Reviewer*** Robert Howd, Ph.D.	***Website Posting*** Edna Hernandez Laurie Monserrat
Report Template/Reference Guide Hanafi Russell Yi Wang, Ph.D.	***Final Reviewers*** Anna Fan, Ph.D. George Alexeeff, Ph.D. Michael DiBartolomeis, Ph.D.	
Revisions/Responses Joseph Brown, Ph.D. Michael DiBartolomeis, Ph.D.	***Education and Outreach/Summary Documents*** David Morry, Ph.D. Hanafi Russell Yi Wang, Ph.D.	
	Format/Production Edna Hernandez Hanafi Russell	

We thank the U.S. EPA (Office of Water; Office of Prevention, Pesticides and Toxic Substances; National Center for Environmental Assessment) and the faculty members of the University of California with whom OEHHA contracted through the UC Office of the President for their peer reviews of the PHG documents, and gratefully acknowledge the comments received from all interested parties.

PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

TABLE OF CONTENTS

PUBLIC HEALTH GOAL FOR HEPTACHLOR AND HEPTACHLOR EPOXIDE IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 8 x 10^{-6} mg/L (8 ppt) was developed for heptachlor and 6 x 10^{-6} mg/L (6 ppt) for heptachlor epoxide in drinking water. The current California Maximum Contaminant Level (MCL) is 1 x 10^{-5} mg/L (10 ppt) for heptachlor or heptachlor epoxide in drinking water.

Heptachlor is a chlorinated cyclodiene insecticide. Heptachlor epoxide is an oxidation product of heptachlor. Heptachlor was used for about 30 years as a contact insecticide, mainly in the control of termites and soil insects. All uses of existing stocks of heptachlor were prohibited after April 15, 1988. Technical grade heptachlor consists of about 73% heptachlor and 22% trans-chlordane, and has low water solubility. Heptachlor epoxide is more stable than heptachlor and only slightly water-soluble. Both compounds are persistent and bioconcentrate in the environment.

Animal studies in rats and mice provide sufficient evidence for the carcinogenicity of heptachlor and heptachlor epoxide. From a quantitative assessment viewpoint these studies are mostly limited to liver tumors in mice. The incidences of liver tumors in male and female mice were taken from the NCI (1977) and Davis (1965) studies in the case of heptachlor and from IDRC (1973) and Davis (1965) in the case of heptachlor epoxide. Data from human epidemiological studies are fragmentary and insufficient to support quantitative assessment. The U.S. Environmental Protection Agency (U.S. EPA) has classified heptachlor and heptachlor epoxide as probable human carcinogens, Group B2. The International Agency for Research on Cancer (IARC) has classified heptachlor as possibly carcinogenic for humans (Group 2B). On the basis of cancer risk calculations employing carcinogen slope factors of 4.1 $(mg/kg\text{-}day)^{-1}$ for heptachlor and 5.5 $(mg/kg\text{-}day)^{-1}$ for heptachlor epoxide, and based on the *de minimis* theoretical excess individual lifetime cancer risk level of 1 x 10^{-6}, PHGs of 8 ppt and 6 ppt are proposed respectively.

The proposed PHG values are considered to provide adequate margins of safety for noncarcinogenic adverse effects including potential effects on the endocrine system with low exposures (e.g., increases in male-typical mating behavior in male rats). The health protective drinking water concentrations of heptachlor for non-cancer health effects ranged from 0.2 ppb based on increased male-typical mating behavior (LOAEL = 0.1 mg/kg-day) to 3 ppb based on increased liver weights (NOAEL = 0.15 mg kg-day) in rats. The uncertainty factors range from 100 for the liver weight effect to 1,000 for the endocrine effect. The health protective concentration for heptachlor epoxide is based on increased liver weights in rats is 25 ppb with an uncertainty factor of 1,000.

INTRODUCTION

This document represents an update of our earlier health risk assessment of heptachlor and heptachlor epoxide which provided part of the technical support for California's primary drinking water standard or MCL (DHS, 1988). [Prior to the establishment of the California

Environmental Protection Agency (Cal/EPA) in 1991 OEHHA was a division in the California Department of Health Services, or DHS.] This document does not attempt to repeat all descriptions and information found in DHS (1988) but rather it focuses on new information and data, or new analyses or interpretations of earlier studies. As noted above the PHG is a stand alone drinking water goal as well as an initial step in setting or revising a California drinking water MCL.

Heptachlor is absorbed from the gastrointestinal tract of rats and residues appear in blood within an hour of oral dosing. Absorption of heptachlor by humans can be inferred from reports of the occurrence of heptachlor epoxide in adipose tissue of the general population. Heptachlor epoxide, the major metabolite of heptachlor, is distributed to tissues of animals; the highest levels are detected in adipose tissue, where it persists. Heptachlor epoxide is dechlorinated and hydroxylated to a metabolite eliminated in the feces. Rat liver microsomes form four times more heptachlor epoxide from heptachlor than human microsomes (85.8% vs. 20.4%); otherwise, the in vitro pattern of metabolism is similar. Rats eliminated >50% of administered heptachlor as fecal metabolites; <5% is eliminated in urine.

The acute LD_{50} of heptachlor is about 100 mg/kg bw for rats, 70 mg/kg bw for mice and 105 mg/kg bw for hamsters. The acute LD_{50} of heptachlor epoxide in rats is about 60 mg/kg bw. Symptoms of acute intoxication of heptachlor and heptachlor epoxide include tremors, convulsions, paralysis and hypothermia.

Oral exposure to heptachlor has been associated with induction of several hepatic microsomal enzymes in rodents. Chronic dietary exposure to heptachlor or heptachlor epoxide resulted in hepatocytomegaly, hyperplasia, hepatic vein thrombosis and cirrhosis in mice.

Long-term carcinogenicity bioassays in rats and mice with heptachlor have shown dose dependent increases in hepatocellular carcinoma in the latter. Similarly, four carcinogenesis bioassays of heptachlor epoxide have been performed in mice and all exhibited significant induction of hepatocellular carcinoma. Relatively few effects have been noted in rat carcinogenicity bioassays with heptachlor or heptachlor epoxide aside from hepatic nodules and hepatomegaly.

Concern about the carcinogenic potential for heptachlor, heptachlor epoxide and related chlorinated cyclodienes has been long standing. However recent findings with respect to the endocrine disrupting potential of these and certain other persistent pesticide residues in the environment have raised new concerns about low level exposures. The U.S.EPA (1997) does not consider endocrine disruption per se to represent an adverse endpoint, but rather as a mode or mechanism of action that could lead to toxicity such as cancer, reproductive or developmental effects. There are many uncertainties at present with regard to the significance of such data for human risk assessment.

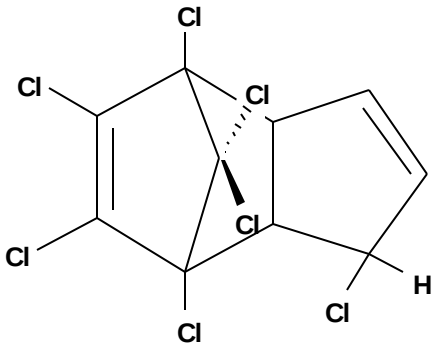
CHEMICAL PROFILES

Heptachlor

Heptachlor is not known to occur naturally. Heptachlor was first introduced as a contact insecticide under the trade names Velsicol 104 and E 3314 (WHO, 1984). The use of heptachlor before its prohibited use in 1988 was confined almost exclusively to the control of soil insects and termites. In the period July 1975-December 1976, an estimated 4.5 million kg were

produced in the USA where it was used as an insecticide (registered from June 1971 for use on 22 crops) applied both as foliar and as a seed treatment: 58% on corn, 26.8% by pest control operators, 13.2% as seed treatment, and 2% for miscellaneous uses (IARC, 1979). Sales of heptachlor in the United States were voluntarily stopped by the sole U.S. manufacturer in 1987.

Chemical structure:



Molecular formula: $C_{10}H_5Cl_7$

M.W.: 373.32

CAS NO.: 76-44-8

Chemical name:1,4,5,6,7,8,8-heptachloro-3_a 4,7,7_a - tetrahydro-4,7-methano-l *H*-indene

Common trade names:

Aahepta, Agroceres, Basaklor, Drinox, E 3314, GPKH, Heptachlorane, Heptagran, Heptagranox, Heptamak, Heptamul, Heptasol, Heptox, Rhodiachlor, Soleptax, Velsicol 104 and E3314.

Technical heptachlor consists of 70% heptachlor, 22% trans-chlordane and 5% nonachlor (Deichmann, 1981).

The chemical and physical properties of 99% pure heptachlor, a white crystalline solid, are given in Table 1 (IARC, 1991).

Table 1. Chemical and Physical Properties of Heptachlor

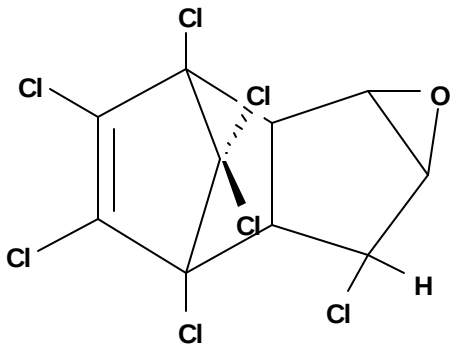
Property	Value or Description	Reference
Boiling point	135 - 145^{0}C at 1-1.5 mm Hg	IARC, 1991
Melting Point	95-96^{0}C pure compound	IARC, 1991
Specific gravity	1.57 - 1.59	Deichmann, 1981
Solubility	insoluble in water, 0.056 mg/L at 25^{0}C; soluble in many organic solvents	IARC, 1991
Vapor pressure	3 x 10^{-4} mm Hg (20°C)	Montgomery,1993
Oil-water partition coeff.(Kow)	4.4-5.5	Montgomery,1993
Log Kow		
Soil-organic carbon-water (Koc)	4.38	Montgomery, 1993
Log Koc		
Henry's law constant	2.3 x 10^{-3} atm m^3/mol	Montgomery, 1993

Several investigators have studied the fate of heptachlor in aquatic media. This compound may undergo significant photolysis in ambient aquatic media (Callahan et al., 1979). The hydrolysis of heptachlor in aquatic media is also an important process. The half-life of heptachlor in water ranges from 1-3 days (Callahan et al., 1979; Mabey et al., 1981). The half-life of heptachlor in soil was 9-10 months when used at recommended agricultural rates (WHO, 1984). Vrochinsky et al. (1980) described a half-life of 2 years; and residues could be detected in soil 14 years after initial application. Soil surveys have shown 1-hydroxy-chlordene to be a major residue in soils from 5 areas, while only small amounts of heptachlor epoxide and the hydroxy epoxide were present (Brooks, 1974). Tzapko et al. (1967) concluded that heptachlor penetration into ground water was likely to be insignificant.

Heptachlor Epoxide

Heptachlor epoxide is not commercially available in the United States, but it is an oxidation product of heptachlor (IARC, 1991).

Chemical structure:



Molecular formula: C_{10} H_5 $C1_7$ 0

M.W: 389.32

CAS No.: 1024-57-3

Chemical name: 1,4,5,6,7,8,8,-Heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-4,-7-mathanoindan

Common names: Epoxyheptachlor; Hepox; Heptepoxide; Velsicol 53-CS-17; ENT 25, 584.

The chemical and physical properties of heptachlor epoxide are given in Table 2.

Table 2. Chemical and Physical Properties of Heptachlor Epoxide

Property	Value or Description	Reference
Melting point	160 - 161.5^{0}C	IARC, 1991
Vapor Pressure	3 x l0^{-4} mm Hg at 25^{0}C 2.6 x 10^{-6} mm Hg at 20°C	Mabey et al., 1981 Montgomery, 1993
Solubility in water	0.35 mg/L at 25^{0}C	IARC, 1991
Octanol-water partition (Kow) Log Kow	 3.65, 5.40	Montgomery, 1993
Soil-organic carbon-water (Koc) Log Koc	 4.32(calc.)	Montgomery, 1993
Henry's law constant	3.2 x 10^{-5} atm m^3/mol	Montgomery, 1993

The two processes that may determine the fate of heptachlor epoxide in aquatic media are volatilization and sorption (Huang, 1970; Mabey et al., 1981; Callahan et al., 1979).

ENVIRONMENTAL OCCURRENCE

Heptachlor is rapidly oxidized to 2,3-heptachlor epoxide (Davidow and Radomski, 1953). This is a microsomal oxidation and it also occurs both photochemically and biologically in soils and plant tissues. It occurs in all animals studied. Thus, the stable heptachlor epoxide appears in the environment as the major contaminant after the use of heptachlor (NAS, 1977). During the 1960's and 1970's heptachlor was used by farmers to kill insects in seed grains and on crops, as well as by exterminators to kill termites. Since late 1978, most uses of heptachlor were phased out so that heptachlor became unavailable to the general public (ATSDR, 1989; 1993). In August 1987, Velsicol, the only U.S. producer of heptachlor, stopped selling this product. All other uses of existing stocks of chlordane and heptachlor were prohibited after April 15, 1988.

Heptachlor epoxide remains in the soil for long periods of time. Heptachlor and heptachlor epoxide may also be present at numerous hazardous waste sites. It is possible for people off-site to be exposed from release of heptachlor and heptachlor epoxide into the air or neighboring bodies of water (ATSDR, 1989; 1993). Humans may be exposed to chemicals from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products (U.S. EPA, 1985). Drinking water, food and ambient air are media considered to be sources of heptachlor and heptachlor epoxide.

Soil

A survey conducted on agricultural soils in 37 states of the USA in 1971 revealed heptachlor residues in 4.9% of samples, while heptachlor epoxide was detected in 6.9% of samples with maximum values of 1.37 and 0.43 ppm, respectively (Carey et al., 1978). Heptachlor residue levels found in soil samples taken from seven out of eight cities in the USA in 1969 ranged from 0.01 to 0.53 mg/kg (Wiersma et al., 1972a; 1972b). In streambed sediment and sediment from natural drainage ditches the concentrations were as high as 174 and 4.7 ppb, respectively (Burns et al., 1975). Heptachlor is stable to light and moisture, and volatilization is the major transport mechanism for topically applied material. Its half-life in soil in temperate regions is 0.75 to 2 years depending on soil type. Residues have been detected in soil 14 years after use (IARC, 1991).

Water

Heptachlor or heptachlor epoxide are seldom found in California drinking water or ground water. A sampling of well water in California during the period 1986-1992 involving over 260,000 analyses of over 17,000 wells showed no detections (DPR,1992). Historically these organochlorine contaminants have been found in water in other parts of the U.S.

Several studies have addressed concentrations of heptachlor and heptachlor epoxide in drinking water. Sandhu et al. (1978) summarized the results from a rural water supply study in South Carolina. The range of residues varied from undetected to 44 ng/L for heptachlor and from undetected to 87 ng/L for heptachlor epoxide. Of 22 drinking water samples taken from the northern New Jersey area, two samples (9%) contained 0.007 and 0.02 μg/L heptachlor and none contained heptachlor epoxide. Tucker and Burke (1978) found in groundwater sampled from a public drinking water supply well a concentration of heptachlor epoxide of 0.6 μg/L.

Food

The Food and Drug Administration's (FDA) Market Basket Studies for fiscal years (FY) 1975 through 1979 reported that heptachlor was "not detected" in any of the food samples analyzed in either adult or infant/toddler diet surveys. Dietary heptachlor epoxide intake was reported for adults, as well as infants and toddlers, in the FDA Market Basket Studies for fiscal year 1979 (FDA, 1982a; 1982b). Total dietary intake of heptachlor epoxide for adults in FY79 was 0.397µg/day (FDA, 1982a). The adult dietary intake included 0.255 µg/day from dairy products; 0.130 µg/day from meat, fish and poultry; 0.006 µg/day from potatoes; 0.002 µg/day from root vegetables; and 0.004 µg/day from oils and fats. The intake of heptachlor epoxide in the 1982-84 period averaged 0.14 µg/day for 25-30 year old males, a 70% decrease from the 1980-82 period (Gunderson, 1988). The most recent FDA total diet study shows intake levels of 0.5 to 2.5 ng/kg-day (FDA, 1996). Heptachlor and/or heptachlor epoxide was present in 32% of 590 fish samples in the U.S. in 1967-68, at levels of 0.01-8.46 mg/kg (Henderson et al.,1969). Heptachlor and heptachlor epoxide accumulate in aquatic and terrestrial organisms (Schmitt et al.,1990). Biomagnification of heptachlor epoxide is more significant in terrestrial organisms and higher trophic levels of aquatic organisms since these organisms readily metabolize heptachlor to heptachlor epoxide (ATSDR, 1993).

Air

Kutz et al. (1976) reported levels of heptachlor in the ambient air of 16 states between 1970 and 1972. The maximum level measured was 27.8 ng/m^3 in Tennessee; the mean value for all positive samples was 1.0 ng/m^3. Heptachlor was detected in 42% of the 2479 samples collected during the monitoring period. The maximum value of heptachlor measured in the 30 samples of a pilot suburban air monitoring program conducted between April 1975 and June 1975 was 22.1 ng/m^3. Arthur et al. (1976) collected and analyzed 156 air samples from the Mississippi Delta between 1972 and 1974. The maximum heptachlor and heptachlor epoxide levels reported were 0.8 and 9.3 ng/m^3, respectively. More recently a sampling of nine homes in North Carolina with years of construction ranging from 1930 to 1989 found the highest levels in and around a 1962 home. Maximum heptachlor levels were 0.72 µg/g in carpet dust and 0.20 µg/m^3 in indoor air. Mean levels of 0.27 µg/g for 8/9 homes and 0.07 µg/m^3 for 8/8 homes were observed (Lewis et al., 1994).

A survey of 16 states between 1970 and 1972 detected heptachlor in 42% of 2479 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). Heptachlor was used primarily for the control of subterranean termites. Wright and Leidy (1982) conducted one study on pre- and post-treatment air levels of chlordane and heptachlor. They measured the indoor air levels of chlordane and heptachlor in six houses for a period of one year after a termiticide application. The ambient air concentrations of heptachlor found in these houses ranged from 0.01 to 1.8 µg/m^3.

Human Exposure and Tissue Residues

Almost all environmental data are from studies conducted prior to 1980 when heptachlor was still being used as an agricultural pesticide. Few 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.

The data available for residues in human tissue are more extensive and reliable than the data for food levels. Heptachlor and heptachlor epoxide have been detected in human blood, adipose tissue, and in breast milk. Mussalo-Rauhamaa et al. (1991) summarized the levels of heptachlor epoxide in whole blood, serum and human adipose tissue samples from a number of studies including pesticide workers. Mean concentrations ranged from nondetect (ND) to 10.9 ng/g for whole blood, ND to 15.8 ng/g for blood serum and ND to 0.24 µg/g for adipose tissue. IARC (1991) reported a range of mean heptachlor epoxide levels for the general population of 0.01 to 0.46 µg/g tissue. Adeshina & Todd (1990) reported the levels of heptachlor epoxide in adipose tissues of 35 residents in North Texas as a mean of 0.086 µg/g and a 95% confidence level of 0.064-0.108 µg/g tissue.

Heptachlor epoxide was detected in human tissue from 77 autopsies performed from 1966 to 1968 at 1 to 32 ppb (wet weight), with highest concentrations in bone marrow and liver (Klemmer et al., 1977). Studies carried out by Zavon et al. (1969) and Curley et al. (1969) suggested that, in the USA at that time, trace quantities of heptachlor were found in the adipose tissue of stillborn babies at autopsy, and that the levels there were slightly lower than those found in the adult population. Heptachlor epoxide has been detected in human adipose tissue in surveys conducted in Great Britain (Abbott et al., 1972), Brazil (Wasserman et al., 1972), Japan (Curley et al., 1973), Israel (Wasserman et al., 1974), Texas (Burns, 1974), Louisiana (Greer et al., 1980) and in other regions in the United States (Kutz et al., 1979; Sovcool and Lewis, 1975). Unchanged heptachlor was not detected (detection limit = 0.06 ppm) in adipose tissue from healthy individuals (Barguet et al., 1981). Lordo et al. (1996) reported results from the U.S. EPA's 1986 National Human Adipose Tissue Survey (NHATS). Analyses were performed on 50 composite samples of a total of 671 subjects. Each composite was obtained from the same census region and age group. For heptachlor epoxide the national average was 57.6 ng/g tissue. Regional averages ranged from 48.4 ng/g in the Northeast to 70.5 ng/g in the South. Among the age groups the 0-14 years gave the lowest value (32.6 ng/g) and 45+ years the highest (84.7 ng/g).

METABOLISM AND PHARMACOKINETICS

Absorption

Limited information on the absorption of heptachlor following ingestion by animals was available. However, the systemic toxicity of heptachlor following oral, dermal, or inhalation exposure as well as human tissue residues are indications of the absorption of the insecticide. The EPA (1980) reviewed an abstract of a Russian study (Mizyukova and Kurchatov, 1970) and reported that heptachlor administered intragastrically in a single oral dose of 120 mg/kg bw to

rats was detected in blood within 0.5-1 hour of administration. Heptachlor is readily absorbed via most routes of exposure and is metabolized to heptachlor epoxide in mammals (ATSDR, 1993; Fendick et al., 1990).

Arthur et al. (1975) placed 10 rabbits of each sex in open-air cages so that they were exposed to the ambient air of Stoneville, Mississippi, an area where insecticides had been heavily used. Control groups of male and female rabbits (10 each) were housed in a room at Mississippi State University, a low pesticide use area. The average air levels of heptachlor epoxide in Stoneville air was 1.86 ng/m^3; the air at Mississippi State was not sampled. Heptachlor epoxide residue levels in adipose tissue of the test rabbits was 0.039 ppm compared with 0.016 ppm in controls ($p < 0.001$). The average respiratory intake of heptachlor epoxide was calculated as 0.002 µg/day for rabbits in the Stoneville area.

Distribution

Heptachlor is readily metabolized to heptachlor epoxide by mammals (WHO, 1984; Fendick et al., 1990). Klein et al. (1968) showed that the metabolism of heptachlor in rats gave rise to heptachlor epoxide and a hydrophilic metabolite, 1-*exo*-hydroxy-2,3-epoxychlordene. Heptachlor epoxide was found mainly in fat, but also in liver, kidney, and muscle in rats and dogs, and in urine and feces. The hydrophilic metabolite was also excreted in the urine and feces of rats and rabbits treated with heptachlor (Klein et al.,1968). Another metabolite, a dehydrogenated derivative of 1-*exo*-hydroxy-2,3-epoxychlordene, has been isolated from rat feces (Matsumura & Nelson, 1971).

Mizyukova and Kurchatov (1970) reported that following a single intragastric dose of 120 mg/rat heptachlor to female rats, heptachlor was detected in blood, liver, kidney and adipose tissue within 1 hour. After 4 hours, heptachlor epoxide, a metabolite of heptachlor, was detected in blood, liver and fat and persisted in the adipose tissue for 3-6 months. With dietary administration of heptachlor to rats for two months or to dogs by capsule for 12 to 18 months, Radomski and Davidow (1953) reported similar tissue distribution. Heptachlor epoxide levels in the fat of female rats, however, were 5 to 10 times higher than those in male rats. Twelve weeks after cessation of exposure (30 mg heptachlor/kg diet) heptachlor had completely disappeared from the adipose tissue. When groups of cows were fed heptachlor at doses of 1.5-2.0 mg/cow per day for a period of 8 weeks, the level of heptachlor epoxide in the adipose tissue was found to be below 0.1 mg/kg (Vreman et al., 1977). Yamaguchi et al. (1979) detected 3.15 ppm heptachlor epoxide in brain tissue of rats 5 hours after an intraperitoneal injection of 200 mg heptachlor/kg bw.

Metabolism

Although studies in humans given oral doses of heptachlor were not available, based on an <u>in vitro</u> liver microsome study (Tashiro and Matsumura 1978), qualitatively, humans and rats metabolize heptachlor to the same products (Figure 1). Tashiro and Matsumura (1978) proposed a metabolic pathway (Fig. 1) based on the following: over a 10-day period following a single oral unspecified dose of [^{14}C]-heptachlor in corn oil, rats excreted >50% of the administered radioactivity in feces and <5% in urine. The relative abundance of fecal metabolites, expressed

as percent total [^{14}C]-compounds, were as follows: unchanged heptachlor, 26.2%; heptachlor epoxide, 13.1%; 1-hydroxy-chlordane, 19.5%; 1,2-dihydroxy-dihydrochlordene, 3.5%; and two other unnamed metabolites, one of which accounted for 19% of the radioactivity, the other for 0.1%.

Matsumura and Nelson (1971) administered heptachlor epoxide to four rats in dietary concentrations of 10 ppm for 30 days. The authors estimated that each rat consumed 5 mg of heptachlor epoxide over the test period and excreted 950 µg of a fecal metabolite and 66 µg of heptachlor epoxide in the feces. Brooks et al. (1968, 1970) investigated the in vitro metabolism of heptachlor epoxide by pig liver microsomes. The product, following incubation at 45^0 C for 60 hours, was identified as heptachlor epoxide diol.

Incubation of heptachlor epoxide with rabbit microsomes also resulted in the formation of heptachlor epoxide diol as well as another unidentified product (U.S. EPA, 1985).

Heptachlor epoxide is a substrate for glutathione-S-transferase but the conjugate has not been identified (Scheufler & Rozman, 1984).

Excretion

Tashiro and Matsumura (1978) reported the elimination of [14C]-heptachlor in male rats. When a single oral dose of [^{14}C]-heptachlor was administered to male rats, most of the radioactivity was eliminated in the feces, with approximately 36 and 62% of the dose being eliminated 1 and 10 days after dosing. Elimination in urine in 10 days accounted for only 6% of the dose. Approximately 26.2% of the total radioactivity recovered from the feces was the unchanged parent compound; the remainder was in the form of metabolites.

In an abstract of a Soviet study (Eramakov, 1977), it was reported that 16-40 percent of an orally administered dose of heptachlor (28 to 50 mg/kg bw to rats and rabbits) was excreted unchanged in the feces and that heptachlor epoxide was excreted over at least a 12-month period.

Heptachlor and other components of technical-grade chlordane and their metabolites are excreted in human milk in quantities that vary with exposure, metabolic capacity, and time of milk sampling. In Israel the mean levels of heptachlor epoxide in the milk of 29 women 2-4 days after delivery were 9.1 µg/L in whole milk and 720 µg/kg fat (Polishuk et al., 1977). The levels of heptachlor epoxide in 50 women in Switzerland were <10-110 µg/kg fat with a mean of 30 µg/kg fat (Schuepbach & Egli, 1979).

The only data available on human excretion of heptachlor are reports of heptachlor epoxide detected in milk of lactating women. Excretion of heptachlor epoxide in the milk of 50 lactating women in Hawaii was at a mean concentration of ~34 ppb (Takahashi et al., 1981). Heptachlor epoxide, in trace amounts up to concentrations of 5 ppb, was detected in 10 of 40 milk samples collected from women in Colorado in 1971-1972 (Savage et al., 1973). Kroger (1972) detected an average of 0.16 ppm heptachlor epoxide in 53 human milk samples. A mean concentration of 0.003 mg/kg of heptachlor epoxide in milk was reported by Ritcey et al. (1972) in 147 human milk samples collected in Canada in 1967-1968. Of 51 human milk samples collected in St. Louis, MO in 1973, 12 were positive for heptachlor epoxide (mean = 0.0027 ppm) and 3 were positive for heptachlor (mean = 0.019 ppm) (Jonsson et al., 1977). Strassman and Kutz (1977) detected heptachlor epoxide in 35.1% of 57 human milk samples from Arkansas and Mississippi in 1973-

1974 in a mean concentration of 0.004 ppm. This excretion reduced the body burden of heptachlor epoxide in these women but increased the exposure of breast-fed infants.

Quinsey et al. (1996) estimated breast-fed infants' exposure to organochlorines. They found the daily intake of heptachlor epoxide from breast milk to average 0.25 μg/kg body weight/day (N = 17; s.d. = 0.14; range 0.11-0.71). Interestingly 100% of the samples and intake estimates exceeded the ADI for heptachlor epoxide (WHO, 1986). In this study the heptachlor epoxide concentrations ranged from 0.02 to 0.15 μg/g milk fat. In women who followed a strict vegetarian diet, the mean levels of heptachlor epoxide in breast milk were 1-2% of the average for the U.S. general population (Hergenrather et al., 1981).

TOXICOLOGY

Because of the rapid transformation of heptachlor into heptachlor epoxide in the mammalian body, the toxicity data for the two substances will be discussed together.

Acute Toxicity

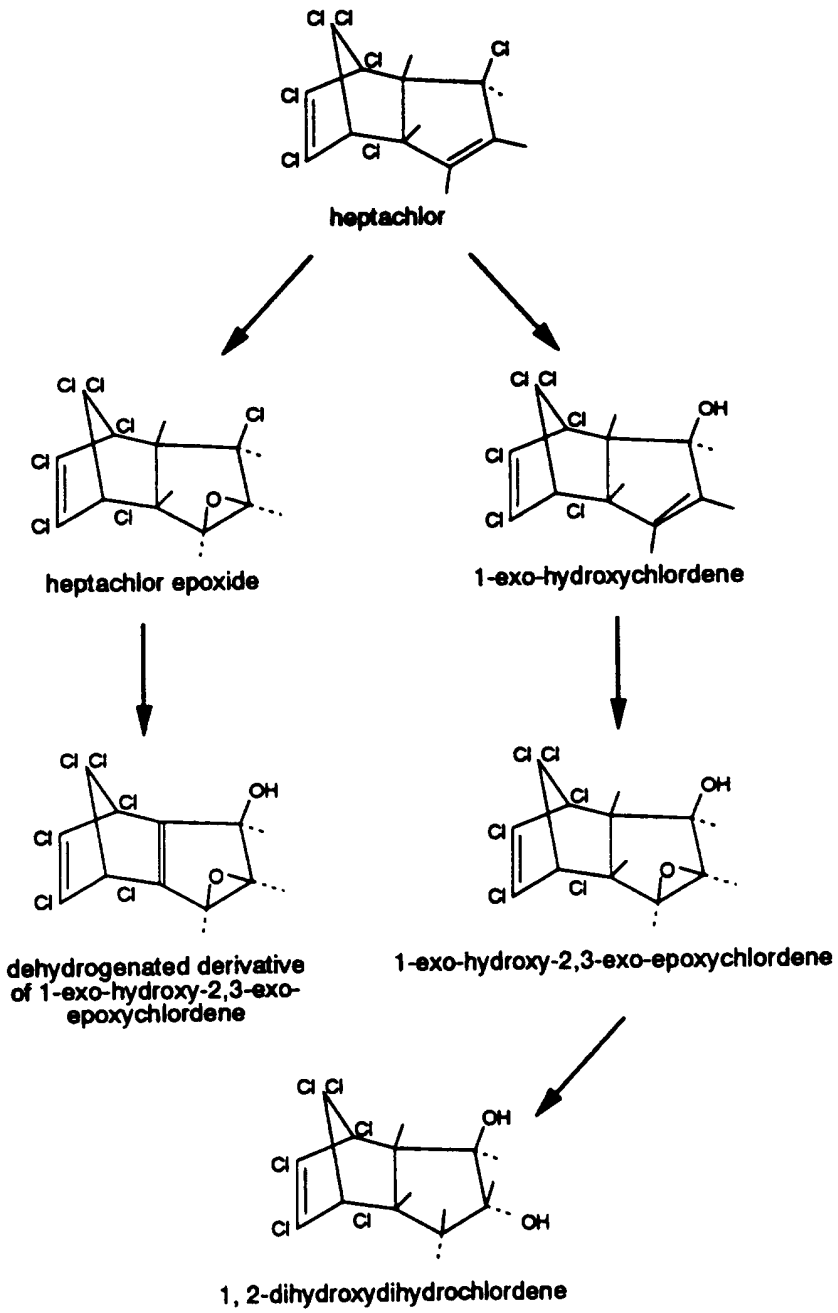
Studies on Experimental Animals

The acute toxicity of heptachlor in several animal species by different routes of exposure was summarized in WHO (1984) and Fendick et al. (1990). The range of oral LD_{50} values for rats was 40 mg/kg (Ben-Dyke et al., 1970) to 162 mg/kg (Gaines, 1960). The signs of heptachlor poisoning include hyperexcitability, tremors, convulsions, and paralysis (Hrdina et al., 1974; Yamaguchi et al., 1980). Oral doses (a single dose of 60 mg/kg or repeated doses of 7 or 12 mg/kg/day for 3-14 days) resulted in significantly elevated levels of serum glutamic-pyruvic transaminase (SGPT) and serum aldolase, coincident with histologically observed liver damage (Krampl, 1971).

Daily oral doses of pure heptachlor at 50 and 100 mg/kg were lethal to rats after 10 days. In animals given 5 mg/kg , hyperreflexia, dyspnoea and convulsions occurred and pathological changes were observed in liver, kidney, and spleen (Pelikan et al.,1968).

Heptachlor epoxide has a higher acute toxicity than the parent compound with oral LD_{50} values in rats ranging from 46.5 to 60 mg/kg (NAS, 1977; Podowski et al., 1979). Single oral or intraperitoneal doses (30 or 100 mg/kg) of a heptachlor: heptachlor epoxide (27:75) preparation in CD-1 mice resulted in moderate to severe hypoactivity and ruffled fur (Arnold et al., 1977).

Figure 1 Metabolic Scheme for Heptachlor in Rats*



*** Adapted from Tashiro and Matsumura 1978**

Human Studies

No studies were found with respect to death in humans after oral exposure to heptachlor or heptachlor epoxide ATSDR (1993). Since heptachlor is a component of chlordane, chlordane poisoning can be considered when evaluating heptachlor toxicity data (ATSDR, 1993). A retrospective mortality study of 1403 white male workers engaged for at least three months in the manufacture of chlordane, heptachlor, and endrin between 1946 and 1976 showed a statistically significant increase ($p < 0.05$) in deaths due to cerebrovascular disease compared to U.S. mortality data (Wang and MacMahon, 1979b).

Sub-Chronic and Chronic Toxicity

Studies on Experimental Animals

A preliminary subchronic study was conducted to determine the dose levels of heptachlor to be administered to Osborne-Mendel rats and $B6C3F_1$ mice for carcinogenicity testing (NCI, 1977). Male and female rats, five of each sex per group, were administered diets containing technical grade heptachlor (about 73% heptachlor, 22% trans-chlordane, 5% nonachlor) in concentrations of 0 (control) and 320 ppm (320 mg/kg diet or about 32 mg/kg-day) for 42 days. The rats were then maintained on heptachlor-free diets for 2 weeks. No effects on body weight gain or food consumption were observed at <40 ppm. At 80 ppm, female rats exhibited reduced body weight during the first week. Diets containing 160 ppm resulted in deaths of 4/5 females. A level of 320 ppm resulted in the deaths of 2/5 male and all five female rats.

Groups of five male and five female mice received diets containing 0-80 ppm heptachlor for 42 days followed by observation for 14 days (NCI, 1977). No deaths and no effects on body weight gain or food consumption occurred at <40 ppm diet. At 80 ppm diet all males and two female mice died.

Four groups of 10 male and 20 female rats were given daily oral doses of pure heptachlor, at 0, 5, 50, or 100 mg/kg body weight, starting at about 4 months of age (Pelikan et al., 1968). Administration was continued for 200 days or until the animals died. By the tenth day, all the animals in the groups fed 50 or 100 mg/kg-day had died. On day 200, the surviving animals in the 5 mg/kg-day group and the control group were sacrificed for autopsy. Prior to death, the 50 and 100 mg/kg-day groups became irritable and had accelerated respiration by the second day. In the group given 5 mg/kg, no clinical abnormalities were seen until the 50th day, when hyper-reflexia, dyspnea and convulsions were observed. Two males and two females in this group died before completion of the study, compared with only one female in the controls. Histological examination showed fatty degeneration of the liver cells and moderate fatty infiltration of the renal tubular epithelium, as well as hyperplasia of the smooth endoplasmic reticulum of the liver parenchyma in the group fed 5 mg/kg-day.

Groups of 10 rats of each sex were fed diets containing heptachlor epoxide at 5, 10, 20, 40, 80, 160, or 300 ppm in diet (about 0.05 to 15.0 mg/kg-day) for 2 years (WHO, 1984). Concentrations of 80 ppm or higher resulted in 100% mortality in 2-20 weeks. All the female

animals given 40 ppm died within 54 weeks. Diets containing 20 ppm or less did not produce any signs of illness in male or female rats during a 2-year period, but an increase in liver weight was observed in male rats dosed with more than 10 ppm and in females administered 5 ppm. Groups comprised of 25 male and 25 female rats were fed 0, 100, 250, 500, 1000 or 2000 mg of the heptachlor metabolite 1-hydroxychlordene per kg diet for up to 224 days (Ingle, 1965). Growth and food consumption were normal at all levels, and mortality appeared to be unaffected by the test compound.

Witherup et al. (1959) studied the effect of heptachlor epoxide in groups of 23 male and 25 female rats for 110 weeks. The dietary concentrations ranged from 0.5-10.0 ppm (0.025-0.5 mg/kg-day). Control rats received heptachlor epoxide-free diets. No differences were observed with respect to food consumption or growth rate. There was a dose-related increase in liver weight in females. Hepatic cell vacuolization occurred in treated males. Mortality was higher than the control for all treated groups, but a dose-response relationship was not observed.

Reuber (1977a; 1978), using slides from the Davis study (1965), found hepatic vein thrombosis and cirrhosis among the heptachlor and heptachlor epoxide (10 ppm in diet) treated mice. These conditions were not observed in any of the 127 control slides available for review. For heptachlor-treated mice 13% (10% of males, 15% of females) had hepatic vein thrombosis and 6% had venous occlusion with recent liver infarctions. Thrombosis of the cardiac atrium was also present in some mice with hepatic vein thrombosis. The incidence of cirrhosis was 2/86 treated males and 5/77 treated females. For heptachlor epoxide, 10% of treated mice (7% of males, 11% of females) had hepatic vein thrombosis and 9% had venous occlusion. Cardiac atrium thrombosis was present in some mice. The incidence of cirrhosis was 12/78 treated males and 12/81 treated females.

Jolley et al. (1966) found a dose-related increase in mortality in rats fed 5 to 12.5 ppm diet of a 75% heptachlor and 25% heptachlor epoxide mixture for 2 years.

Heptachlor administered orally to dogs at 5 mg/kg-day caused the deaths of all animals within 21 days; at 1 mg/kg per day, 3 of 4 dogs died within 424 days, and one was still living at 455 days (Lehman, 1952).

Three dogs given heptachlor epoxide orally, at 2, 4, or 8 mg/kg-day for 5 days per week died after 22, 10, and 3 weeks, respectively. Daily oral doses of 0.25 and 0.5 mg/kg-day failed to produce signs of illness during 52 weeks, but 0.25 mg/kg-day, estimated to be equivalent to 6 ppm in diet, was reported to be the minimal dose producing a pathological effect (WHO, 1984).

Diets containing 0.5, 2.5, 5.0, or 7.5 ppm heptachlor epoxide (0.0125 to 0.188 mg/kg-day) were given to groups of 5 dogs (2 males and 3 females, 23-27 weeks of age) for 60 weeks (Velsicol Corp. unpublished data cited in WHO, 1984). No deaths attributed to heptachlor epoxide treatment occurred. The body weight of the male dogs increased in inverse proportion to the concentration of the compound in the diet whereas the body weights of the females were normal. Liver weights were increased at 5 ppm and above. Degenerative liver changes were seen in but a single dog at the 7.5 ppm level.

Human Studies

There are no data on the effects of heptachlor and/or heptachlor epoxide in man without concomitant exposure to chlordane. Exposure to chlordane and heptachlor via skin contact

and/or inhalation has been associated with blood dyscrasias, including four cases of aplastic anemia (Infante et al., 1978; Klemmer et al., 1977), one case of refractory megaloblastic anemia (Furie and Trubowitz, 1976), one case of acute stem cell leukemia (Infante et al., 1978), one case of acute lymphoblastic leukemia and one case of acute myelomonocytic leukemia (Infante et al., 1978). Exposure was a result of indoor or outdoor applications or a combination of the two. However, in a case-control study, no association between blood dyscrasias and occupational exposure to heptachlor was found (Wang and Grufferman, 1981).

Wang and MacMahon (1979a) studied mortality in 1,403 white males occupationally exposed to chlordane or heptachlor during manufacturing. The workers were exposed for at least 3 months from 1946 to 1976. The 113 deaths were lower than the 157 deaths expected giving a standardized mortality ratio (SMR) of 0.72. A statistically significant increase in deaths from cerebrovascular disease (17 observed, 9.3 expected) was observed. Death from cerebrovascular disease was not related to duration of exposure or latency, and occurred exclusively after termination of employment.

Epstein and Ozonoff (1987) reported new cases of blood dyscrasia, including leukemias, production defects, and thrombocytopenic purpurea, generally following home termite treatment with the chlorinated hydrocarbon pesticides chlordane and heptachlor (C/H). These newly reported cases are consistent with 34 previously published case reports associating blood dyscrasias with C/H exposure. The newly reported leukemias were considered consistent with epidemiological evidence of excess risk of leukemia and other cancers in C/H-exposed populations and with the carcinogenic action of C/H in animals.

Genetic Toxicity

Heptachlor was not mutagenic in *Salmonella typhimurium* or *Escherichia coli* in the presence or absence of rat liver microsomal preparations (S-9) (Marshall et al., 1976; Moriya et al., 1983). Heptachlor was not active in the rec assay with *Bacillus subtilis* (Shirasu et al., 1976). Heptachlor also failed to induce mitotic gene reversion in *Saccharomyces cerevisiae* in the presence or absence of S-9 (Gentile et al., 1982).

Rats fed 1 or 5 ppm heptachlor in diet (0.05 to 0.25 mg/kg-day) for three generations showed an increased incidence of abnormal mitosis in bone-marrow cells in the second and third generations (Cerey et al., 1973). After a 7-month intragastric administration of heptachlor to albino rats at doses of 1/30, 1/50, and 1/100 of the LD_{50} (LD_{50} = 82 mg/kg body weight), it was established that doses of 1/30 and 1/50 of LD_{50} elicited changes in the mitotic activity of bone-marrow cells, inhibition of prophase, and chromosomal adhesion. A heptachlor dose of 1/100 of the LD_{50} (0.82 mg/kg-day) exerted a slight effect on rat bone-marrow cells (WHO, 1984).

Heptachlor administration failed to elicit a significant mutagenic response in tests designed to monitor testicular DNA synthesis in mice (Seiler, 1977) and in in vitro clastogenesis assays of plasmid DNA in E. coli (Griffin and Hill, 1978). Positive mutagenic results were reported for unscheduled DNA synthesis in transformed human fibroblasts with S-9 activation (Ahmed et al., 1977).

Heptachlor epoxide was negative in bacterial systems (Moriya et al., 1983; Marshall et al., 1976), in the recessive lethal assay in fruit flies (Benesh and Shram, 1969) and in the dominant lethal assay in mice (Arnold et al., 1977). The Genetic Activity Profile data base lists 59 test results for

heptachlor of which only nine were positive without activation and one with activation (GAP, version 4.06, 1994). Aside from positive tests in a few plant systems, positive

results for gene mutation in mouse L5178Y cells in vitro (TK locus), inhibition of intercellular communication in rodents in vitro (both without exogenous metabolic activation), and induction of unscheduled DNA synthesis in animal cells in vitro (with activation) are the few relevant findings listed.

Carcinogenicity

An evaluation of carcinogenicity studies in animals has been published by the U.S. EPA (1986c) and is summarized in the agency's IRIS online files for heptachlor and heptachlor epoxide last updated in 1993 (U.S.EPA 1993a,b). Presented below are data extracted from the EPA document and a discussion based on EPA's presentation. Many of the reports on the carcinogenicity of heptachlor and heptachlor epoxide have not been published, but Epstein (1976) has reviewed the results of those studies. Reuber (1987) has published a comprehensive review of all studies on the carcinogenic potential of heptachlor and heptachlor epoxide in animals.

Studies with Mice

Epstein (1976) and Reuber (1987) reported on a study carried out by the FDA in 1965. C3H male and female mice, 100 per group, 3 weeks of age, ingested 0 or 10 ppm heptachlor, or 10 ppm of heptachlor epoxide in diet for 2 years (Davis, 1965; Reuber, 1977b). Many mice were lost or discarded, sacrificed for transplant purposes or died (U.S. EPA, 1986a). The incidence of hepatocellular carcinoma in male and female control groups were 22/73 (30%) and 3/53 (4%), respectively. FDA pathologists found a two-fold increase in benign liver lesions in the treated animals over the controls, although the incidence of malignant liver tumors was less (U.S. EPA, 1986c). Reuber (1987) reported that carcinomas of the liver occurred in 64 of 87 male mice (74%) ($p < 0.0001$) and in 57 of 78 female mice (73%) ($p < 0.0001$) ingesting heptachlor; carcinomas of the liver occurred in 73 of 79 male mice (92%) ($p < 0.001$) and 77 of 81 female mice (95%) ($p < 0.001$) ingesting heptachlor epoxide in the diet. Four other independent pathologists reviewed a sample of 19 slides and generally concurred with the Reuber findings (U.S. EPA, 1986). One possible limitation of Reuber's evaluation is that those data were based on a smaller number of mice than in the original FDA study, particularly in control groups. Reuber's prepublication data were reanalyzed (Epstein, 1976), assuming that all missing control animals had liver carcinomas, and none of the missing test animals had liver carcinomas. On the basis of this calculation, the p values for the heptachlor and heptachlor epoxide males are 0.020 and 0.000731, respectively; similarly, the p values for the heptachlor epoxide-fed females were highly significant, $p = 0.000038$. The p values for the heptachlor females were not significant ($p = 0.1607$).

Epstein (1976) and Reuber (1987) also reviewed an unpublished study carried out in 1973 by the International Research and Development Corporation (IRDC) under contract to the Velsicol Chemical Corporation. Charles River CD-1 male and female mice, 7 weeks of age and 100 per group, were used. Mice ingested 0, 1.0, 5.0 or 10 ppm of a mixture of 75% heptachlor epoxide and 25% heptachlor in diet for 18 months. Additional groups of comparable size included a negative control and a positive control fed 250 ppm 2-acetaminofluorene. Body weight and food consumption were recorded weekly. Groups of l0 mice of each sex from all groups were killed at 6 months and the liver examined histologically. Female mice in the 10 ppm test group

and male mice in the positive control group failed to gain as much weight as the negative controls. A dose-related increase in liver weights of treated mice (particularly male mice) was observed as early as 6 months. The increases in liver weights of mice of both sexes ingesting 5 or 10 ppm for 18 months were highly significant ($p < 0.01$) and the liver weights of females given 1 ppm were also increased significantly ($p < 0.05$). Carcinomas of the liver were present in 2/61 (3%) male mice ingesting 1 ppm, 18/68 (26%) of mice ingesting 5 ppm ($p < 0.0001$), and 52/80 (65%) of mice fed 10 ppm heptachlor/heptachlor epoxide ($p < 0.00001$), compared to 0/62 (0%) in the control male mice (Reuber, 1987). Carcinomas of the liver developed in 1/70 (1%) female mice ingesting 1 ppm, 6/65 (9%) ingesting 5 ppm, and 30/57 (53%) of female mice fed 10 ppm heptachlor/heptachlor-epoxide ($p < 0.0001$), compared with 6/76 (8%) in control mice. Five other pathologists examined a portion of the slides and agreed with Reuber that the incidence of hepatic carcinoma was considerably under diagnosed in the original analysis (U.S. EPA, 1985a). The U.S. EPA IRIS file reports the male liver carcinoma incidence as 2/68 (3%) in the 1 ppm group(U.S. EPA, 1993b).

Epstein (1976) and Reuber (1987) concluded that the IRDC study, despite the limitations, showed that ingestion of a heptachlor/heptachlor epoxide mixture induced a dose-related increased incidence of nodular hepatic hyperplasia and that the increase was statistically significant.

In an NCI (1977) chronic oral bioassay, the carcinogenicity of technical grade heptachlor (73% heptachlor, 22% trans-chlordane and 5% nonachlor) was studied using Osborne-Mendel rats and B6C3F1 mice (U.S.EPA, 1985a). There were 50 treated mice in each group and 109 control mice of each sex. Male mice ingested an average dose of 6 or 14 ppm and female mice received 9 or 18 ppm for 80 weeks. These animals were killed after 89 to 92 weeks. The incidence of liver carcinoma in matched, pooled, low and high doses respectively were for the males: 5/19 (26%); 19/92 (21%); 11/46 (24%); 34/47 (72%) ($P = 0.00076$ vs. matched control). The respective tumor incidences for the female mice were: 2/10 (20%); 3/78 (4%); 3/47 (6%); and 30/42 (71%) ($P = 0.0043$ vs. matched control) (Reuber, 1987).

Studies with Rats

Technical grade heptachlor was fed to 50 male and 50 female Osborne-Mendel rats, 5 to 6 weeks of age, for 80 weeks (NCI, 1977). Male rats received an average of 38.9 or 77.9 ppm and female rats 18.9 or 37.8 ppm of heptachlor. Ten rats of each sex served as the matched controls, and 60 rats of each sex served as pooled controls. Rats were killed after 109 to 110 weeks.

Complete necropsies and histological examination were made. According to EPA (1986), no hepatocellular carcinomas were observed in any of the rats, with one cholangiocarcinoma diagnosed in one low-dose male. Neoplastic nodules were observed in all treated and control groups, with no statistically significant dose-related trend. A statistically significant exact test for a dose-related trend ($p < 0.002$) was found for follicular-cell carcinomas of the thyroid in females, but not in males, when they were combined with adenomas. This finding was discounted by NCI because the incidences of carcinomas were low and because of the variability of thyroid tumors in the control rat population.

In reassessing the NCI study, Reuber (1987) concluded that heptachlor was carcinogenic in rats and that the results of the NCI study had not previously been adequately examined and analyzed. Reuber's interpretation demonstrated that there was an increase in benign and malignant neoplasms at all sites in males ingesting the low dose (39/42, 93%) ($p < 0.00001$) or the high

dose (27/37, 73%) (p = 0.0095) of heptachlor, compared to the controls (27/58, 47%). The increase in benign neoplasias was striking because of the lower incidence in the pooled controls 9/58 (16%), and the increased incidence in the low-dose (26/42, 62%) ($p < 0.00001$) and the high-dose (21/37, 57%) (p = 0.00003) male rats. Fifty-seven percent (24/42) of low-dose rats and 33% (19/58) of control male rats had malignant neoplasms (p = 0.013). The increase in malignant neoplasms involved carcinomas, not sarcomas. There were insignificant increases in total neoplasms in female rats ingesting heptachlor; however, there were unusually large numbers of female control rats with neoplasms.

Neoplasms of the liver (hyperplastic nodules and carcinomas) developed in 13/42 (31%) (p = 0.00065) of low dose and 12/37 (32%) of high dose male rats fed heptachlor. The incidences of liver neoplasms in female rats in control, low and high dose groups were 4/59, 13/45 (p = 0.0029), and 8/37 (p = 0.036) respectively. The incidences of thyroid carcinoma in male rats were 3/58, 13/42 (p = 0.00065), and 2/37, respectively. The total of thyroid adenomas and carcinomas were 7/58, 24/42 ($p < 0.00001$), and 9/37, respectively. Significant increases in carcinomas of the pituitary and adrenal gland were also seen in male rats administered heptachlor. Neoplasms of the female reproductive system were seen in the mammary gland, uterus and ovary. Benign and malignant neoplasms (all sites) were observed in 40% (p = 0.0021) of low dose female rats, 73% (p = 0.00001) of high dose rats and 14% of controls (Reuber,1987).

Studies with Dogs

Dogs were fed heptachlor epoxide in a diet containing various concentrations for 2 years (IRDC, unpublished report cited in U.S. EPA, 1985). A level of 1 ppm caused no adverse effect on any of the parameters measured. Dose-related changes in biochemical values related to liver function and microscopic changes in liver were noted at the higher dose levels (3,5,7 and 10 ppm equivalent to about 0.075-0.25 mg/kg-day).

In a Kettering Laboratory study (U.S. EPA, 1986c) groups of two male and three female dogs were exposed to dietary levels of 0, 0.5, 2.5, 5, or 7.5 ppm (0-0.188 mg/kg-day) heptachlor epoxide (purity not indicated) for 60 weeks. No tumors were reported. The liver weights of both males and females tended to increase in proportion to the amounts of heptachlor in the diet and only one male at the highest dose had observable hepatic damage. The study duration is considered too short and the number of animals too small for this to be a valid carcinogenicity study.

Other Studies

Nomata et al. (1996) studied the ability of heptachlor and heptachlor epoxide to inhibit gap junctional intercellular communication (GJIC) in human breast epithelial cells (HBEC). Both heptachlor and heptachlor epoxide were noncytotoxic at concentrations up to 10 μg/L but at this concentration inhibited GJIC after 1 hr of treatment. GJIC completely recovered after a 12 hr treatment of 1 μg/L heptachlor epoxide, but did not recover after a 24 hr treatment of 1 μg/L heptachlor. GJIC inhibition may be associated with an observed hypophosphorylation of connexin 43 alternatively an heptachlor-induced increase of intracellular free Ca^{+2} may be involved. The authors' conclude that the results are consistent with observations showing that these pesticides are tumor promoters in rodent systems and suggest that they have potential of being human breast tumor promoters.

Epidemiological Studies

Wang and MacMahon (1979a; 1979b) studied a cohort of workers engaged in the manufacture of chlordane, heptachlor, and endrin together with another cohort of 16,000 pesticide-spraying personnel, including termite-control workers. Both studies showed a deficit of deaths from all cancers and slight excesses of lung, skin, or bladder cancers that were not statistically significant. In 1982, an IARC Working Group concluded that the above studies were inadequate to evaluate the carcinogenicity of chlordane for human beings (IARC, 1982). In one of these studies there was a statistically significant excess of deaths from cerebrovascular disease (17 observed, 9.3 expected). This excess was not related to duration of exposure or latency and occurred exclusively after termination of employment.

Shindell et al. (1981) studied the mortality of 783 workers engaged in the manufacture of chlordane and heptachlor. Workers had been employed for a minimum of 3 months and 5, 10, 15, or 20 years. SMRs for cancer were not increased among 124 deaths.

In a retrospective cohort study of workers involved in the production of chlorinated hydrocarbon pesticides, Ditraglia et al. (1981) studied the workers in a chlordane-manufacturing plant; Wang and MacMahon (1979a) had studied the same workers. SMRs for all cancer deaths were lower than expected; the slight excess of stomach cancer (3 vs 0.99 expected) was not statistically significant. There are limitations to this study. No information on quantitative exposures were provided. It was not possible to assess the effects of chlordane or heptachlor independently of the other chemical exposures at the two plants, some of which were known to be carcinogenic. No attempt was made to exclude or adjust for the effects of sex or race, nor was there an effort to control for other confounding variables such as smoking or alcohol consumption. This study provided inadequate evidence to link chlordane or heptachlor exposure to cancer (U.S. EPA, 1986c). MacMahon and Wang (1982) carried out a second follow-up study of mortality rates in a cohort employed in spraying pesticides, including termite-control workers. Among 540 deaths for which the cause was ascertainable, small excesses of bladder cancer in termite-control operators and of skin and lung cancer in other operators were observed, but these changes were not statistically significant.

Developmental and Reproductive Toxicity

No information was found indicating that heptachlor or heptachlor epoxide are reproductive or developmental toxicants at levels measured in human populations (ATSDR,1993;U.S. EPA, 1987c). Most controlled studies in experimental animals have been conducted with relatively high doses compared to likely levels of environmental exposure. It is possible that potentially adverse sex hormone-mediated effects of chlorinated cyclodienes may be apparent only with low dose test regimens (see Endocrine Toxicity below and Cassidy et al.,1994). There is sufficient evidence that heptachlor is a developmental toxicant in experimental animals based on the finding of reduced offspring viability.

Male and female rats fed exclusively on diets containing a mixture of heptachlor and heptachlor epoxide (3:1) at 0, 0.3, 3, or 7 ppm (mg/kg diet) were mated throughout three succeeding generations (Witherup et al., 1976a). The number of pregnancies in the F_1 and F_2 generations was slightly reduced in the 0.3 ppm group, but not in the higher dose groups. There was a slight

increase in the mortality rate of the pups in the second and third week after birth in the 3 ppm group. The doses in this study were approximately 0, 0.015, 0.15, 0.35 mg/kg-day.

In a study by Witherup et al. (1976b), male and female rats were fed diets containing heptachlor at 0, 0.3, 3, 6 or 10 ppm throughout three generations, and allowed to reproduce. Mortality of the pups was slightly increased in the 10 ppm group during the second and third weeks after birth, only in the 2nd generation. No adverse effects were reported at the lower dose levels. The doses in this study were approximately 0, 0.015, 0.15, 0.3, and 0.5 mg/kg-day.

The feeding of rats with heptachlor at 10 mg/kg body weight per day during a 3-generation reproduction study resulted in an increased number of resorptions and in lower viability and lactation indices (Cerey et al., 1971). Cataracts were found in 68% of the young and became obvious between the 19th and 26th day after birth. Among the parents, 15.2% of the animals were affected, and the lesions appeared after 4-9 months. A decrease in litter size was observed.

Twenty-four male and 24 female adult beagle dogs were used for a 2-generation reproduction and teratology study with heptachlor epoxide. The treated dogs were fed the compound at 1, 3, 5, 7, or 10 ppm in diet. No differences in body weight or food consumption were seen between control and treated dogs. All but one of the F_1, pups at the 10 ppm dietary level died between birth and 10 weeks of age. Abnormal hematological values were reported in some pups at the 1, 3, and 7 ppm levels. No compound-related abnormalities were observed in pups from the F_1 and F_2 generations. An increase in liver weight among P_2 (F_l) dogs from the 7 ppm level was the only organ weight variation considered compound-related. Granular "ground glass" cytoplasm in liver parenchymal cells of some P 2 (Fl) dogs at the 5, 7, and 10 ppm dietary levels was also reported (IRDC, 1973c). The doses in this study were approximately 0.025, 0.075, 0.125, 0.175, 0.25 mg/kg-day.

Pregnant female rabbits were treated orally with heptachlor epoxide at 0 (22 animals) or 5 mg/kg body weight/day (20 animals) from day 6 to 11 of gestation (Wazeter, 1967) and fetuses recovered by Cesarean section on day 28. There were no maternal deaths. No compound-related effects were observed with respect to numbers of viable and non-viable term fetuses, resorptions, implantation sites, corpora lutea, and non-gravid females. A significant increase in fetal weight was evident in the treated groups; this was considered to be compound-related. There were no teratogenic effects attributable to the compound.

Le Marchand et al. (1986) reported no observable 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.

The non-additive developmental toxicity of mixtures of trichloroethylene (TCE), di(2-ethylhexyl) phthalate (DEHP), and heptachlor has been studied in 5 x 5 x 5 designs in Fischer-344 rats. Dose levels of 0, 10.1, 32, 101, 320 mg/kg-day for TCE, 0,24.7, 78, 247, 780 mg/kg-day for DEHP, and 0, 0.25, 0.8, 2.5, 8 mg/kg-day for heptachlor were administered by gavage on days 6-15 of gestation. The dams were allowed to deliver and the pups were weighed and examined postnatally (Narotsky et al.,1995). Three maternal and six developmental endpoints were evaluated. Several significant two-way interactions but no significant three-way interactions were observed. Maternal death exhibited no single chemical or main effects but DEHP and heptachlor were synergistic. For maternal weight gain on gestational days 6-8, main chemical effects were seen for all three agents as well as TCE-DEHP synergism and DEHP-heptachlor antagonism. Maternal weight gain on gestational days 6-20 adjusted for litter weight showed effects for TCE and heptachlor, but no interactions. Effects of all three agents were seen for full-litter resorptions and prenatal loss. The heptachlor effects were unexpected, particularly as seen with pooled data

(heptachlor only plus heptachlor combinations) for each heptachlor dose, with 23% of (253) dams with resorbed litters at 8 mg/kg-day and 18% of (247) dams at 2.5

mg/kg-day vs. 12 % in the controls. For full-litter loss, the TCE-heptachlor and DEHP-heptachlor interactions were antagonistic. For prenatal loss, the TCE-DEHP interaction was synergistic. Postnatal loss showed DEHP and heptachlor effects but no interactions. Analysis of pup weights on day 1 revealed TCE and DEHP effects and DEHP-heptachlor antagonism; on day 6 DEHP and heptachlor effects and DEHP-heptachlor antagonism, and TCE-DEHP synergism were evident. The authors note that some antagonistic interactions of prenatal loss and full litter resorptions may reflect a ceiling effect and, based on heptachlor main effects, that heptachlor potentiated the other two agents. The authors thus regard all three two-way interactions to be synergistic for these related endpoints. Microphthalmia and anophthalmia incidences showed TCE and DEHP effects but no interactions.

Genning (1996) analyzed a subset of the Narotsky et al. data to illustrate the use of ray designs in mixtures of chemicals. Such ray designs provide a more economical way to study the effects of mixtures (Mantel,1958; Bruden et al.,1988). Mixtures of chemicals are evaluated along rays of fixed ratios. For example, for a mixture of three chemicals with fixed ratios represented by Chemical 1:Chemical 2:Chemical 3, a 1:0:0 ratio represents a ray of Chemical 1 alone, while a 1:1:1 ratio represents a ray of equal levels of the three chemicals. A ray design for a small number of chemicals and many mixture rays can support the estimation of a response surface. However, the advantage of a ray design is that it can also be used with a mixture of many chemicals and a few mixture rays where a predictive univariate model is fit along each ray with total dose as the independent variable (Genning, 1996). The selected response was prenatal loss. The rays selected were one for each single chemical and one mixture ray. The dose ratios for the rays were for (DEHP:heptachlor:TCE): (1:0:0); (0:1:0); (0:0:1); and (70:1:29). A threshold model was fitted along each of the four rays simultaneously. The predicted thresholds were 503, 8.4, 486, and 328 mg/kg-day, respectively. The author concluded that departure from additivity could not be claimed along the 70:1:29 ratio mixture ray.

Neurotoxicity

Seizures and cortical excitability are prime CNS symptoms following acute heptachlor exposure. Intravenous administration of 2-10 mg/kg bw heptachlor to cats (Joy, 1976) resulted in seizure activity in 20-40 min. While heptachlor produced enhanced cortical responses to sensory stimuli, primary responses along the somatosensory pathways were depressed. Although seizures have been attributed to increased neurotransmitter release, acetylcholine (ACh) concentrations were increased 2.3 fold only during the period of increased motor activity, and decreased and returned to normal during the most severe seizure activity. Hrdina et al. (1974) found that chronic heptachlor (3-15 mg/kg) or heptachlor epoxide (1-5 mg/kg) administration significantly decreased cerebrocortical ACh, increased levels of brainstem serotonin and produced no change in brainstem norepinephrine levels with no signs of neurotoxicity.

Two theories have been advanced to explain the cortical excitability and altered neurotransmitter levels associated with heptachlor exposure. The first claims that heptachlor inhibits a Ca^{2+}, Mg^{2+}-ATPase, causing elevated intracellular Ca^{2+} levels with subsequent increased release of excitatory neurotransmitters. The second involves the γ-aminobutyric acid (GABA) binding sites on postsynaptic membranes. GABA is the major inhibitory neurotransmitter in the CNS. The GABA receptor is part of a complex containing the GABA site and a Cl^- ionophore with binding capacities for benzodiazepines and picrotoxin (Fendick et al., 1990). Activation of GABA

receptors increased membrane conductance for Cl^- in postsynaptic membranes. The non-competitive inhibitor t-butylbicyclophosphorothionate (TBPS) is highly specific for GABA and

binds to the Cl^- ion channel of the complex. Both heptachlor and heptachlor epoxide were effective in displacing [^{35}S]TBPS from GABA binding sites in rat brain membrane preparations with IC_{50} values of 400n*M* and 70 n*M*, respectively (Abalis et al., 1985). The correlation between the efficiency of heptachlor in inhibiting GABA, its ability to inhibit GABA-induced $^{36}Cl^-$ influx, and its ability to inhibit binding of [^{35}S]TBPS in rat brain microsacs, indicates that the GABA receptor is the main target of the toxic action of heptachlor.

Immunotoxicity

Heptachlor may affect components of the immune system. Heptachlor can cause contact dermatitis in humans. Heptachlor and heptachlor epoxide (0.01-16 mg/L) stimulated dose-dependent histamine release from rat peritoneal mast cells and human basophils in vitro (Rohr et al., 1985), and also stimulated mast cells to release leukotrienes C3 and C4 which are chemotactic for eosinophils and neutrophils (Fendick et al., 1990).

Biochemical Toxicity

Heptachlor exposure may affect a number of xenobiotic metabolizing enzymes in liver and possibly other organs. Heptachlor stimulated NADPH oxidase in male rat microsomes in vitro, and increased the rate of cytochrome P-450 reduction by 150-200%. These effects were markedly less evident in female rat microsomes. Other microsomal enzymes induced by heptachlor include: aldrin epoxidase; aminopyrene demethylase; aniline hydroxylase; benzo[a]pyrene hydroxylase; ethoxyresorufin-*O*-deethylase; hexobarbital oxidase; *N*-demethylase; and *O*-demethylase (Fendick et al., 1990; Haake et al.,1987). While enzyme induction is not necessarily an indication of toxicity, increased P-450 activity is probably an exposure marker, and some enzyme induction may have unwanted effects such as enhancing the influence of certain toxic metabolites.

Endocrine Toxicity

There is a relationship between potent liver enzyme inducers, hepatocyte smooth endoplasmic reticulum (SER) proliferation, and increased metabolic activity of the thyroid. Effects on the thyroid include elevation of thyroid stimulating hormone (TSH) and depletion of T4 (Fendick et al., 1990). An increased uptake of ^{125}I-T4 by liver is associated with microsomal induction and SER proliferation in rats exposed to chlordane (Bernstein et al., 1968). These findings are of interest in view of the induction of thyroid carcinomas in female rats exposed to heptachlor (see above and Reuber, 1987).

Cassidy et al. (1994) studied the effects of technical chlordane exposure during pre- and postnatal periods on sex steroid-mediated behaviors and functions in the rat. Technical chlordane is a mixture of chlorinated cyclodienes: *trans*-chlordane, 24%; chlordane isomers, 21.5%; *cis*-chlordane,19%; heptachlor, 10%; and nonachlor, 7%. Time-pregnant Sprague-Dawley dams (Day 4 of gestation through Day 21 of lactation) and offspring (Day 22 of age through Day 80) were fed three dose levels of technical chlordane (0.1, 0.5, 5.0 mg/kg bw) in peanut oil supplemented peanut butter (1 cm^3 of peanut butter) on a daily schedule. The measurements made on 3-5 animals/sex were: cyclodiene concentrations in rat blood and milk; serum

testosterone; body weight; mating behavior; Cincinnati maze; open field activity; auditory startle; and chloride-36 uptake into brain microsacs. The plasma concentrations of heptachlor

epoxide and other cyclodienes increased during gestation and then decreased during lactation. In contrast, the plasma levels of cyclodienes in the offspring increased throughout the postweaning period. Concentrations of the analytes in dam milk on Day 8 of lactation for the 0.1 mg/kg dose level were: heptachlor, non-detect; heptachlor epoxide, 51 ng/mL; *trans*-chlordane, 2.4 ng/mL; oxychlordane, 46 ng/mL. Testosterone levels were significantly reduced in females at 0.5 and 5.0 mg/kg exposure levels. The levels were 20, 60, and 55% below control values for the 0.1, 0.5, and 5.0 mg/kg doses. Treated males showed very little effect with only a 10% increase at 5.0 mg/kg. Dose-related increases in body weight were observed in female offspring at all doses but only female offspring at the 0.5 mg/kg level were significantly different from controls ($p < 0.05$).

Of the behavioral tests conducted only mating behavior, visiospatial, and auditory-evoked startle tests produced significant effects at the 0.1 mg/kg level. The chlorine-36 uptake in 5.0 mg/kg dosed male offspring was significantly reduced. The authors conclude that chlordane, or more specifically its oxidized metabolites oxychlordane and heptachlor epoxide, are mimicking sex steroids and/or altering their levels. Only chlordane-dosed females were significantly different in plasma cyclodiene levels, in the Cincinnati maze, and in body weight. Treated females exhibited more masculine effects that often mirrored dose dependent effects in steroid-treated rats. Chlordane-dosed males exhibited increased male-typical mating behaviors and 5.0 mg/kg dosed males had decreased chloride-36 uptake. It is consistent with previous findings that cyclodienes from chlordane would bind with sex-steroid receptors in the central nervous system and alter sexually dimorphic behaviors and functions. The study indicates a LOAEL of 0.1 mg/kg-day for sex steroid-related behavioral effects. The authors note that even a lower LOAEL might have been observed with lower doses and the U.S. EPA recommended 20 dams/dose. Since heptachlor is a significant component of technical chlordane and heptachlor epoxide was found in the blood and milk at levels similar to oxychlordane, it is possible that heptachlor and/or heptachlor epoxide played a role in the adverse effects noted.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The current oral RfD given by U.S. EPA (1993a) in the IRIS file is 5E-4 mg/kg bw/day. This value was derived from the 3 ppm dietary NOAEL in a 2-year rat feeding study where the critical effect was liver weight increase (Velsicol Chemical, 1955 cited in U.S. EPA online IRIS file). The LOAEL in this study was 5 ppm or 0.25 mg/kg-day and an uncertainty factor of 300 was employed. The assumed rat feed consumption was 0.05 mg/kg-day/ppm in feed. The RfD for heptachlor epoxide (U.S. EPA, 1993b) is 1.3E-5 mg/kg-day. This value was derived from the LOAEL of 0.5 ppm (0.0125 mg/kg-day) in a 60-week dog feeding study showing increased liver-to-body weight ratio in both males and females (Dow Chemical Co., 1958 cited in U.S. EPA IRIS online file). An uncertainty factor of 1000 was employed. U.S. EPA lists both RfDs as having low confidence.

Carcinogenic Effects

The mechanism of carcinogenic action of heptachlor or heptachlor epoxide is uncertain. Heptachlor is not mutagenic in the large majority of genotoxicity tests conducted. However, positive activity in selected systems such as gene mutation in mammalian cells in vitro, unscheduled DNA synthesis in mammalian cells in vitro, and inhibition of intercellular communication indicate that a genotoxic mechanism cannot be totally ruled out. There is no evidence or valid biological model supporting a threshold or non-linear approach for heptachlor or heptachlor epoxide or related chlorinated cyclodienes (OEHHA, 1997).

The most relevant data sets for estimating the carcinogenic potencies or cancer slope factors (CSF's) are the four data sets for heptachlor in C3H and B6C3F1 mice (Davis,1965; NCI,1977), and the four data sets for heptachlor epoxide in C3H and CD-1 mice (Davis,1965; IRDC (Velsicol),1973) which show significant dose-dependent increases in liver carcinomas (Reuber, 1987). Earlier quantitative estimates using the linearized multistage model and (body weight)$^{2/3}$ interspecies scaling are provided in Tables 3 and 4 for comparison with the present estimates which are based on the LED_{10} and (body weight)$^{3/4}$ scaling. The LED_{10} is the 95% lower confidence limit on the dose that gives a 10% extra lifetime risk of cancer. Potency values based on the LED_{10} or the LMS were calculated from the data sets using Tox_Risk (Version 3.5) software (K. S. Crump Division, Clement International Corp., Ruston, LA). All procedures are for estimates of extra risk. For determination of the LED_{10} a goodness of fit criterion of $p>0.05$ was adopted for the Chi-squared test, whereas $p > 0.01$ is usually considered sufficient for the LMS. The LED_{10} values for heptachlor ranged from 0.0071 to 0.067 mg/kg-day and CSF's ranged from 1.5 to 14.1 (mg/kg-day)$^{-1}$ (Table 3). The geometric mean CSF (Gmean 1) of the four data sets was 3.2 (mg/kg-day)$^{-1}$. The geometric mean for the LMS potency or q_1* value was 2.2 (mg/kg-day)$^{-1}$. The geometric mean CSF for three data sets meeting the fit criterion (Gmean 2) was 4.1 (mg/kg-day)$^{-1}$.

The potency values in Table 3 differ from those provided by U.S. EPA (IRIS, 1993) primarily because U.S. EPA did not correct these potencies for experiments of shorter duration than two years, the life span typically assumed for rats and mice. U.S. EPA considered the mouse lifespan to be 18 months. The present estimates include an intercurrent mortality correction of about 1.5 for a study duration of 90 weeks ($(104/90)^3$). Also most listed U.S. EPA potency values are based on (body weight)$^{2/3}$ scaling and have not yet been recalculated based on the newer (body weight)$^{3/4}$ scaling policy. Not included in Table 3 is an analysis of the combined reproductive neoplasms in female Osborne-Mendel rats fed 0, 18.9 and 37.8 ppm heptachlor for 80 weeks with tumor incidences of 8/59, 18/45, and 27/37, respectively (Reuber, 1987). This data set gave LED_{10} of 0.21 mg/kg-day and a CSF of 4.8 (mg/kg-day)$^{-1}$. Thus the heptachlor potency estimates from both species are comparable. The OEHHA 1987 potency value of 5.7 (mg/kg-day)$^{-1}$ for heptachlor is currently that listed in the "California Environmental Protection Agency Criteria for Carcinogens" compiled by Cal/EPA's Risk Assessment Coordination Work Group (Cal/EPA, 1994). The best current estimate for cancer potency of heptachlor is the CSF of 4.1 (mg/kg-day)$^{-1}$.

Table 3.Cancer Potencies for Heptachlor Based on Mouse Liver Carcinoma.

Data Set	q_1* $(mg/kg\text{-}d)^{-1}$	X^2	p	k	MLE_{10} mg/kg-d	LED_{10} mg/kg-d	CSF $(mg/kg\text{-}d)^{-1}$	U. S. EPA '93 $(mg/kg\text{-}d)^{-1}$	OEHHA '88 $(mg/kg\text{-}d)^{-1}$
C3H Male	1.6	0	1	1	0.0095	0.0071	14.1	12.4	12.4
C3H Female	8.6	0	1	1	0.091	0.056	1.8	14.9	15.0
$B6C3F_1$ Male	2.36	2.6	0.11	2	0.059	0.037	2.7	2.79	4.1
$B6C3F_1$ Female	0.71	14.1	0.0002	2	0.083	0.067	1.5	0.83	1.4
Gmean 1	2.2						3.2	4.5	5.72
Gmean 2	3.2						4.1		

Note: The C3H mouse data sets are from Davis (1965), the $B6C3F_1$ mouse data sets are from NCI (1977). The q_1* is the carcinogenic potency determined by the linearized multistage model. X^2 is the value of the chi squared goodness of fit statistic; p is the significance of the chi squared value where a criterion of ≥ 0.05 is considered an adequate fit of the polynomial equation to a data set; k is the number of nonzero doses used in the fitting procedure. MLE_{10} is the maximum likelihood estimate of the dose that corresponds to a 10% tumor response. LED_{10} is the 95% lower confidence limit on the MLE_{10} dose. The CSF is the carcinogenic potency or cancer slope factor calculated from the LED_{10}. Gmean 1 is the geometric mean of all values. Gmean 2 is the mean of values except the $B6C3F_1$ female data set.

The companion analysis for heptachlor epoxide is shown in Table 4 below. The LED_{10} values ranged from 0.0071 to 0.089 mg/kg-day, the q_1* values ranged from 0.58 to 20.9 $(mg/kg\text{-}day)^{-1}$ and the CSFs ranged from 1.1 to 18.5 $(mg/kg\text{-}day)^{-1}$. The geometric mean CSF value was 5.5 $(mg/kg\text{-}day)^{-1}$ or approximately 60% of the U.S.EPA's current value of 9.1 $(mg/kg\text{-}day)^{-1}$ given in IRIS (U.S.EPA,1993b). The chief difference between this new value and the U.S.EPA value is the interspecies scaling default of (body weight) ¾ vs. the earlier $(body\ weight)^{2/3}$. The OEHHA 1988 value of 13 $(mg/kg\text{-}day)^{-1}$ is that currently listed in the "California Environmental Protection Agency Criteria for Carcinogens" (Cal/EPA,1994). The best current estimate of cancer potency of heptachlor epoxide is the mean CSF of 5.5 $(mg/kg\text{-}day)^{-1}$.

Table 4.Cancer Potencies for Heptachlor Epoxide Based on Mouse Liver Carcinoma.

Data Set	q_1* $(mg/kg\text{-}d)^{-1}$	X^2	p	k	MLE_{10} mg/kg-d	LED_{10} mg/kg-d	CSF $(mg/kg\text{-}d)^{-1}$	USEPA '93 $(mg/kg\text{-}d)^{-1}$	OEHHA '88 $(mg/kg\text{-}d)^{-1}$
C3H Male	15.8	0	1	1	0.0095	0.0071	14.1	27.7	27.72
C3H Female	20.9	0	1	1	0.0071	0.0054	18.5	36.2	36.21
CD1 Male	3.6	0	1	3	0.051	0.031	3.2	6.48	13.79
CD1 Female	0.58	4.3	0.12	3	0.11	0.089	1.1	1.04	2.00
GMean	5.1						5.5	9.1	12.90

NOTE: MLE's and LED's in Tox_Risk were given as dietary concentration on 100% food basis and these values were converted to mg/kg-day assuming 1.5 kg diet/d and 70 kg human body weight. An example of the CSF calculation is CSF = 10% Risk/LED_{10} = 0.1/0.0054 mg/kg-day = 18.5 $(mg/kg\text{-}day)^{-1}$.

CALCULATION OF THE PUBLIC HEALTH GOAL (PHG)

The data available for residues of heptachlor and heptachlor epoxide in human adipose tissue and human milk suggest widespread, albeit declining, contamination of the environment. Food, air and breast milk are the main sources of exposure of the general population to these chlorinated cyclodienes. Relative source contribution from drinking water, based on exposure data, is low primarily due to the hydrophobic properties of these compounds.

Non-Cancer Effects

A new issue surrounding the chronic low level exposures to heptachlor, heptachlor epoxide and related chlorinated cyclodienes, and certain other chlorinated pesticide environmental residues centers on their ability to mimic various hormones and potentially disrupt critical endocrine functions. Such disruptions may be transient or irreversible depending which hormone receptors are affected and the timing of the effect (Cassidy et al.,1994). Based on the current oral RfDs of the U.S. EPA the following water concentrations are unlikely to be associated with any adverse health effects:

Heptachlor

$$C = \frac{NOAEL \times BW \times RSC}{UF \times W} = \frac{0.15\ mg/kg\text{-}day \times 10\ kg \times 0.2}{100 \times 1.0\ L/day} = 0.003\ mg/L$$

$$= 3\ ppb$$

Where:

NOAEL = No-Observed-Adverse-Effect-Level 0.15 mg/kg-day in rats based on liver weight increases in male rats (U.S. EPA, 1993a). This NOAEL is the basis of the current oral RfD for heptachlor. The critical study did not employ a broad range of doses or specific tests to assess adverse effects on endocrine function.

BW = body weight of an exposed child. Developing children may be at special risk from the potential hormone mimicking effects of heptachlor and related cyclodienes.

RSC = 0.2, the relative source contribution of drinking water to overall chlordane exposure. The major exposures are from food including breast milk and the water contribution is low, probably less than 1-5% at the current state MCL of 0.1 ppb. The 0.2 or 20% is the lowest default value currently used by U.S. EPA.

UF = 100, the product of uncertainty factors to account for interspecies variability (10) and interindividual variability (10).

W = 1.0 L/day, the daily water intake by a child.

C = The concentration of the toxicant in water that would not be considered to cause adverse human health effects over a lifetime of exposure

Alternatively, the LOAEL (Lowest-Observed-Adverse-Effect-Level) of 0.1 mg/kg-day of Cassidy et al. (1994) based on increased male-typical mating behavior in male rats could be used to calculate a more health conservative value as follows:

$$C = \frac{LOAEL \times BW \times RSC}{UF \times W} = \frac{0.1\ mg/kg\text{-}day \times 10\ kg \times 0.2}{1{,}000 \times 1.0\ L/day} = 0.0002\ mg/L$$

$$= 0.2$$

ppb

In this calculation the uncertainty factors are LOAEL to NOAEL extrapolation (10) interspecies variability (10), and interindividual variability (10). Also as noted above the study involved dosing animals with technical chlordane containing heptachlor and both oxychlordane and heptachlor epoxide were detected in blood and milk thus the adverse effects noted could be due to either or both parent cyclodienes or their respective oxy-metabolites.

Heptachlor Epoxide

A similar calculation can be made for heptachlor epoxide:

$$C = \frac{LOAEL \times BW \times RSC}{UF \times W} = \frac{0.0125 mg/kg\text{-}day \times 10\ kg \times 0.2}{1{,}000 \times 1.0\ L/day} = 0.000025\ mg/L$$

$$= 0.025\ ppb$$

$$= 25\ ppt$$

Where:

LOAEL	=	Lowest-observed-adverse-effect-level of 0.0125 mg/kg-day for increased liver to body weight ratio in dogs (U.S. EPA,1993b).
BW	=	Body weight (a default of 10 kg for children) of an exposed child because developing children may be at special risk from the potential endocrine disrupting effects of heptachlor epoxide and related chlorinated cyclodienes.
RSC	=	Relative source contribution. A default of 20% or 0.2 is used for heptachlor epoxide with chief exposures being from food, including breast milk, rather than from drinking water.
UF	=	1,000, the product of uncertainty factors to account for the conversion from LOAEL to NOAEL (10), interindividual variability (10) and interspecies variability (10).
W	=	Daily water consumption default of 1 L/day for a child.

Carcinogenic Effects

The primary issue surrounding calculation of the PHG for heptachlor and heptachlor epoxide is the potential for chlordane to induce human cancer. According to the U.S.EPA's proposed guidelines for carcinogen risk assessment (EPA,1996) a greater emphasis is to be placed on other information besides animal tumor data in reaching conclusions about human carcinogenic potential. This aspect of the risk assessment will be discussed below under risk characterization. The risk characterization provides the risk manager with more information about the weight of evidence supporting the PHG and what degree of leeway from a toxicological viewpoint might be available in setting a state MCL.

Heptachlor

Based on the NCI (1977) dose-related increase in the incidence of hepatocellular carcinoma in male and female B6C3Fl mice and the incidence of hepatocellular carcinoma in male and female C3H mice (Davis, 1965), U.S.EPA (1993) derived a human cancer potency value (q_1*) of 4.5 $(mg/kg\text{-}day)^{-1}$ for heptachlor. This estimate is slightly lower than the potency of 5.7 $(mg/kg\text{-}day)^{-1}$ derived by CDHS/OEHHA in 1988. The current best estimate of potency or CSF based on the same data sets, but employing updated low dose and interspecies extrapolation procedures is 4.1 $(mg/kg\text{-}day)^{-1}$.

The following calculation can be made from the heptachlor CSF:

$$C = \frac{R \times BW}{CSF \times W}$$

$$= \frac{1 \times 10^{-6} \times 70\ kg}{4.1\ (mg/kg\text{-}day)^{-1} \times 2\ L/day} = 8.5 \times 10^{-6}\ mg/L = 8\ ppt$$

Where

R	=	1×10^{-6}, the negligible extra theoretical lifetime risk of cancer.
BW	=	70 kg, the average human body weight.
CSF	=	4.1 $(mg/kg\text{-}day)^{-1}$, the carcinogenic potency or cancer slope factor for humans (Table 3).
W	=	2.0 L/day, the average daily water intake including water used in cooking and beverages.
C	=	The concentration of the toxicant in water associated with negligible lifetime extra cancer risk

It is assumed that inhalation exposures from water borne heptachlor due to showering, bathing and household uses of water would be negligible. Also, as typical in such calculations based on animal cancer data extrapolation, no relative source contribution is used.

U.S. EPA's current calculated 10^{-6} risk value for drinking water is also 8 ppt. Since the non-cancer value is less health protective **the PHG is based on the cancer value of 8 ppt (8×10^{-6} mg/L)**. If the margin of exposure (MOE) is defined as the LOAEL for masculinizing endocrine effects in the Cassidy et al. (1994) study of 0.1 mg/kg-day, divided by the intake in mg/kg-day of heptachlor at the proposed PHG, with the same body weight and water intake assumptions noted above, the calculated MOE for a 70 kg adult would be $0.1/2.3 \times 10^{-7} = 4.4 \times 10^{5}$.

Heptachlor Epoxide

Based on the IRDC (1973) dose related increase in the incidence of hepatocellular carcinomas in male and female CD-1 mice and the incidence of hepatocellular carcinomas in male and female C3H mice (Davis,1965), U.S. EPA derived a human cancer potency value (q_1*) of 9.1 (mg/kg-day)$^{-1}$ for heptachlor epoxide. This estimate is lower than the potency of 12.9 (mg/kg-day)$^{-1}$ derived by CDHA/OEHHA in 1988. The current best estimate of potency or CSF of 5.5 (mg/kg-day)$^{-1}$ is based on the same data sets but employs a low dose extrapolation procedure based on the LED_{10} and a different interspecies scaling default of (body weight) ^{¾}.

The following calculation can be made from the heptachlor epoxide CSF:

$$C = \frac{R \times BW}{CSF \times W} = \frac{1 \times 10^{-6} \times 70\ kg}{5.5\ (mg/kg\text{-}day)^{-1} \times 2\ L/day} = 6.4 \times 10^{-6}\ mg/L$$

$$= 6\ ppt$$

U.S. EPA's current calculated 10^{-6} risk value for heptachlor epoxide in drinking water is 4 ppt. Since the non-cancer health-protective value of 25 ppt is higher, **the PHG is based on the cancer value of 6 ppt (6×10^{-6} mg/L).** The calculated MOE for masculinizing endocrine effects of heptachlor epoxide at the proposed PHG for a 70 kg adult is $0.1/\ 1.7 \times 10^{-7} = 5.8 \times 10^{5}$.

RISK CHARACTERIZATION

While practically all uses of heptachlor and heptachlor epoxide have been banned or voluntarily canceled, its persistence in the environment has led to continuing albeit slowly declining exposures largely via the diet, milk, fish etc. Synergistic or antagonistic effects of heptachlor on certain reproductive endpoints have been noted in a study of mixtures of heptachlor, trichloroethylene, and di(2-ethylhexyl)phthalate. Due to its persistence in human body fat, and particularly in breast milk, continuing and possibly critical (temporal) exposures are a cause for concern. The cancer data in rodents are sufficient to consider heptachlor and heptachlor epoxide probably carcinogenic in humans, however from a quantitative assessment viewpoint these studies are mostly limited to liver tumors in mice. Data in human epidemiological studies are fragmentary and insufficient for risk assessment. Some case reports and studies suggest links between heptachlor and chlordane exposure and blood dyscrasias, leukemia, non-Hodgkin's lymphoma, and cancers of the lung, brain, skin, bladder, and stomach. The mechanism of cancer causation is unknown but there is insufficient information to depart from a low dose linear approach to estimate human cancer risks. The draft 1996 proposed U.S. EPA methodology for carcinogen risk assessment used in this document results in a cancer slope factor or potency of 4.1 (mg/kg-day)$^{-1}$ for heptachlor and 5.5 (mg/kg-day)$^{-1}$ for heptachlor epoxide which are only somewhat less than the current U.S.EPA or OEHHA/Cal/EPA values which range from 4.5 to 5.7 (mg/kg-day)$^{-1}$ for heptachlor and 9.1 to 12.9 (mg/kg-day)$^{-1}$ for heptachlor epoxide. These differences are almost wholly the result of the use of the new interspecies scaling default of (body weight)$^{3/4}$ versus the old default of (body weight)$^{2/3}$.

A new concern with respect to heptachlor, heptachlor epoxide and related chlorinated cyclodienes, and certain other persistent pesticide residues in the environment is their potential

role as endocrine disrupters. U. S. EPA (1997) is concerned about the possibility of impacts to human health and the environment resulting from exposure to these agents, however the Agency does not consider endocrine disruption to be an adverse endpoint *per se* but rather as a step that could lead to toxic outcomes such as cancer or adverse reproductive effects. The masculinizing effects of chlordane (containing heptachlor) in rats exposed to low doses raise questions about potential effects in humans who are exposed via diet and adipose tissue body burdens as well as the adequacy of common descriptive toxicity testing protocols. There are many uncertainties regarding the use of such data for human risk assessment (Rhomberg, 1997). Additional studies will be needed to better characterize these effects in experimental animals. While at this time the data on endocrine effects are not sufficient in themselves to support the proposed PHG, they are of sufficient concern, in the context of the PHG, to be taken into account with the other toxic endpoint of significant potential for adverse human health effects i.e., cancer.

The proposed PHGs of 6 and 8 ppt are similar to the 10^{-6} risk levels of 4 and 8 ppt cited by U.S.EPA (1993a,b) although the derivation is based on a different procedure. The cancer slope factors in the data sets examined varied by a factor of 9 for heptachlor and 17 for heptachlor epoxide and a geometric mean CSF derived from the best fit data sets was considered the best overall value. If the highest CSFs were chosen instead of the geometric means the proposed PHGs would be 2 ppt or 25 -33% of the value chosen. This is not considered a significant difference in view of the uncertainties and limitations in the data sets, mode of action etc. noted above and in the text.

OTHER REGULATORY STANDARDS AND CRITERIA

The World Health Organization (WHO) has recommended an acceptable daily intake of heptachlor plus heptachlor epoxide in food of 0 to 0.5 µg/kg body weight (WHO, 1984). WHO also has recommended a guideline concentration of 0.1 µg/L in drinking water based on the cancer endpoint (ATSDR,1993).

The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted an 8-hour TWA threshold limit value (TLV) for exposure to heptachlor of 0.5 mg/m^3 (ACGIH, 1986b). This TWA limit was considered to be sufficiently low to prevent systemic poisoning (ACGIH, 1986a). The ACGIH has not adopted a TWA-TLV for heptachlor epoxide, and NIOSH has not recommended a permissible exposure limit for the compound. The U.S. National Research Council has recommended an interim guideline for airborne heptachlor in military housing of 2 µg/m^3 (U.S. EPA, 1987b).

Tolerances for residues of heptachlor and heptachlor epoxide in or on various raw agricultural commodities are set at zero, 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 (U.S. EPA, 1986b).

The Office of Drinking Water of the EPA has recommended the following health advisories (HAs) for heptachlor: one-day or ten -day HA for a 10 kg child of 1.0E-2 mg/L (10 ppb); longer-term HA of 5E-3 mg/L (5 ppb) for a child and 0.0175 mg/L (17.5 ppb) for an adult. Due to its probable carcinogenicity no lifetime HA has been proposed. A drinking water equivalent level (DWEL) of 1.75E-2 mg/L (17.5 ppb) has been derived for heptachlor from the oral RfD of 5E-4 mg/kg-day. For heptachlor epoxide no one-day or ten-day HAs have been set. For a longer-term

HA EPA has recommended 1.5E-4 mg/L for a child and 5E-4 mg/L for an adult. No lifetime HA has been proposed for heptachlor epoxide. A DWEL of 4.4E-4 mg/L (440 ppt) has been derived from the oral RfD of 1.3E-5 mg/kg-day. Maximum contaminant levels (MCLs) of 4E-4 mg/L (400 ppt) for heptachlor and 2E-4 mg/L (200 ppt) for heptachlor epoxide have been established. The federal maximum contaminant level goals (MCLGs) for both compounds are zero. The 1E-6 or negligible risk levels for heptachlor and heptachlor epoxide in drinking water are 8E-6 mg/L (8 ppt) and 4E-6 mg/L (4 ppt) respectively.

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 (U.S. EPA 1987b).

The EPA has established a National Ambient Water Quality Criterion for Human Health for heptachlor or heptachlor epoxide of 2.8E-7 mg/L for water and fish and 2.9E-7 mg/L for fish only (U.S.EPA,1993a,b).

The State of California has established maximum contaminant levels (MCLs) of 1E-5 mg/L (10 ppt) for heptachlor or heptachlor epoxide in drinking water (Section 64444, California Health and Safety Code).

REFERENCES

Abalis. I.M., M.E. Eldefrawi, and A.T. Eldefrawi. 1985. High affinity stereospecific binding of cyclodiene insecticides and γ-hexachlorocyclohexane for γ-aminobutyric receptors of rat brain. Pestic. Biochem. Physiol. 24:95-102.

Abbott, D.C., G.B. Collins and R. Goulding. 1972. Organochloride pesticide residues in human fat in the United Kingdom 1969-1971. Br. Med. J. 2:553-556.

Adeshina, F. and E.L. Todd. 1990. Organochlorine compounds in human adipose tissue from North Texas. J Toxicol. Environ. Health. 29:147-156.

Ahmed, F.E., R.W. Hart and N.J. Lewis. 1977. Pesticide-induced DNA damage and its repair in cultured human cells. Mutat. Res. 42:161-174.

ACGIH. 1986a. Documentation of the Threshold Limit Values and Biological Exposure Indices. 5th ed, Cincinnati, OH: American Conference of Governmental Industrial Hygienists. p. 296.

ACGIH. 1986b. TLV'S. Threshold Limit Values and Biological Exposure Indices for 1986-1987. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. pp. 5, 20.

Arnold, D.W., G.L. Kennedy, Jr., M.L. Keplinger, J.C. Calandra and C.J. Calo. 1977. Dominant lethal studies with technical chlordane, HCS-3260 and heptachlor: heptachlor epoxide. J. Toxicol. Environ. Health. 2:547-555.

Arthur, R.D., J.D. Cain and B.F. Barrentine. 1975. The effect of atmospheric levels of pesticides on pesticide residues in rabbit adipose tissue and blood sera. Bull. Environ. Contam. Toxicol. 14:760.

Arthur, R.D., J.D. Cain and B.F. Barrentine. 1976. Atmospheric levels of pesticides in the Mississippi Delta. Bull. Environ. Contam. Toxicol. 15(2):129-134.

ATSDR. 1989. Toxicological Profile for Heptachlor/Heptachlor Epoxide. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, Washington, DC.

ATSDR. 1993. Toxicological Profile for Heptachlor/Heptachlor Epoxide. Update TP-92/11. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, Washington, DC.

Barguet, A., C. Morgade and C.D. Pfaffenberger. 1981. Determination of organochlorine pesticides and metabolites in drinking water, human blood serum and adipose tissue. J. Toxicol. Environ. Health. 7(3-4):469-479.

Ben-Dyke, R., D.M. Sanderson and D.N. Noakes. 1970. Acute toxicity data for pesticides. Wildl. Rev. Pestic. Control. 9:119.

Benesh, V. and R. Shram. 1969. Mutagenic activity of some pesticides in Drosophila melanogaster. Ind. Med. 38:442-444.

Bernstein, G., S.A. Artz, J. Hasen and J.H. Oppenheimer. 1968. Hepatic accumulation of I-125-thyroxine in the rat: Augmentation by phenobarbital and chlordane. Endocrinology 82:406.

Breidenbach, A.W., C.G. Gunnerson, F.K. Kawahara, J.J. Lichtenberg and R.S. Green. 1967. Chlorinated hydrocarbon pesticides in major river basins, 1957-65. Public Health Rep. 82:139-156.

Brooks, G.T., S.E. Lewis and A. Harrison. 1968. Selective metabolism of cyclodiene insecticide enantiomers by pig liver microsomal enzymes. Nature (London). 220:1034-1035.

Brooks, G.T., A. Harrison and S.E. Lewis. 1970. Cyclodiene epoxide ring hydration by microsomes from mammalian liver and houseflies. Biochem. Pharmacol. 19:225.

Brooks, G.T. 1974. Chlorinated Insecticides. Biological and Environmental Aspects. CRC Press, Cleveland, Vol. 2. (As cited in WHO, 1984).

Bruden, M.N., T.J. Vidmar and J.W. McKean. 1988. Drug Interaction and Lethality Analysis.

CRC Press, Boca Raton, FL, pp11-41.

Burns, B.G., M.E. Peach and D.A. Stiles. 1975. Organochlorine pesticide residues in a farming area, Nova Scotia, 1972-1973. Pestic. Monit. J. 9:34-38.

Burns, J.E. 1974. Organochlorine pesticide and polychlorinated biphenyl residues in biopsied human adipose tissue - Texas, 1969-1972. Pestic. Monit. J. 7:122.

Cal/EPA. 1994. Criteria for Carcinogens. Standards and Criteria Work Group. California Environmental Protection Agency, Sacramento.

Callahan, M.A., M.W. Slimak, N.W. Gabel et al. 1979. Water-related environmental fate of 129 priority pollutants, Vol. II. Off. Water Plan. Stand., Office Water Waste Management, U. S. EPA, Washington, DC. EPA 440/4-79-029b (as cited in U.S. EPA, 1985a).

Carey, A.E., J.A, Gowen, H. Tai, W.G. Mitchell and G.B. Wiersma. 1978. Pesticide residue levels in soils and crops, 1971. National Soils Monitoring Program (III). Pestic. Monit. J. 12:117-136.

Cassidy, R. A., C. V. Vorhees, D. J. Minnema, and L. Hastings. 1994. The effects of chlordane exposure during pre- and postnatal periods at environmentally relevant levels on sex steroid-mediated behaviors and functions in the rat. Toxicol. Appl. Pharmacol. 126:326-337.

Cerey, K., V. Izakovic and J. Ruttkay-Nedecka. 1971. The influence of heptachlor on rat fertility and growth. Z. Versuchstierkd. 13:243-244 (as cited in WHO, 1984).

Cerey, K., V. Izakovic and J. Ruttkay-Nedecka. 1973. Effect of heptachlor on dominant lethality and bone marrow in rats. Mutat. Res. Sect. Environ. Mutag. Relat. Subj. 21 (1):26. (As cited in WHO, 1984).

Curley, A., M.F. Copeland and R.K. Kimbrough. 1969. Chlorinated hydrocarbon insecticides in organs of stillborn and blood of newborn babies. Arch. Environ. Health 19:628-632.

Curley, A., V.M. Burse, R.W. Jenning. E.C. Villaneuva, L. Tomtis and K. Akazaki. 1973. Chlorinated hydrocarbon pesticides and related compounds in adipose tissue from people of Japan. Nature. 242:338-340..

Davidow, B. and J.L. Radomski. 1953. Isolation of an epoxide metabolite from fat tissues of dogs fed heptachlor. J. Pharmacol. Exp. Therap. 107:259.

Davis, H.J. 1965. Pathology report on mice fed aldrin, dieldrin, heptachlor or heptachlor epoxide for two years. Internal FDA memorandum to Dr. A.J. Lehman, July 19. (Cited in Epstein, 1976).

Deichmann, W.B. 1981. Halogenated cyclic hydrocarbons. In: Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B, G.D. Clayton and F.E. Clayton, Eds. John Wiley and Sons., Inc., NY. p. 3603-3769.

DHS. 1988. Proposed Maximum Contaminant Level Heptachlor and Heptachlor Epoxide. Hazard Evaluation Section, California Department of Health Services (Currently the Pesticide and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency) Berkeley, CA.

DPR. 1992. Sampling for Pesticide Residues in California Well Water. 1992 Well Inventory Data Base, Cumulative Report 1986-1992. Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

Ditraglia, D., D.P. Brown, T. Namekata and N. Iverson. 1981. Mortality study of workers employed at organochlorine pesticide manufacturing plants. Scand. J. Work Environ. Health 7 (Suppl. 4): 140-146.

Epstein, S.S. 1976. carcinogenicity of heptachlor and chlordane. Sci. Total Environ. 6:103.

Epstein, S.S and D. Ozonoff. 1987. Leukemias and blood dyscrasias following exposure to chlordane and heptachlor. Teratogen. Carcinogen. Mutagen. 7:527-540.

Ermakov, V.V. 1977. Metabolism of heptachlor and dilor in animals. Skh. Biol. 12(3):402-411. (Russian) Chem. Abstr. 87:128395w.

Fendick, E.A., E. Mather-Mihaich, K.A. Houck, M.B. St. Clair, J.B. Faust, C.H. Rockwell, and M. Owens. 1990. Ecological toxicology and human health effects of heptachlor. Rev. Environ. Contam. Toxicol. 111:61-142.

FDA. 1982a. Compliance program report of findings. FY79 total diet studies -- Adults (7305.002). Food and Drug Administration, U.S. Department of Health and Human Services, Washington DC. FD/BF-82/98.

FDA. 1982b. Compliance program report of findings. FY79 total diet studies -- infants and toddlers (7305.002). Food and Drug Administration, U.S. Department of Health and Human Services, Washington, D.C. FDA/BF-82/97.

FDA.1989. Food and Drug Administration pesticide program - Residues in foods - 1988. J. Assoc. Off. Anal. Chem. 72:133A-152A.

FDA. 1990. Food and Drug Administration pesticide program - Residues in food - 1989. J. Assoc. Off. Anal. Chem. 73:127A-146A.

FDA. 1991. Food and Drug Administration pesticide program - Residues in foods - 1990. J. Assoc. Off. Anal Chem. 74:121A-141A.

FDA. 1993. Food and Drug Administration pesticide program - Residues in foods - 1992. J. Assoc. Off. Anal. Chem. 76:127A-148A.

FDA. 1996. *Pesticide Program Residue Monitoring 1995*. U.S. Food and Drug Administration, Department of Health and Human Services. (Available on-line at http://vm.cfsan.fda.gov/) Washington, DC.

Furie, B. and S. Trubowitz. 1976. Insecticides and blood dyscrasias: Chlordane exposure and self-limited refractory megaloblastic anemia. J. Am. Med. Assoc. 235:1720-1722.

Gaines, T.B. 1960. The acute toxicity of pesticides to rats. Toxicol. Appl. Pharmacol. 2:88.

Gennings, C. 1996. Economical designs for detecting and characterizing departure from additivity in mixtures of many chemicals. Food Chem. Toxicol. 34:1053-1058.

Gentile, J.M., G.J. Gentile, J. Bultman, R. Sechriest, E.D. Wagner and M.J. Plewa. 1982. An evaluation of the genotoxic properties of insecticides following plant and animal activation. Mutat. Res. 101(l):19-29.

Greer, E.S., D.J. Miller, F.N. Bruscato and R.L. Holt. 1980. Investigation of pesticide residues in human adipose tissue in the northeast Louisiana area. J. Agric. Food Chem. 28(l):76-78.

Griffin, D.E. and W.E. Hill. 1978. In vitro breakage of plasmid DNA by mutagens and pesticides. Mutat. Res. 52:161-169 (as cited in WHO, 1984).

Gunderson, E.L. 1988. Chemical contaminants monitoring - FDA total diet study, April 1982 - April 1984, Dietary intakes of pesticides, selected elements, and other chemicals. J. Assoc. Off. Anal. Chem. 71:1200-9.

Haake, J., M. Kelly, B. Keys, and S. Safe. 198. The effects of organochlorine pesticides as inducers of testosterone and benzo[a]pyrene hydroxylases. Gen. Pharmacol. 18:165-169.

Harbison, R.D. 1975. Comparative toxicity of selected pesticides in neonatal and adult rats. Toxicol. Appl. Pharmacol. 32:443-446.

Henderson, C., W.L. Johnson and A. Inglis. 1969. Organochlorine insecticide residues in fish (National Pesticide Monitoring Program). Pestic. Monit. J. 3:145-171.

Hergenrather, J., G. Hlady, B. Wallace and E. Savage. 1981. Pollutants in breast milk of vegetarians. (Letter to the Editor) New Engl. J. Med. 304:792.

Hrdina, P.D., R.L. Singh and D.A.V. Peters. 1974. Changes in brain biogenic amines and body temperature after cyclodiene insecticides. Toxicol. Appl. Pharmacol. 29:119 (Abstract).

Huang, J.C. 1970. Fate of organic pesticides in the aquatic system. Eng. Bull. Purdue Univ. Eng. Ext. Series. p. 449-457.

Infante, P.F., S.S. Epstein and W.A. Newton, Jr. 1978. Blood dyscrasias and childhood tumors and exposure to chlordane and heptachlor. Scand. J. Work Environ. Health 4:137-150.

Ingle, L. 1965. A monograph on chlordane, toxicological and pharmacological properties. Univ. Illinois, Urbana, IL.

IARC. 1979. Some Halogenated Hydrocarbons. In: IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans., Vol.20, WHO, International Agency for Research on Cancer, Lyon, France pp.45-65, 129-154.

IARC. 1982. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. WHO, International Agency for Research on Cancer, Lyon, France, p. 80-82.

IARC. 1991. Chlordane and Heptachlor. In: Occupational Exposures in Insecticide Application, and Some Pesticides. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 53, WHO, International Agency for Research on Cancer , Lyon, France, p. 115-175.

IRDC. 1973a. Unpublished report to Velsicol Chemical corporation, Eighteen Month Oral Carcinogenic Study in Mice, December 14. (Cited in Epstein, 1976), International Research and Development Corporation, Mattawan, MI.

IRDC. 1973b. Unpublished report Velsicol Chemical corporation, Eighteen Month Oral Carcinogenic Study in Mice, September 26. (Cited in Epstein, 1976), International Research and Development Corporation, Mattawan, MI.

IRDC. 1973c. Heptachlor epoxide, two generation reproduction and teratology study in Beagle dogs, International Research and Development Corporation, Mattawan, Michigan, IRDC. (Report No. 163-048) (as cited in WHO, 1984).

Irwin, G.A. and H.G. Healy. 1978. Chemical and physical quality of selected public water supplies in Florida, August-September 1976. Water Resources Division, U.S. Geological Survey, Tallahassee, FL. USGS/WRI 78-21.

Ivie, G.W., J.R. Knox, S. Khalifa, T. Yamamoto and J.E. Casida. 1972. Novel photoproducts of heptachlor epoxide, trans-chlordane and trans-nonachlor. Bull. Environ. Contam. Toxicol. 7:376-382.

Jensen, A.A. 1983. Chemical contaminants in human milk. Residue Rev. 89:1-128.

Jensen, G.E. and J. Clausen. 1979. Organochlorine compounds in adipose tissue of Greenlanders and southern Danes. J. Toxicol. Environ. Health 5:617-629.

Jolley, W.P., H.L. Stemmer and E.A. Pfitzer. 1966. The effects of feeding diets containing a mixture of heptachlor and heptachlor epoxide to female rats for 2 years. Unpublished report from the Kettering Lab. to Velsicol Chemical Corporation, January 28. (Cited in Epstein, 1976).

Jonsson, V., G.J.K. Liu, J. Armbruster and L.L. Kettelhut. 1977. Chlorohydrocarbon pesticide residues in human milk in greater St. Louis, MO. Am. J. Clin. Nutr. 30:1106-1109.

Joy, R.M. 1976. Convulsive properties of chlorinated hydrocarbon insecticides in the cat central nervous system. Toxicol. Appl. Pharmacol. 35:95-106.

Klein, W., F. Korte, I. Weisgerber, R. Kaul, W. Mueller and A. Djirsarai. 1968. The metabolism of endrin, heptachlor and telodrin. Qdal. Plldt. Mater. Veg. (Den Haag), 15:225-238 (as cited in WHO, 1984).

Klemmer, K.W., A.M. Budy, W. Takahasdhi and T.J. Haley. 1977. Human tissue distribution of cyclodiene pesticides. Hawaii, 1964-1973. Clin. Toxicol. 11(l):71-82.

Krampl, V. 1971. Relationship between serum enzymes and histological changes in liver after administration of heptachlor in the rat. Bull. Environ. Contam. Toxicol. 5:529.

Kroger, M. 1972. Insecticide residues in human milk. J. Pediatr. 80:401-405.

Kutz, F.W., A.R. Yobs and H.S.C. Yang. 1976. National pesticide monitoring programs. In: Air Pollution from Pesticides and Agriculture Processes. Lee, R.E., Ed., CRC Press, Cleveland, OH, pp. 95-136.

Kutz, F.W., S.C. Strassman and J.F. Sperling. 1979. Survey of selected organochlorine pesticides in the general population of the United States: Fiscal years 1970-1975. Ann. N.Y. Acad. Sci. 320:60-68.

Lehman, A.J. 1952. Chemicals in foods: A report to the Association of Food and Drug Officials on current developments. Part III. Subacute and chronic toxicity. Assoc. Food Drug Office. U.S. Q. Bull. 16:47-53.

Le Marchand, L., L.N. Kolonel, B.Z. Siegel and W.H. Dendle, III. 1986. Trends in birth defects for an Hawaiian population exposed to heptachlor and for the United States. Arch. Environ. Health 41(3):145-148.

Lewis, R. G., R. C. Fortmann and D. E. Camann. 1994. Evaluation of methods for monitoring the potential exposure of small children to pesticides in the residential environment. Arch. Environ. Contam. Toxicol. 26:37-46.

Lordo, R.A., K.T. Dinh and J.G. Schwemberger. 1996. Semivolatile organic compounds in adipose tissue: estimated averages for the US population and selected subpopulations. Am. J. Pub. Health 86:1253-1259.

Mabey, W.R., J.H. Smith, R.P. Podoll, et al. 1981. Aquatic fate process data for organic priority pollutants. Monit. Data Support Div., Off. Water Regul. Stand., Washington, DC EPA 440/4-81-014.

MacMahon, B. and H.H. Wang. 1982. A second follow-up of mortality in a cohort of pesticide applicators. Boston, Harvard School of Public Health, Department of Epidemiology (as cited in WHO, 1984).

Mantel, N. 1958. An experimental design in combination chemotherapy. Ann. N. Y. Acad. Sci. 76:583-590.

Marshall, T.C., W. Dorough and H.E. Swim. 1976. Screening of pesticides for mutagenic potential using Salmonella typhimurium mutants. J. Agric. Food Chem. 24:560.

Matsumura, F. and J.D. Nelson. 1971. Identification of the major metabolic product of heptachlor epoxide in rat feces. Bull. Environ. Contam. Toxicol. 5:489.

Mizyukova, I.G. and G.V. Kurchatov. 1970. Metabolism of heptachlor. Farmacol. Toksikol. (Moscow). 33(4):496-499. (Russian) Chem. Abstr. 73:86885J.

Montgomery, J.H. 1993. Agrochemicals Desk Reference. Environmental Data. Lewis Publishers, Chelsea, MI

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116(3-4):185-216.

Mussalo-Rauhamaa, H., H. Pyysalo, and K. Antervo. 1991. Heptachlor, heptachlor epoxide, and other chlordane compounds in Finnish plywood workers. Arch. Environ. Health.46:340-346.

Narotsky, M.G., E.A.Weller, V.M.Chinchilli, and R.J.Kavlock. 1995. Nonadditive developmental toxicity in mixtures of trichloroethylene, di(2-ethylhexyl) phthalate, and heptachlor in a 5 x 5 x 5 design. Fund. Appl. Toxicol. 27:203-216.

NAS. 1977. Drinking Water and Health. National Academy of Sciences, Washington, DC pp. 564, 568, 794.

NCI. 1977. Bioassay of Heptachlor for Possible Carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 9 111 p. [Also publ. as DHEW Publication No. (NIH) 77-809], National Cancer Institute, Washington, DC.

NCI. 1982. An assessment of the health risks of seven pesticides used for termite control. Prepared for Dept. Navy, National Cancer Institute, Washington, DC, NTIS PB 83-136374.

Nomata, K., K.-S. Kang, T. Hayashi, D. Matesic, L. Lockwood, C.C. Chang and J.E.Trosko. 1996. Inhibition of gap junctional intercellular communication in heptachlor- and heptachlor epoxide-treated normal human breast epithelial cells. Cell Biol. Toxicol. 12:69-78.

OEHHA. 1997. Public Health Goal for Chlordane in Drinking Water. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency, Sacramento.

Peirano, W.B. 1980. Heptachlor - maximum acceptable limit in drinking water. U.S. EPA Washington, DC, (as cited in WHO, 1984).

Pelikan, Z., K. Halacka, M. Polster and E. Cerny. 1968. Intoxication a long terme chez les rats par heptachlor a petit doses. Arch. Belg. Med. Soc. Hyg. Med. Trav. Med. Leg., 26:529-538. (As cited in WHO, 1984).

Pellizzari, E.D., M.D. Erickson and R.A. Zweidinger. 1979. Formulation of a preliminary assessment of halogenated organic compounds in man and environmental media. Prepared by Research Triangle Institute, Research Triangle Park, NC, for office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC EPA 560/13-79-006.

Podowski, A.A., B.C. Banerjee, N. Feroz, M.A. Dudek, R.L. Willey and M.A.Q. Khan. 1979. Photolysis of heptachlor and cis-chlordane and toxicity of their photoisomers to animals. Arch. Environ. Contam. Toxicol. 8:509-518.

Polishuk, Z.W., M. Ron, M. Wassermann, S. Cucos, D. Wassermann, and C. Lemesch. 1977. Organochlorine compounds in human blood plasma and milk. Pestic. Monit. J. 10:121-129.

Quinsey, P. M., D. C. Donahue, F. J. Cumming and J. T. Ahokas 1996. The importance of measured intake in assessing exposure of breast-fed infants to organochlorines. Eur. J. Clin. Nutr. 50:438-442.

Radomski, J.L. and B. Davidow. 1953. The metabolite of heptachlor, its estimation, storage and toxicity. J. Pharmacol. Exp. Therap. 107:226.

Reuber, M.D. 1977a. Hepatic vein thrombosis in mice ingesting chlorinated hydrocarbons. Arch. Toxicol. 38:163-168.

Reuber, M.D. 1977b. Histopathology of carcinomas of the liver in mice ingesting heptachlor or heptachlor epoxide. Exp. Cell Biol. 45:147-157.

Reuber, M.D. 1978. Carcinomas and other lesions of the liver in mice ingesting organochlorine pesticides. Clin. Toxicol. 13 (2) :231-256.

Reuber, M.D. 1987. Carcinogenicity of heptachlor and heptachlor epoxide. J. Environ. Path. Toxicol. Oncol. 7(3):8-114.

Rhomberg, L. 1997. Beyond screening: Problems and prospects for risk characterization of endocrine disruptors. Regul. Toxicol. Pharmacol. 26:74-79.

Ritcey, W.R., G. Savary and K.A. McCully. 1972. Organochlorine insecticide residues in human milk, evaporated milk and some milk substitutes in Canada. Canad J. Publ. Health. 63:125-132.

Rohr, U., W. Konig and F. Selenka. 1985. Influence of pesticides on the release of histamine, chemotactic factors and leukotrienes from rat mast cells and human basophils. Zentralbl. Bakteriol. Mikrobiol. Hyg. Abt. 1 Orig. B 181:469-486.

Sandhu, S.S., W.J. Warren and P. Nelson. 1978. Pesticidal residue in rural potable water. J. Am. Water Works Assoc. 70(l):41-45.

Savage, E.P., J.D. Tessari, J.W. Malberg, H.W. Wheeler and J.R. Bagby. 1973. Organochlorine pesticide residues and polychlorinated biphenyls in human milk, Colorado 1971-1972. Pestic. Monitor. J. 7:1-5.

Scheufler E. and K. Rozman. 1984. Enhanced total body clearance of heptachlor from rats by *trans*-stilbene oxide. Toxicology 32:93-104.

Schuepbach, M.R. and H. Egli. 1979. Organochlorine pesticides and polychlorinated biphenyls in human milk.(Ger.) Mitt. Geb. Lebensmitteluntersuch. Hyg. 70:451-463.

Seiler, J.P. 1977. Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens. Preliminary results in the validation of a novel short-term test. Mutat. Res. 46:305-310 (as cited in WHO, 1984).

Selby, L.A., K.W. Newell, G.A. Hauser and G. Junker. 1969. Comparison of chlorinated hydrocarbon pesticides in maternal blood and placental tissues. Environ. Res. 2:2477-255.

Shain, S.A., J.C. Shaeffer and R.W. Boezel. 1977. The effect of chronic ingestion of selected pesticides upon rat ventral prostate homeostasis. Toxicol. Appl. Pharmacol. 40(l):115-130.

Shindell and Associates. 1981. Epidemiologic study of the employees of Velsicol Chemical Corporation plant, Memphis, Tennessee, January 1952-Deceiaber 1979, Milwaukee, Wisconsin (as cited in WHO, 1984).

Shirasu, Y., M. Moriya, K. Kato, A. Furuhashi and T. Kada. 1976. Mutagenicity screening of pesticides in the microbial system. Mutat. Res. 40:19-30.

Sovocool, G.W. and R.G. Lewis. 1975. The identification of trace levels of organic pollutants in human tissues: Compounds related to chlordane/heptachlor exposure. Trace Subst. Environ. Health, 9:265.

Strassman, S.C. and F.W. Kutz. 1977. Insecticide residues in human milk from Arkansas and Mississippi, 1973-1974. Pestic. Monitor. J. 10:130-133.

Takahashi, W., D. Saidin, G. Takei and L. Wong. 1981. Organochloride pesticide residues in human milk in Hawaii, 1979-1980. Bull. Environ. Contam. Toxicol. 27(4):506-511.

Tashiro, S. and P. Matsumura. 1978. Metabolism of trans-nonachlor and related chlordane components in rat and man. Arch. Environ. Contam. Toxicol. 7(l):113-127.

Tucker, R.K. and T.A. Burke. 1978. A second preliminary report on the findings of the state groundwater monitoring project. Department of Environmental Protection, New Jersey (as cited in U.S. EPA, 1985a).

Tzapko, V.V., G.F. Rogovsky and V.N. Kurinov. 1967. On the possibility of hexachlorane and heptachlor penetrating into subsoil water. In: Hygiene of Settlements. Kiev: Zdoravie Publishers, pp. 93-95. (As cited in WHO, 1984).

U. S. EPA. 1980. Ambient Water Quality Criteria for Heptachlor. EPA 440/5-80-052 Environmental Criteria and Assessment Office, U. S. Environmental Protection Agency, Cincinnati, OH.. NTIS PB 81-117632.

U. S. EPA. 1985. Drinking Water Criteria Document for Heptachlor, Heptachlor Epoxide, and Chlordane. EPA-600/84-197-1, U.S. Environmental Protection Agency, Washington, DC.

U. S. EPA. 1986a. 40 CFR 180. Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities. Sections 180.1, 180.104, and 180.319, pp. 248, 260, 285-286, 348-349. U. S. Environmental Protection Agency, Washington, DC.

U. S. EPA. 1986b. Carcinogenicity Assessment of Chlordane, Heptachlor/Heptachlor Epoxide. EPA/600/6-871004, Office of Health and Environmental Assessment, U. S. Environmental Protection Agency Washington, DC.

U. S. EPA. 1987. Heptachlor and heptachlor epoxide. Health Advisory. Office of Drinking Water, U. S. Environmental Protection Agency ,Washington, DC.

U. S. EPA. 1993a. Heptachlor. Integrated Risk Information System (IRIS). EPA online file last revised 07/01/93.

U. S. EPA. 1993b Heptachlor Epoxide. Integrated Risk Information System (IRIS). EPA online file last revised 07/01/93.

U. S. EPA. 1996a. Proposed Guidelines for Carcinogen Risk Assessment. U. S. Environmental Protection Agency, Washington, DC. Fed. Reg. 61:17961-18011.

U. S. EPA. 1996b. Benchmark Dose Technical Guidance Document. EPA/600/P-96/002A, U.S. Environmental Protection Agency, Washington, DC.

U. S. EPA. 1996c. Drinking Water Regulations and Health Advisories. EPA 822-R-96-001, Office of Water, U. S. Environmental Protection Agency, Washington, DC.

U. S. EPA 1997. Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis. Office of Research and Development, U. S. Environmental Protection Agency, Washington, DC.

Vreman, K., L.G.M.T. Tuinstra, J. Bakker, J. Van Den Hoek, A.H. Roos, H. De Visser and J.H. Westerhuis. 1977. Aldrin, heptachlor and beta-hexachlorocyclohexane to dairy cows at three oral dosages: 2. Residues post partum in milk and body fat of cows fed on pesticides in the dry period. Nat. J. Agric. Sci., 25:303-312. (As cited in WHO 1984).

Vrochinsky, K.K., M.M. Gemetchenko and A.L. Merezhko. 1980. Hydrobiological migration of pesticides. Moscow: Moscow University Press, pp. 8-14, 33-37, 59-63, 87-94, 119-120. (As cited in WHO, 1984).

Wang, H.H. and B. MacMahon. 1979a. Mortality of workers employed in the manufacture of chlordane and heptachlor. J. Occup. Med. 21:745-748.

Wang, H.H. and B. MacMahon. 1979b. Mortality of pesticide workers. J. Occup. Med. 21:741-744.

Wang, H.H. and S. Grufferman. 1981. Aplastic anemia and occupational pesticide exposure: A case-control study. J. Occup. Med. 23:364-366.

Wassermann, M., D.P. Nogueira, L. Tomatis, et al. 1972. Storage of organochlorine insecticides in people of Sao Paulo, Brazil. Ind. Med. 41:22.

Wassermann, M., L. Tomatis, D. Wassermann, et al. 1974. Epidemiology of organochlorine insecticides in the adipose tissue of Israelis. Pestic. Monit. J. 8:1.

Wazeter, F.X. 1967. Unpublished report. (Cited in Vettorazzi, 1975).

Wiersma, G.B., H. Tai and P.F. Sand. 1972a. Pesticide residue levels in soils. FY 1969-National Soils Monitoring Program. Pestic. Monit. J. 6:194-228 (as cited in IARC 1979).

Wiersma, G.B., H. Tai and P.F. Sand. 1972b. Pesticide residue levels in soil from eight cities-1969. Pestic. Monit. J. 6:126-129 (as cited in IARC, 1979).

Winell, M.A. 1975. An international comparison of hygienic standards for chemicals in the work environment. Ambio. 4:34.

Witherup, S., F.P. Cleveland, F.G. Shaffer, H. Schlecht and L. Musen. 1955. The physiological effects of the introduction of heptachlor into the diet of experimental animals in varying levels of concentration. Unpublished report from the Kettering Laboratory to Velsicol Corporation, August 17. (Cited in Epstein, 1976.)

Witherup, S., F.P. Cleveland and K. Stemmer. 1959. The physiological effects of the introduction of heptachlor epoxide in the varying levels of concentration into the diet of CFN rats. Unpublished report from the Kettering Laboratory to Velsicol Corporation, November 10. (Cited in Epstein, 1976.)

Witherup, S., K.L. Stemmer, P. Taylor and L. Hull. 1976a. The effects exerted on the fertility of rats and upon the viability of their offspring by the introduction of heptachlor and its epoxide into their daily diets. Cincinnati, Ohio, The Kettering Laboratory (Reports prepared for the Velsicol Chemical Corporation as cited in WHO, 1984).

Witherup, S., K.L. Stemmer, P. Taylor and L. Hull. 1976b. The effects exerted upon the fertility of rats and upon the viability of their offspring by the introduction of heptachlor into their daily diets. Cincinnati, Ohio, The Kettering Laboratory (Report prepared for the Velsicol Chemical Corporation as cited in WHO, 1984).

WHO. 1984. Environmental Health Criteria 38. Heptachlor. World Health Organization, Geneva, Switzerland.

WHO. 1986. Principles of evaluating health risks from chemicals during infancy and early childhood: The need for a special approach. Environmental Health Criteria 59. World Health Organization, Geneva, Switzerland.

Wright, C.G. and R.B. Leidy. 1982. Chlordane and heptachlor in the ambient air of houses treated for termites. Bull. Environ. Contam. Toxicol. 28:617-623.

Yamaguchi, I., F. Matsumura and A.A. Kadous. 1979. Inhibition of synaptic ATPases by heptachlor epoxide in rat brain. Pestic. Biochem. Physiol. 11:285-293.

Yamaguchi, I., F. Matsumara and A.A. Kadous. 1980. Heptachlor epoxide: Effects on calcium-mediated transmitter release from brain synaptosomes in rat. Biochem. Pharmacol. 29:1815-1823.

Zavon, M.R., R. Tye and L. Latorre. 1969. Chlorinated hydrocarbon insecticide content of the neonate. Ann. NY Acad. Sci. 160:196-200.