Appendix B
Section C

CHLORDANE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

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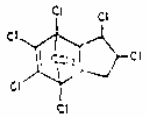
EXECUTIVE SUMMARY

Chlordane is a wide-spectrum insecticide produced by condensing hexachlorocyclopentadiene with cyclopentadiene to form chlordene, which is chlorinated to form chlordane. Human exposure to chlordane has occurred by occupational and accidental means. Toxic effects following acute exposure to this chemical include central nervous system sensitization and gastrointestinal disorders. Toxic effects of chronic exposure include skin irritation, blurred vision, exhaustion, liver damage, anorexia and weight loss, severe gastroenteritis and death. The odor threshold of chlordane in water is 3.0 parts per billion. The odor threshold in air and the taste threshold in water were not reported. Exposure to this chemical was associated with an increased incidence of hepatocellular adenoma in mice. A health-based maximum contaminant level of 0.013 ug/L in drinking water is predicted to result in an excess lifetime cancer risk of one in a million.

TABLE OF CONTENTS

BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties (U.S.EPA, 1985a or HASDB, 1985; unless otherwise stated)

Chemical Name	Chlordane
Synonyms	1,2,4,5,6,7,8,8-Octachloro-2,3,3A,4,7,7A-Hexahydro-4,7-Methanodene 1,2,4,5,6,7,8,8-Octachloro-3A,4,7,7A-Hexahydro-4,7-Methylene Indane Chlorindan
CAS#	57-74-9 (Sax, 1984)
Chemical Formula	$C_{10}H_6Cl_8$ (Sax, 1984)
Chemical Structure	
Molecular Weight	409.80
Physical State	amber-colored, viscous liquid (at room temperature)
Melting Point	106-107 °C - cis-(α) isomer 104-105 °C - trans-(β) isomer
Boiling Point	175 °C at 2 mm Hg
Vapor Pressure, Volatility	1×10^{-5} mm Hg at 25 °C
Specific Gravity, Density	1.59-1.63 at 25 °C
Water Solubility	Insoluble; technical grade: 9 ug/L at 25 °C (Verschueren, 1983) 56 ug/L for cis:trans (75:25) at 25 °C (Verschueren, 1983)
Log Octanol/Water Partition Coefficient	3.32
Taste Threshold (water)	Not reported
Odor Threshold (water)	3 ppb (MMWR, 1981) 0.005 mg/L (U.S.EPA, 1985b)

Odor Threshold (air)	Not reported
Conversion Factors	1.67 ug/L = 1 ppm 0.60 ppm = 1 ug/L

Production and Use

Chlordane is a cyclodiene, wide-spectrum insecticide produced by condensing hexachlorocyclopentadiene with cyclopentadiene to form chlordene, which is chlorinated to yield chlordane. Commercial production began in 1947. Improved production methods in 1950 and the late 1970s have resulted in a less toxic endproduct containing fewer contaminants. There are two grades of chlordane, pure- and technical-grade and two isomers, cis- (α-alpha) and trans- (β-gamma). Pure chlordane is composed of 70% cis-isomer; 25% trans-isomer and less than 1% heptachlor (HASDB, 1985). Technical-grade chlordane, which is used commercially, is composed of approximately 24% trans-isomer, 19% cis-isomer, 21.5% chlordene isomers, 10% heptachlor isomers, 7% nonachlor, and 18.5% other compounds. It is available in 45% or 75% concentrations in kerosene or xylene for commercial pest control (MMWR, 1981).

Production has been reduced within the last 10 years due to federal U.S.EPA cancellation proceedings and settlement that determined a schedule to phase-out legal chlordane use (IARC, 1979). The pesticide is not produced in Europe and has never been produced in, or exported to, Japan.

Until April 1976, chlordane was used on agricultural crops such as corn, potatoes, and tomatoes, as well as home garden crops, to control soil insects and ants (NAS, 1979 and U.S.EPA, 1985b). The use of the pesticide on flax, citrus fruit, strawberries, and grapes was terminated by the end of 1980. In 1980, 10 million pounds of chlordane was used to treat soil for termites by subsurface injection (U.S.EPA, 1985a). The only approved use of chlordane since July 1, 1983 is for underground termite control (IARC, 1979).

The phase-out of acceptable uses for chlordane has caused a reduction in its production. In 1971, 25 million pounds (1.13×10^7 kg) were produced. This dropped to 20.9 million pounds (9.5×10^6 kg) in 1974. Production was reduced even more in 1978 to 9.9 million pounds (4.6×10^6 kg). New Jersey businesses purchased between 500,000 and one million pounds in 1978 through 1979 (N.J.DEP/OSR, 1984). Production dropped to 5.8 million pounds (2.6×10^6 kg) in 1982 (IARC, 1979, NAS, 1979, and HASDB, 1985). Chlordane is produced in the United States by Velsicol Chemical Corporation, a subsidiary of Northwest Industries, Inc., of Marshall, Illinois.

Regulations, Guidelines, and Standards

The American Conference of Governmental and Industrial Hygienists (ACGIH) and the U.S. Occupational Safety and Health Administration (OSHA) set a threshold limit value (TLV) of 0.5 mg/m^3 for an eight-hour exposure period. ACGIH recommended a short term exposure limit (STEL) of 2 mg/m^3 for a 15 minute period. OSHA stipulated that the 0.5 mg/m^3 level was required to protect individuals from toxic effects through absorption of chlordane through the skin (HSDB, 1985).

The National Research Council (NRC, 1982) set an interim guideline of 0.005 mg/m^3 for airborne chlordane in military housing, feeling that the 0.5 mg/m^3 level was unacceptable in the home environment where the potential for exposure exists 24 hours per day (Wright and Leidy, 1982).

The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) recommended an Acceptable Daily Intake (ADI) of 1.00 mg/kg body weight (U.S.EPA, 1985a).

The Federal Water Pollution Control Administration criterion was 0.003 mg/L to protect surface water intended for public water supplies (1968).

Various levels in water have been proposed to protect aquatic and human health. It was determined by the U.S.EPA (1980) that in order to protect freshwater life a level averaging 0.0043 ug/L in 24 hours should not exceed 2.4 ug/L at any time. In order to protect saltwater life a level averaging 0.004 ug/L in 24 hours should not exceed 0.09 ug/L. The ideal level that would guarantee protection to human life is zero ug/L (U.S.EPA, 1985b). Realistically, a level that would result in a one in a million excess cancer occurrence as determined by a carcinogenic risk assessment of National Cancer Institute data is 0.00046 ug/L (Sittig, 1985).

The U.S.EPA has recommended an ambient water concentration of zero ug/L chlordane to protect humans against the potential carcinogenic effects of exposure through ingestion of contaminated water and aquatic organisms. The U.S.EPA proposed a recommended maximum contaminant level of zero ug/L for chlordane, based on both its carcinogenic effects in animals and its occurrence in potable supplies. The National Academy of Sciences (NAS) and the U.S.EPA's Carcinogenic Assessment Group (CAG) based their carcinogenic risk assessment on the NCI data and calculated a lifetime excess cancer risk of one in a million for 0.02 ug/L in drinking water (U.S.EPA, 1985b). WHO (1984) based its carcinogenic risk assessment on the premise of an ADI of 0.001 mg/kg per day with 1% of the ADI coming from the consumption of one liter of chlordane-contaminated water per day. WHO suggests a level of 3 ug/L per day. This value is the same as the Canadian Drinking Water tentative maximum permissible limit.

ENVIRONMENTAL EXPOSURE

Fate and Transport

Chlordane contamination has occurred in all facets of the environment: air, soil, surface and ground waters. Air contamination resulted from the aerial application of chlordane dusts and sprays, wind erosion of contaminated soils and the volatilization from soils as well as from surface waters. Surface water contamination resulted from the accumulation of chlordane in bottom sediments. This contamination is thought to have occurred in surface runoff and chlordane-tainted rain, even though substantiating data are lacking. Ground water contamination occurred in areas where chlordane was applied over or near existing wells, leached from a pesticide waste dump, was accidentally injected via commercial use operations or intentionally injected into a public supply (WHO, 1984).

In general, chlordane components are poorly degraded in the environment. Photodegradation can occur in the environment. Trans- and cis-chlordane are altered by photosensitizers such as ultraviolet radiation, rotenone or benzophenone. In air, cis-chlordane degraded 65-69% within 16 to 20 hours (HSDB, 1985). These photoisomers are more biodegradable than the parent compound and demonstrate higher bioaccumulation values (HSDB, 1985). They may have a greater effect on foodchains due to this greater affinity to bioaccumulate. It was demonstrated that degradation products of trans- and cis-chlordane on various agricultural crops were chlordane chlorohydrin, dihydroxy-B-dihydroheptachlor, 1,2-dichlorochlorodene, oxychlordane, and photo-2-chlordane. Cis- and trans-chlordane degraded to 1,2-dichlorochlordene that further degraded to oxychlordane (WHO, 1984).

In soil, photodegradation usually does not occur because the chlordane is injected into lower soil layers to control termites. It is hydrolyzed poorly and does not undergo significant biodegradation. The chlordane persists in the soil in both isomer forms. The extent of degradation that does exist via volatilization is dependent upon organic matter and moisture content. Organic matter enhances adsorption of chlordane components onto soil particles, thus reducing volatilization. Soil moisture increases volatilization. The reported half-life of chlordane in soil is estimated to be two to four years, even though residues may exist for 14 years. If the pesticide is exposed to the environmental elements, the half-life can be reduced to weeks. The half-life in agricultural soil is approximately one year (IARC, 1979 and WHO, 1984). The persistence of chlordane and its stable epoxide oxidation products in soil and bottom sediments of lakes and other surface bodies of water is directly related to the ability of these products to bioconcentrate in the lipids of members in the food chain. This involves terrestrial and aquatic animals and plants, including humans.

Ambient Levels

Chlordane has been found in both indoor and outdoor air. The Suburban Air Sampling Program in 1975 sampled air from three suburban areas and found that 9 of the 15 samples were positive with a maximum value of 59 mg/m^3. It has been detected in ambient air as high as 204 mg/m^3 (U.S.EPA, 1985b). The pesticide was also found in air samples at levels from below detection to 0.90 mg/m^3 taken from around Bermuda and between Bermuda and Rhode Island (sampled February-June 1973). In general outdoor ambient air levels are thought to be insignificant when compared to indoor air pollution caused by chlordane treatment for termites (WHO, 1984). Military bases have been the focus of studies that have quantified the amount of chlordane in the indoor air after treatment with chlordane. In 1980, such a survey was conducted at seven Air Force bases. A total of 474 housing units were included in the study. Air samples were taken after chlordane was applied by either subslab injection or exterior ditching after construction. The results of the survey showed that 86% of the units had levels under 3.5 to ug/m^3, 12% had levels between 3.5 to 6.5 ug/m^3 and 2% had levels above 6.5 ug/m^3 with a maximum concentration of 379 ug/m^3 (Wright and Leidy, 1982).

The pesticide has been found in both natural and potable waters. Rain water in Hawaii was found to contain levels in the parts per trillion range. River water in Ontario, Canada had levels ranging from less than 1.0 to 21 ng/L (trans-chlordane) (IARC, 1979). Reservoirs, wells and ponds in Nova Scotia had levels ranging from 0.0 to 31.3 ug/L (cis-chlordane). The lower Mississippi River had levels ranging from 0.4 to 1.2 ng/L (trans-chlordane) varying according to season (IARC, 1979). In general, chlordane contamination of natural waters is not a major problem occurring at levels of 0.001 ug/L to 0.01 ug/L in ground and surface water, except in areas where heavy chlordane use occurred, such as in Hawaii.

Chlordane contamination of drinking water supplies has many sources. One source is back syphonage from tanking filling operations during pesticide application (U.S.EPA, 1985b). One such incident resulted in chlordane levels as high as 1.2 g/L (Harrington et al., 1978). Another source was due to pesticide production waste leaching into a public ground water supply (Clark et al., 1982). An intentional contamination of a public water supply (MMWR, 1981) occurred in late 1980 and resulted in a maximum level of 6,600 ppb with the concentrations decreasing in a few days to 0.0 to 105 ppb. Chlordane has been found in the drinking water of five states. One state reported that 49% of all its potable supplies (87% of these were ground water sources) were contaminated with chlordane (U.S.EPA, 1985b). Five wells in New Jersey have been found contaminated with levels ranging from 0.01 to 0.02 ug/L (U.S.EPA, 1985b). In the second round of A-280 (New Jersey Assembly Bill that mandates MCL development) testing in New Jersey, one purveyor reported a concentration of chlordane in water of 0.10 ppb. This could not be verified (N.J.DEP, 1986).

Soil contamination is a frequent result of chlordane application. In 1970, the National Soils Monitoring Program detected levels ranging from 0.01 to 13.34 mg/kg dry weight (mean of 0.08 mg/kg, 165 out of 1,506 cropland samples) in 11% of the samples taken in a 35 state study region (IARC, 1979). Urban soils from 14 U.S. cities were analyzed for chlordane contamination in 1970. Values ranging from 0.01 to 1.27 mg/kg dry weight were reported (WHO, 1984). Another urban study of eight cities found levels ranging from 0.02 to 20.48 mg/kg in 16% to 64% of the 400 samples taken (IARC, 1979).

The persistence, low water solubility, and soil-binding properties of chlordane are major reasons why it has been found at substantial levels in bottom sediments of rivers, streams, and lakes. Trans-chlordane has been reported in sediments at levels ranging from 0.0 to 51 ug/kg in Nova Scotia and Ontario, and cis-chlordane has been found in sediments at levels ranging from 0.0 to 664 ug/kg in Nova Scotia (IARC, 1979).

The persistent, stable, and lipophilic nature of chlordane and its metabolites predispose this substance to bioaccumulate. High levels have been found in fish, agricultural crops, animals, humans, and human milk. Saltwater species have been found to have large body burdens of chlordane. A sample of oysters from the South Atlantic Ocean and Gulf of Mexico had levels greater than 0.01 mg/kg (20 out of 133). Different fish species in the Tokyo Bay were found to have body burdens ranging from 4.6 to 60 ppb total chlordane (HSDB, 1985). Freshwater species from major rivers and the Great Lakes had levels of 0.1 mg/kg whole fish and fish from the Hudson River had levels ranging from 2.2 to 7.3 mg/kg chlordane per whole fish (HSDB, 1985). The N.J.DEP/OSR (1985) reported chlordane levels in several fish species from New Jersey waters ranging from 5.06 to 226.14 ppb. Chlordane levels in agricultural crops and lifestock have averaged 2 ug/kg (78% trans-isomer) and 1.0 ug/kg (81% cis-isomer) in eggs; ranged from 0.02 to 0.06 mg/L in 87% of a sample of cow's milk; 0.0 to 106 ug/kg in beef; 0.0 to 32 ug/kg in pork; and 0.0 to 70 ug/kg in fowl (IARC, 1979).

METABOLISM AND PHARMACOKINETICS

Absorption

Quantitative data on the absorption of chlordane following oral, dermal, and inhalation exposure is limited. It has been demonstrated in animals exposed to chlordane that absorption occurs through the skin, gastrointestinal tract, and the respiratory tract (IARC, 1979, U.S.EPA, 1985a, and WHO, 1984). Oral absorption was estimated to be between 2 and 8.5% of the administered dose in male and female Spraque-Dawley rats and 33% in a white male rabbit fed 25 ppm chlordane in the diet for two days (Barnett and Dorough, 1974). It was reported in an abstract by Ambrose et al. (1953) that oil or organic solvents, such as cotton seed oil, increased the absorption of chlordane through the skin. It appeared that chlordane toxicity was greater when the chemical was dissolved in a lipophilic

vehicle and then applied to the skin. There was no evidence of systemic toxicity in rats breathing air passed through chlordane at 25 °C for 120 hours (Ambrose et al., 1953).

Distribution

In humans, a mean concentration of 0.14 ppm of chlordane and oxychlordane was reported in 21 of 27 adipose samples taken during autopsy (U.S.EPA, 1985a).

Chlordane and its major metabolite, oxychlordane, appear to be preferentially distributed to, and stored in, adipose tissue (U.S.EPA, 1985a). Chlordane residues were distributed at levels less than 1 ppm in muscle, brain, kidney, and liver tissues and at a level of 14.73 ppm in the fat of male rats exposed for 56 days to 5 mg/kg body weight chlordane in their diet (Barnett and Dorough, 1974). Adipose tissue was found to have concentrated most of the cis-photochlordane and its metabolites by the end of the third week after male rats were exposed to 3.12 mg, orally or by intraperitoneal injection (HSDB, 1985). The metabolite most often found in fat, liver, and kidney was oxychlordane (cis-chloro-epoxide).

Metabolism

Chlordane metabolism occurs mainly in the liver. The major toxic reactive metabolite of both isomers is oxychlordane (IARC, 1979). Oxychlordane is formed via the epoxidation of the intermediate metabolite, 1,2-dichlorodene which is formed during the dehydrogenation of chlordane. Trans-chlordane is converted to oxychlordane at a seven times greater rate than is cis-chlordane (U.S.EPA, 1985a). There is evidence that some metabolism of chlordane occurs in the gastrointestinal tract. Various chlordane metabolites were found in the feces of rats given chlordane in a single oral dose of 0.2 mg/kg body weight or in the diet at doses of 25 mg/kg for 14 days or 5 mg/kg for 56 days. The 24-hour feces of a male rabbit fed 25 mg/kg in his diet contained the same metabolites as those found in the rat feces. However, rats fed only the metabolite oxychlordane excreted unchanged oxychlordane in their fecal material (Barnett and Dorough, 1974). There appear to be few interspecies differences (including in humans), in the metabolism of chlordane (U.S.EPA, 1985a). It was reported that chlordane induced non-specific, hepatic microsomal enzyme activity in the rat (WHO, 1984). Some heptachlor is formed during chlordane metabolism (IARC, 1979). Figure 1 shows the simplified metabolism of chlordane in rats (IARC, 1979).

Excretion

Male rats were treated orally or by intraperitoneal injection with a single dose of 3.12 mg of cis-photochlordane. Seven-day elimination rates were 86% and 88%, respectively. The half life of orally administered

chlordane was less than a day, while the half life of the intraperitoneal (i.p.) dose was approximately seven days (HSDB, 1985). In Wistar rats that received radioactively labeled chlordane by a single intravenous (i.v.) injection, 29% of the administered dose was excreted in fecal material within 60 hours and 1% in the urine (HSDB, 1985). Rats eliminated 70, 75, and 80% of chlordane in their fecal material after receiving levels of 1, 5 and 25 mg/kg, respectively, in their diet for a 56 day period (Barnett and Dorough, 1974).

A documented case of accidental ingestion of an unknown amount of chlordane by a four-year old girl resulted in acute symptoms of toxicity. The serum half-life was 88 days. Residue levels in the urine fluctuated during the first three post-exposure days from 1.93 to 0.05 ppm and then increased to 0.13 ppm by the 35th post-exposure day, as residues stored in body fat were released. Fecal levels of chlordane residues decreased during the first three days following exposure and fell below detection one and two months later (U.S.EPA, 1985a).

The U.S.EPA (1985a) reported a study by Strassman and Kutz (1977) in which lactating women in Arkansas and Mississippi were surveyed during 1973 and 1974. Oxychlordane was found in 54.4% of the samples, at levels ranging from trace amounts to higher. The mean level of residues in the quantifiable samples (45.6%) was 0.012 ppm. Therefore, it was concluded that lactation is an elimination route of chlordane in the human system.

Human Exposure and Body Burden

Humans have been exposed to chlordane via many sources. These include occupational exposures (by commercial pesticide applicators, farmers, and pesticide formulators); domestic exposures from living in, or downwind of, areas treated with chlordane; consumption of contaminated food and water; and babies being nursed by exposed mothers (U.S.EPA, 1980).

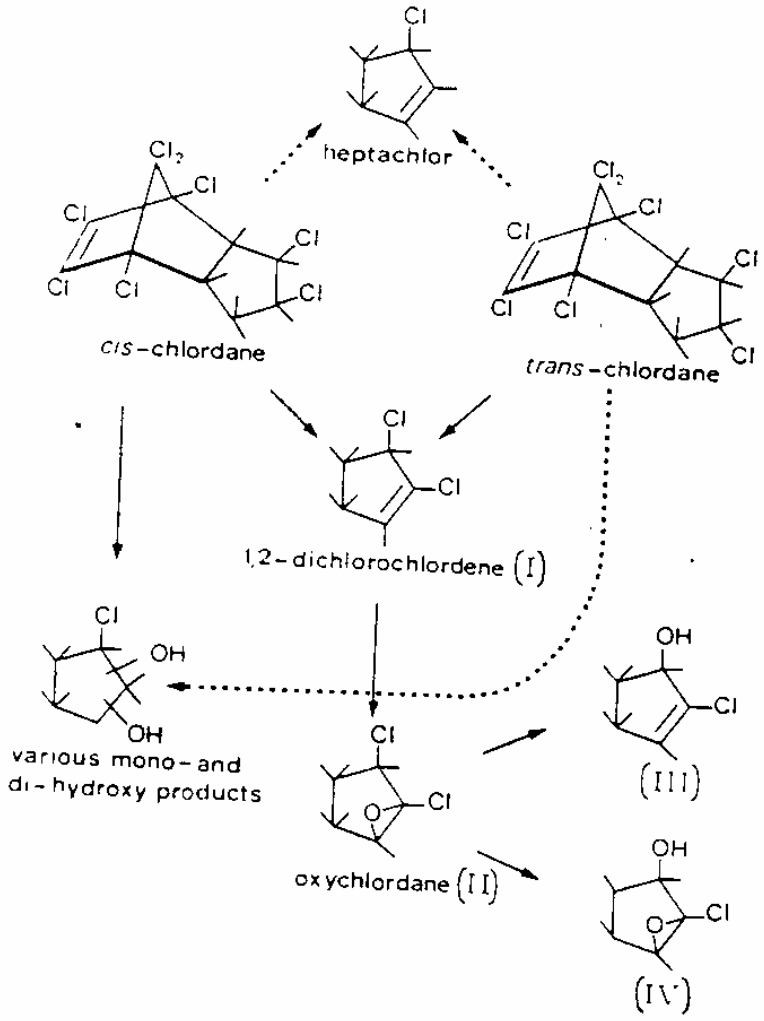
In general, U.S. residents have been found to contain chlordane and/or oxychlordane in their fat averaging 0.14 mg/kg (range is 0.03 to 0.4 mg/kg wet weight). This compound is included in the Tissue Residue Monitoring Program (1976) (WHO, 1984). The daily respiratory intake of chlordane for an average adult was estimated by the U.S.EPA to be 0.6 ug (HASDB, 1985).

Occupation has been shown to be a factor in exposure. The compound persisted on the hands of a former pest control operator for two years or more after termination of employment (HSDB, 1985).

Human milk was found to have a mean oxychlordane concentration of 5 ug/L, with a maximum level of 20 ug/L in 57 samples (46% were positive) taken in 1973-74 in Arkansas and Mississippi. Another study looked for hydrocarbon pesticides in human milk in a sample of 1436 women in the U.S. Oxychlordane was found in 74% of the samples tested. In Japan, a country that never produced or used chlordane, human milk samples contained from

FIGURE 1

SIMPLIFIED METABOLISM OF CHLORDANE IN RATS.



Source: IARC, 1979.

0.1 to 1.1 ppb chlordane residues (HSDB, 1985).

HEALTH EFFECTS

Overview

Chlordane is a very powerful systemic toxicant. The observed toxic effects following acute and chronic exposures to chlordane involved the central nervous system (CNS), heme synthesis, behavioral changes, gastrointestinal tract function, and death. It is considered to be a weak mutagen and a carcinogenic promoter.

Human

Acute. Chlordane poisoning causes many central nervous system effects which are manifested by apprehension, disorientation, dizziness, and muscular weakness. Accidental ingestion of chlordane by babies and children resulted in tremors, incoordination, confusion, convulsions, vomiting, and diarrhea. Delirium, coma, and death due to complications of respiratory depression have resulted from overexposure (WHO, 1984). Absorption of chlordane via the lungs and skin resulted in similar effects (HSDB, 1985, IARC, 1979, U.S.EPA, 1985a,b, and WHO, 1984). Absorption through the skin potentiates the symptoms of chlordane poisoning because it is absorbed faster than through ingestion or inhalation (Chemical Fact Sheet, 1984). Harrington et. al. (1978) reported the effects of an accidental contamination of the public water supply of Chattanooga, Tennessee in 1976. People were exposed to levels as high as 1.2 g/L. Thirteen people reported gastrointestinal and/or neurologic symptoms related to exposure.

Chronic. Chronic effects of exposure include skin irritation, blurred vision, exhaustion, liver damage, anorexia and weight loss, severe gastroenteritis, and death, due to the cumulative effects of chlordane (HSDB, 1985, Chemical Fact Sheet, 1984, and WHO, 1984).

Twenty-five cases of blood dyscrasias, 3 cases of aplastic anemia, 3 cases of acute childhood leukemia and 5 of 14 children with neuroblastoma were determined to have been exposed in utero or at a very young age to chlordane (Infante et al., 1978 and U.S.EPA, 1985a).

Clinical and epidemiological studies of workers involved in the production or application of chlordane have been conducted (Wang and MacMahon, 1979a,b, Ditraglia et. al., 1981, Shindell and Associates, 1981, Wang and Guffman, 1981, and MacMahon and Wang, 1982). No statistically significant results were reported in any of these studies. However, small excesses of lung, skin, bladder, and stomach cancers were found. The studies were limited by small sample sizes, short follow-up time since first exposure, and a large number of current employees in the cohorts.

Further follow-up studies need to be conducted on these cohorts (IARC, 1979 and WHO, 1984).

Animal

Acute. Oral LD_{50} values for rats exposed to chlordane range from 83 mg/kg (cis-isomer) to 590 mg/kg (unspecified mixture) (Ambrose et al., 1953). These values vary with the purity of the compound and the vehicle used. Oral LD_{50} values for rabbits range from 20 to 300 mg/kg (Ambrose et al., 1953). Dermal LD_{50} values for rats range from 205 to 530 mg/kg (WHO, 1984) and for rabbits from 780 to 1,200 mg/kg (Ingle, 1963).

Symptoms of acute poisoning include tremors, convulsions, lethargy, refusal of food and water with resultant weight loss, diarrhea, respiratory failure, cyanosis, and death (U.S.EPA, 1985a and WHO, 1984). These symptoms correlate with pathological findings of hemorrhaging in the gastrointestinal tract, kidney, lung and heart, and also showed concurrent pulmonary congestion and edema (WHO, 1984).

Ambrose et al. (1953) reported exposing groups of five albino rats to oral doses of chlordane at 6.25, 25, 50, 100, or 200 mg/kg body weight for 15 days. Mortality in the last three dose groups was 2, 5, and 5 animals, respectively. No symptoms of toxicity developed in the two lower dose groups except for the development of intracytoplasmic bodies in liver cells. Pathological findings of cytoplasmic bodies in all dose groups were found to be dose related (Ambrose et al., 1953).

The National Cancer Institute (1977) determined maximum tolerated doses of chlordane in Osborne-Mendel rats and $B6C3F_1$ mice in preparation for a carcinogenic bioassay. Male and female rats, five of each sex per dose, were given diets containing analytical-grade chlordane consisting of 0, 50, 100, 200, 400, 800, and 1600 ppm for 42 days. This was followed with a chlordane free diet for 2 weeks. No effect on body weight was observed at concentrations lower than 400 ppm. Four females died in the 800 ppm dose group and all rats died in the 1600 ppm dose group. Male and female mice, five of each sex per dose group, were given diets containing analytical-grade chlordane consisting of 0, 20, 40, 80, 160, and 320 ppm for 42 days. This was followed by a chlordane free diet for two weeks. Two male mice died in the 160 ppm diet group, and 2 males and 5 females died in the 320 ppm diet group. No deaths occurred in the lower dose groups. Body weight in the treated mice did not change significantly from the control mice. The mice did show toxic symptoms of alopecia (hair loss) and had a hunched appearance.

Chronic. Chronic effects of chlordane poisoning cause inflammation of the gastrointestinal tract, including stomach ulcers, nephritis, hepatitis and increased liver weights. Coma and death may often result from over-

exposure (Boyd and Taylor, 1969 and IARC, 1984).

Ingle (1965) conducted a study comparing the toxicity of cis-, trans-, and a 1:1 isomer mix of chlordane. Groups of 20 male and 20 female Osborne-Mendel rats were exposed to the following levels of chlordane isomers in their diet over an eight-month period:

1) cis-isomer: 0, 5, 15, 25, or 35 mg/kg/day,
2) trans-isomer: 15, 25, 35, or 75 mg/kg/day, and
3) 1:1 isomer mix: 5, 15, 25, 35, or 50 mg/kg/day.

The no observed adverse effect level (NOAEL) for the cis-isomer was 15 mg/kg per day; for the trans-isomer was 35 mg/kg per day; and for the 1:1 mixture was 25 mg/kg per day. Effects at higher doses were increased mortality, growth retardation, and compression of the hepatic sinusoids caused by slight cellular proliferation.

In a two-year feeding study, male and female dogs, of 4 to 7 per treatment group, were given 0, 0.3, 3.0, 15, and 30 mg/kg per day in their diet. The NOAEL was 3.0 mg/kg per day. At the higher dose levels the dogs had increased liver weights and enlargement of centrolobular hepatocytes with some margination of coarse cytoplasmic granules (Wazeter, 1967; as reported in IRDC, 1967).

Groups of 80 male and female F-344 rats were fed dietary levels of technical grade chlordane at 0, 1, 5, or 25 ppm for 130 weeks. Eight animals per sex per group were sacrificed at 26 and 52 weeks to determine gross and microscopic pathology on all tissues. The daily dose levels per kilogram body weight were calculated using the dietary levels, food consumption and animal body weight. These daily dose levels were 0, 0.045, 0.229 and 1.175 mg/kg, respectively. Males developed hepatocellular necrosis at all dose levels. These were 3 of 64 animals, 13 of 64 animals, 11 of 64 animals, and 27 of 64 animals, respectively. Liver adenomas developed in the high-dose males. Females in the high-dose group developed hepatocellular swelling (Yonemura et al., 1983).

Behavioral and Central Nervous System

Chlordane exposure has caused apprehension, irritability, belligerence or aggressiveness and a number of CNS effects as a result of its sensitizing effects in rats (HSDB, 1985). These CNS effects were discussed in an earlier section.

Reproduction, Embryotoxic, and Teratogenic

In order to determine if chlordane was teratogenic, Ingle exposed groups of 10 male and 20 female rats to 0, 0.3, 3, 15, 30, and 60 mg/kg/day of the chemical for three generations. There was no effect on fertility,

the number of offspring, weight, growth, or mortality of the animals to weaning age at 30 mg/kg or less a day. The highest dose affected mortality, increasing it 10.6% in the second F_3 generation with some pups showing signs of chlordane intoxication (WHO, 1984). Ingle concluded that there was no evidence that chlordane was a teratogen, even though it showed a fetotoxic effect.

Keplinger et al. (1968) exposed mice to chlordane at levels of 25, 50 and 100 mg/kg for six generations. In the 50 mg/kg dose group viability in the fourth and fifth generations decreased, while in the 100 mg/kg dose group there were no offspring in the third generation. The authors concluded that chlordane was not teratogenic but did show some signs of being both fetotoxic and embryotoxic.

In another study examining the teratogenic potential of chlordane, rabbits were given oral doses of 1.0, 5.0, and 15.0 mg/kg body weight per day on day 6 through day 18 of gestation. A control group and positive control group were used. No changes in behavior, appearance or body weight were noted, however miscarriages occurred in three rabbits in the 1.0 mg/kg dose group and in one rabbit in the 15 mg/kg dose group (IRDC, 1972). No other maternal or fetal toxic responses were noted.

Genetic

Chlordane has been tested for mutagenicity and related effects in a number of systems. Negative results for mutagenicity were reported for nine strains of Salmonella typhimurium, in rat, mouse and hamster primary hepatocyte cultures for unscheduled DNA synthesis, and in the dominant lethal assay in mice. Positive results were found in Saccharomyces cerevisiae for mitotic gene conversion with metabolic activation, and in maize there was evidence of reverse mutation (U.S.EPA, 1985a). Chlordane was considered weakly mutagenic because it increased the number of ouabain-resistant mutants in chinese hamster V79 cells (WHO, 1984). In SV-40 human cells, chlordane induced unscheduled DNA synthesis without activation in culture. The chlordane-treated cells never re-entered mitosis (WHO, 1984). In other work, using rat, mouse and hamster hepatocytes, chlordane was inactive in the hepatocyte primary culture/DNA repair assay (Williams, 1979 and Maslansky and Williams, 1981). Telang et al. (1982) tested chlordane's mutagenic potential in the ARL-HGPRT mutagenesis assay. The test was negative. The authors concluded that chlordane was not genotoxic and acted as an inhibitor to intercellular communication by accumulating in the lipid layer of the cell membrane and altering its functions.

Carcinogenicity

There have been at least three studies dealing with the possible carcinogenic effects of chlordane on the liver. One was reported by Epstein (1976) and conducted by the International Research and Development

Corporation (IRDC, 1973); the second by the National Cancer Institute (NCI, 1977); and the third by the Research Institute for Animal Science in Biochemistry and Toxicology (RIAST, 1983).

Epstein (1976) reported that the IRDC (1973) under contract with Velsicol Chemical Corporation, exposed groups of 100 male and 100 female Charles River CD-1 mice to 5, 25, and 50 ppm analytical-grade chlordane in the diet beginning at six weeks of age and continuing for 18 months. Mortality ranged from 27 to 49%, except in the highest dose group where mortality in males was 86% and in females 75%. Mice in the 25 and 50 mg/kg dose groups experienced a dose-related increase in the incidence of liver hyperplastic nodules. However, Epstein (1976) reported the results of a re-examination of the IRDC slides by Reuber, who found a highly significant increase in the incidence of hepatic carcinomas rather than hyperplastic nodules, in the 25 and 50 ppm groups. These results have been confirmed by three pathologists. There was a dose-related increase in the incidence of liver hypertrophy in all groups and a significant increase in the incidence of heptocellular carcinomas compared to the controls. Males in the 0, 5, 25, and 50 mg/kg groups had the following incidence of tumors: 3/33, 5/55, 41/52 and 32/39, respectively. Females in the 0, 5, 25, and 50 mg/kg groups had the following incidence of tumors: 0/45, 0/61, 32/50 and 26/37, respectively (Table I).

The NCI (1977) exposed groups of 50 male and 50 female B6C3F1 mice to analytical-grade chlordane (94.8% pure) for 80 weeks beginning at 5-6 weeks of age, followed by a 10-week observation period. Time-weighted-average doses were 30 and 56 ppm for males and 30 and 64 ppm for females. There were 20 males and 10 female matched controls and 100 male and 80 female pooled controls. Survival was 60% in the treated males, 80% in the treated females and 90% in the controls. A statistically significant ($p < 0.0001$) dose-related increase in the incidence of hepatocellular carcinomas in both the males and females was observed (Table I).

The NCI study also exposed groups of 50 male and 50 female Osborne-Mendel rats to technical grade-chlordane in their food for 80 weeks followed by a 29-week observation period. Time-weighted-average doses of 203 and 407 mg/kg, and 121 and 241 mg/kg a day were calculated, respectively. Matched controls were composed of 10 males and 10 females per group, and pooled controls were composed of 60 male and 60 female rats. Survival in males was 50% in both the treated groups and the control groups. Survival in the females was 60% in the treated groups and 90% in the control groups. There was an excess of follicular-cell thyroid carcinomas in all treated females (10/75) and all treated males (7/65) as compared to the matched control females (0/10) and males (0/6) and the pooled control females (3/58) and males (4/51). There was also an excess of malignant fibrous histiocytomas (dermatofibroma) in all treated males (8/88) as compared to the matched male controls (0/8) and pooled male controls (2/58). However, these dose-related trends were inconsistent and ambiguous. They were not believed to be related to chlordane treatment.

The main result of the NCI study was evidence of chlordane-linked carcinogencity in mice. When hepatocellular carcinoma figures were combined with nodular hyperplasia figures, or when a life table adjustment of the data was performed, high levels of statistical significance resulted. No other tumors were found to be significant.

The third study, contracted by Velsicol Chemical Corporation was conducted by the Research Institute for Animal Science in Biochemistry and Toxicology (RIAST, 1983). Groups of 80 male and 80 female ICR specific-pathogen-free mice were exposed to 0, 1, 5, or 12.5 ppm technical-grade chlordane in their feed for 104 weeks. Treatment-induced effects were not noted and mortality did not differ significantly from the controls in either sex group. In general, male mortality was higher than female mortality. Both sexes showed an increase in the incidence of hepatocellular degeneration and necrosis in the treatment groups as compared to the controls. Males in the highest dose group exhibited significant increases in the incidence of hepatic hemangiomas (benign), associated with the occurrence of hepatocellular adenoma (benign). The incidence in males in the 1 ppm group was 13/71, in the 5 ppm group was 14/72 and in the 12.5 ppm group was 28/72. There were no significant results in female mice (Table I).

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

There were three studies considered in the quantitative risk assessment of chlordane; IRDC (1973), NCI (1977), and RIAST (1983). The NCI study (1977) was 80 weeks in duration and demonstrated significant incidences of hepatocellular carcinomas in male and female mice. The IRDC study, reported by Epstein (1976), showed a significant increase in the incidence of hepatic carcinomas in the 25 and 50 ppm treatment groups. There was a significant loss of mice due to autolysis in both sexes in the control group and in males in the low- and mid-dose groups. Cause of death was not possible to determine. The results may underestimate the incidence of liver tumors. The RIAST study treated mice over a two-year period and resulted in a significant increase in hepatocellular adenomas in male mice given 12.5 ppm technical-grade chlordane.

The IRDC (1973) study reported a greater tumor incidence at lower doses than the NCI (1977) study. This showed a lower safe dose based on data from IRDC (1973) of 2.4×10^{-6} mg/kg per day versus a safe dose of 9.7×10^{-6} mg/kg per day using NCI data. The human dose in the IRDC study was 1.81×10^{-7} as compared with 7.31×10^{-7} mg/kg per day using NCI data (K.S. Crump and Co., 1986).

Even though this value is lower than the one derived from NCI data,

during the IRDC study large numbers of animals were lost due to autolysis. For example, of the negative controls, 22 of 45 males and 17 of 32 females that died were autolyzed. In the 5 ppm dose group, 33 males died, of which 16 were autolyzed. In the 25 ppm dose group, 45 males died, and 22 of them were autolyzed. Some of these animals had liver masses, therefore it is possible that autolysis resulted in an underestimation of the incidence of tumors (Epstein, 1976). The major concern in discounting this study for risk assessment is this large percentage of deaths, a large portion of which was lost to autolysis. It is uncertain if the large number of deaths were caused by breaches of study protocol.

One weakness of the NCI (1977) study lies in the fact that the doses had to be changed at least once during the study due to acute toxicity. This was accomplished before many animals were lost (Epstein, 1976). It was reported that over 90% of the animals were necropsied. Another weakness of the study is due to the fact that initially only 10 animals per sex were used in the control group. This reduced the sensitivity of statistical tests to detect weak responses.

The RIAST study (1983) covered a two-year period, considered to be the full life-span of mice. The main result was a significant increase in hepatocellular adenomas. This is considered to be a benign tumor type which could progress to carcinoma. The U.S.EPA (1986) published new guidelines concerning the combination of different tumor cell types in calculating carcinogenic risks. Based on this policy change at the U.S.-EPA concerning tumor progression, the RIAST study (1983) is judged to be the appropriate study in which to conduct the risk assessment of chlordane.

Calculation of the Health-Based Maximum Contaminant Level

Telang et al. (1982) concluded that chlordane acted as a promoter by inhibiting intercellular communication. This was due to the accumulation of chlordane in the lipid layer of the cell membrane causing an alteration of its functions. It is important to point out that models of carcinogenic promotion do exist and are being applied in experimental situations (personal conversations with Michael Gallo, Ph.D. at Rutgers University and Richard Thomas, Ph.D., Study Director of the Safe Drinking Water Committee, National Research Council). This topic is elaborated in Drinking Water and Health (Vol. 6, 1986) and also in Chemical Carcinogens; a Review of the Science and Its Associated Principles (Office of Science and Technology Policy, 1985). Both sources concur that due to the lack of information of both the mechanisms of carcinogenesis in humans and the interactions of tissue and the biological effects of promoters, it is premature to classify an agent as acting only through a promotion-type mechanism (OSTP, 1985, Page 24 and NRC, 1986, Pages 284-285). The risk assessment for chlordane was completed on the assumption that the chemical is a complete carcinogen.

K.S. Crump and Co. (1986) fitted incidence data of hepatocellular adenomas in male mice from the RIAST study (1983) to the multistage model,

using the software package, GLOBAL82. K.S. Crump and Co. provided the calculations. This model provided an estimate of the excess risk due to chlordane exposure by using the maximum likelihood methodology. It provided upper and lower bound confidence intervals on the slope of the dose-response curve (q_1^*). The upper 95% confidence limit on the slope was 0.2027. The life-time average dose to the male mice that represented a one in a million excess cancer risk (1×10^{-6}) was 4.93×10^{-6} mg/kg per day.

The animal to human extrapolation was based on the theory that humans are as susceptible to the effects of a chemical or physical agent as is a laboratory animal, in terms of excess risk, when the dose is measured in the same units for both species. Body surface area per day (mg/m^2 per day) is the basis of animal to human extrapolation. The human dose (D_H) is estimated by using the following equation:

$$D_H = D_A \ (W_A/W_H)^{1/3}$$

where D_A is the animal dose correlating with a one in a million excess cancer risk, W_A is the weight of the study animal and W_H is the average weight of an adult human, assumed to be 70 kg.

$$D_H \text{ mg/kg/day} = 4.93 \times 10^{-6} \text{ mg/kg/day } (.03 \text{ kg}/70\text{kg})^{1/3}$$

$$D_H = 3.72 \times 10^{-7} \text{ mg/kg/day}$$

The health-based maximum contaminant level, based on this human dose is:

$$\text{MCL (ug/L)} = \frac{D_H \times W_H \times 1{,}000 \text{ ug/mg}}{\text{WC (L/d)}}$$

where WC is the average daily consumption of water by an adult, assumed to be 2 liter per day.

$$\text{MCL} = \frac{3.72 \text{ x } 10\text{-}7 \text{ mg/kg/day x } 70\text{kg x } 1{,}000 \text{ ug/mg}}{2 \text{ L/d}}$$

$$= 1.30 \times 10^{-2}$$
$$= 0.013 \text{ ug/L}$$

The result is a health-based MCL of 0.013 ug/L.

Assumptions and Uncertainty

The application of animal-to-human extrapolation to estimate human cancer risk based on animal data is an important assumption in the carcinogenic risk assessment.

Table I

Incidence of Hepatocellular Carcinoma or Adenoma in Mice Induced by Chlordane[a] *

Dose Levels[b] Experimental ppm	Adjusted mg/kg/day	Responses (# animals with tumor / # animals at risk) Male	Female
	NCI- B6C3F1 Mice		
0	0	2/18[c]	0/20
29.9	2.28	16/48	
30.1	2.29		3/50
56.2	4.28	43/49	
63.8	4.86		34/50
	RIAST - ICR Mice		
0	0	13/71	
1	0.123	12/71	
5	0.649	13/72	
12.5	1.645	28/72	
	IRDC - Charles River CD-1 Mice		
0	0	3/33[d]	0/45
5.0	0.21	5/55	0/61
25	1.03	41/52	32/50
50	2.05	32/39	26/37

[a]Data are taken from National Cancer Institute (NCI) (1977), Research Institute for Animal Science and Biochemistry and Toxicology (RIAST) (1983), and International Research and Development Corporation (IRDC) (in Epstein, 1976) diet studies.

[b]Dose levels are converted from ppm to mg/kg per day by multiplying by a factor of 0.13 for mice (Hartung, et al., 1984). For the NCI study, a correction factor of $(91/104)^4$ for mice was applied to correct for termination of the experiment before the animals had lived out their normal life span. For the IRDC study, a correction factor of $(78/104)^4$ was applied to compensate for early termination of the experiment.

[c]The number of animals at risk is the number of animals examined for the response.

[d]The number of animals at risk is the number of animals examined in the re-evaluation by Reuber, as reported in Epstein (1976).

*Source: K.S. Crump and Company. 1986. Quantitative Risk Assessment for Selected Volatile Organics in Drinking Water. Final Report. Prepared for Risk Assessment Unit, NJ DEP/OSR, Trenton, NJ. p. 87.

The assumptions used in the calculation of the health-based maximum contaminant level were that the average weight of an adult human is 70 kg and that an adult human consumes two liters of water a day.

Conclusions

The risk assessment was based on a 1983 carcinogenic bioassay of chlordane done by RIAST. Exposure was found to be associated with the occurrence of hepatocellular adenoma in male mice. The health-based MCL was estimated from this data to be 0.013 ug/L for life-time exposure resulting in a one in a million excess cancer risk.

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