

Public Health Goal for LINDANE In Drinking Water

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PREFACE

Drinking Water Public Health Goals
Pesticide and Environmental Toxicology Section
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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.

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PUBLIC HEALTH GOAL FOR LINDANE IN DRINKING WATER

SUMMARY

The Public Health Goal (PHG) developed for lindane (γ -hexachlorocyclohexane) in drinking water is 3.2×10^{-5} mg/L (0.032 ppb) based on induction of liver tumors in mice. The California Maximum Contaminant Level (MCL) is currently 0.0002 mg/L (0.2 ppb). The carcinogenic potency of lindane was estimated from dose response data for liver tumors in male CFI mice reported by Thorpe and Walker (1973). The Office of Environmental Health Hazard Assessment (OEHHA) has previously derived a human potency estimate of $1.1 \text{ (mg/kg-day)}^{-1}$ for lindane (DHS, 1991). At this value, the drinking water concentration associated with negligible theoretical lifetime extra cancer risk (10^{-6}) is 3.2×10^{-5} mg/L (0.032 ppb). Lindane also exhibits immunotoxicity and appears to interfere with endocrine metabolism and function in male and female rodents and in in vitro test systems. The most sensitive noncarcinogenic endpoint was immunotoxicity in mice. A health-preventive concentration of 0.08 ppb was calculated for immunotoxicity (delayed type hypersensitivity response) based on the 24-hour study of Meera et al. (1992). Lindane and related HCH isomers are not currently listed as chemicals known to the State to cause reproductive toxicity under Proposition 65. The proposed PHG of 0.032 ppb will provide an adequate margin of safety for potential immunotoxic, endocrine, or other anticipated chronic effects of lindane via drinking water exposure.

INTRODUCTION

Lindane is used as an insecticide and as a therapeutic scabicide, pediculicide, and ectoparasiticide for humans and animals (Budavari et al., 1989). As an insecticide, it is used on fruit and vegetable crops including greenhouse vegetables and tobacco, for seed treatment, in forestry (including Christmas trees), and for animal treatment. Registered uses also include domestic outdoor and indoor uses by homeowners such as dog dips, house sprays, and shelf paper; commercial food or feed storage areas and containers, farm animal premises, wood or wooden structures, and military use on human skin and clothing (ASTDR, 1998; U.S. EPA, 1985). In 1983, the U.S. Environmental Protection Agency (U.S. EPA) issued a Notice of Intent to cancel pesticide products containing lindane. The notice restricted certain applications of lindane on livestock, structures, and domestic pets to certified applicators or persons under their direct supervision (U.S. EPA, 1985b). In 1993, U.S. EPA issued a notice of receipt of a request for amendments to delete uses for several formulations of lindane powder, 99.5% technical, and dust concentrate which would delete from the pesticide label most uses of lindane on agricultural crops and use on animals and humans (U.S. EPA, 1993).

Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code Section 25249.5 et seq.) lindane was listed on October 1, 1989, as a chemical known to the State to cause cancer. The Department of Health Services (DHS) performed literature searches to evaluate whether a non-default analysis of lindane should be undertaken. There was inadequate information to make pharmacokinetic adjustments for dose-

response and interspecies extrapolations. In addition, data on the genotoxicity and mechanism of action of lindane provided no evidence which suggested that a non-default assessment was warranted.

This document updates the earlier risk assessment of lindane for the purpose of determining a public health goal for drinking water. In this assessment we employ the guidelines for cancer risk assessment recently proposed by U.S. EPA in 1996.

CHEMICAL PROFILE

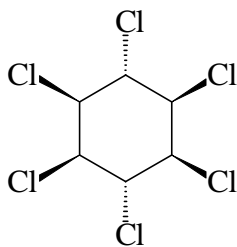
Chemical Identity

The pure gamma isomer of hexachlorocyclohexane (of at least 99.5% purity) was named lindane after the Belgian chemist Van Der Linden, who discovered it in 1912. It should not be confused with benzene hexachloride (BHC), a mixture of various isomers and byproducts, which was discovered by Faraday in 1825. The insecticidal properties of lindane were first demonstrated by Bender in 1933 (Ulmann, 1972). Additional information on lindane is given in Table 1.

Table 1. Chemical Identity of Lindane

Chemical name	lindane, gamma-hexachlorocyclohexane
Synonyms	γ -benzene hexachloride, BHC, γ -BHC, HCCH, HCH, γ -HCH, γ -hexachlorobenzene, γ -hexachlorocyclohexane
CAS No.	58-89-9
Chemical formula	C ₆ H ₆ Cl ₆

Chemical structure



Physical and Chemical Properties

Table 2. Physical and Chemical Properties of Lindane

Property	Value	References
Molecular weight	290.85	Windholz et al., 1983
Color	White	Ulmann, 1972
Physical state	Crystalline solid	Ulmann, 1972
Odor	Faint musty to odorless	Ulmann, 1972
Odor threshold	NA	
Melting point	112.3-113 ⁰ C	IARC, 1979
Boiling point	323.4 ⁰ C	IARC, 1972
Solubility in water	10 mg/L	IARC, 1979
Density	1.85 g/mL	IARC, 1979
Partition coefficients		
Octanol-water (K_{ow})		
Log K_{ow}	3.20-3.89	Montgomery, 1993
Soil-organic carbon-water (K_{oc})		
Log K_{oc}	2.38-3.52	Montgomery, 1993
Vapor pressure	0.03 mm Hg (20°C)	IARC, 1979
	9.4 x 10 ⁻⁶ mm Hg (20°C)	Windholz et al., 1983
Henry's law constant	2.43 x 10 ⁻⁷ atm m ³ /mol (23°C)	Montgomery, 1993

Production and Uses

None of the isomers of technical grade HCH are currently produced in the U.S. The production of lindane exceeded 2.3 x 10⁶ grams in 1976 (HSDB, 1997). Commercial production of lindane in the U.S. reportedly ended in 1976 (U.S. EPA, 1989). However, the Directory of Chemical Producers for 1987 and 1988 lists one producer of lindane, Drexel Chemical Co., Cordele, GA (SRI, 1987, 1988); subsequent volumes give no listings. Lindane is imported to the U.S. from France, Germany, Spain, Japan, and China (U.S. EPA, 1985a). The U.S. imports for lindane declined from 1.5 x 10⁸ grams in 1977 to 8.5 x 10⁷ grams in 1982 (HSDB, 1997).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Lindane present in soil can leach to groundwater, sorb to soil particles, or volatilize to air.

Air

The Toxic Chemical Release Inventory 1994 lists releases of lindane to the air from eight large processing facilities totaling 263 kg (579 lb) (TRI94, 1996). Historically the largest source of lindane release to air was from agricultural applications of lindane pesticides. Atmospheric release of lindane from disposal sites or hazardous waste sites has not been documented but is likely to occur (ATSDR, 1998). Application of lindane to fields of sunflowers and sugar beets resulted in a 54% evaporative loss of the pesticide within 24 hours (Neururer and Womastek, 1991). Air monitoring over southern Ontario, Canada in 1988-89 showed an annual mean air concentration of 60 pg/m³ for lindane (Hoff et al., 1992a). U.S. EPA conducted a study to estimate non-occupational exposure to 32 household pesticides in the U.S. Samples were collected in Jacksonville, FL and Springfield/Chicopee, MA. Detectable levels of lindane were found in personal air samples of 32-70% of the Jacksonville sample population with a range of mean air concentrations of 7-22 ng/m³. For Springfield/Chicopee lindane was found in 8-10% of samples with mean concentrations of 0.7-5 ng/m³ (U.S. EPA, 1990). Lindane has been detected in ground level ambient air samples in College Station, TX in 1979-80 at a mean concentration of 0.23 ng/m³ (range, 0.01-1.6 ng/m³) and in rainfall samples with a weighted mean concentration of 2.81 ng/L (range, 0.30-7.8 ng/L) (Atlas and Giam, 1988). Lindane has been detected in rain and snow water in Portland, OR in 1982 at mean concentrations ranging from 0.45-11 ppt (Pankow et al., 1984).

Soil

Soil releases of lindane from eight large processing facilities were 2.3 kg (5 lb) (TRI94, 1996). Lindane can be released to soil by direct application or indirectly during formulation, storage, and disposal. The application of lindane to laboratory refuse columns simulating municipal landfills indicated that lindane did not volatilize or leach from the refuse surface, and movement through the column was slight (Reinhart & Pohland, 1991; Reinhart et al., 1991). U.S. EPA's STORET database shows lindane was detected in only 0.5% of 596 sediment samples collected throughout the U.S. with a median concentration of 2.0 µg/kg (ppb) (Staples et al., 1985). By contrast lindane was detected in 33% of suspended sediment samples from the Niagara River with an average concentration of 2 ppb (Kuntz & Warry, 1983).

Water

Water releases of lindane from eight large processing facilities were 2.27 kg (5 lb) (TRI94, 1996). Lindane can be released to surface water by surface runoff or by wet deposition of rain or snow. Lake Ontario received less than 2 kg/year of lindane due to suspended sediment loading from the Niagara River between 1979 and 1981 (Kuntz & Warry, 1983). The Great Lakes in general receive from 3.7 to 15.9 metric tons/year of lindane by atmospheric deposition (Eisenreich et al., 1981). Lindane can penetrate to groundwater by soil leachate despite its low mobility in soils (ATSDR, 1998). Surface water concentrations of lindane have been measured

in many areas of the U.S. Reported concentrations ranged from 10-319 ppt (mean 147 ppt, ng/L) in Hampton Co., SC to 0.052-0.1 ppb in Washington, DC (Cole et al., 1984). U.S. EPA's STORET database lists lindane detections in 27% of 4,505 surface water samples collected in the U.S. (median concentration 0.02 ppb) (Staples et al., 1985). In sampling for pesticide residues in California well water mandated by the Pesticide Contamination Prevention Act, no detections of lindane were reported for 3,409 wells in 54 counties during the period 1986-1992 (DPR, 1992).

Food

Lindane residues in foods would appear to be declining according to the Food and Drug Administration's (FDA's) residue monitoring program (Gunderson et al., 1988; FDA, 1988; 1989; 1990; 1991). For the age groups 6-11 months, 14-16 year old males, and 60-65 year old females the estimated daily intakes of lindane were 1.9 ng/kg-day, 3.4 ng/kg-day, and 1.6 ng/kg-day, respectively, in the 1982-84 period. By 1990 these values were 0.5, 1.3, and 0.5 ng/kg-day, respectively, with the intervening years showing declining intermediate values. Lindane was detected in 4/429 onion samples in San Antonio food stores between 1989 and 1991 (Schattenberg & Hsu, 1992). Eighty percent of oyster samples collected in 1987 from the Gulf of Mexico had detectable lindane at a mean concentration of 1.7 ppb (range 0.25-9.1 ppb) (Sericano et al., 1990). In FDA's 1990 Total Diet Study on 936 food items, lindane was detected in 23 items (Yess, 1991). The mean concentration of lindane in 234 ready-to-eat foods was 1.2 ppb (ATSDR, 1988). Macintosh et al. (1996) estimated dietary exposures to 11 contaminants including lindane for about 120,000 U.S. adults by matching food consumption data collected as part of the Nurses' Health Study (NHS) and the Health Professionals' Follow-up Study (HPFS) with residue data for the table-ready food collected as part of the FDA Total Diet Study (TDS). For lindane the estimated dietary exposure ($\mu\text{g}/\text{day}$) for 78,882 females was: $G_{\text{mean}} = 0.2$; $G_{\text{SD}} = 1.51$; $\text{min.} = 0.03$; $\text{max.} = 3.2$; with an $r^2 = 0.986$ from regressing the natural-log transformed data on corresponding z-scores. For 38,075 males the values were 0.2, 1.55, 0.01, 2.9, and 0.989, respectively.

Lindane and other organochlorine compounds have been detected in human milk. While Rogan & Ragan (1994) did not report on lindane in a survey of commonly occurring persistent pesticides and industrial chemicals in breast milk, Currie et al. (1979) reported an average concentration of 6 ppb in Alberta, Canada. Quinsey et al. (1996) in an Australian study of 23 mothers and infants calculated daily intakes of lindane by the infants via breast milk at 0.33 ± 0.22 (range, 0.02-0.09) $\mu\text{g}/\text{kg}\text{-day}$. Unlike the other compounds studied, none of the calculated lindane intakes exceeded allowable levels (i.e., for lindane ADI = 8 $\mu\text{g}/\text{kg}\text{-day}$).

Tissue Residues

Lindane accumulates in adipose tissues as indicated by measurements in humans and animals (Siddiqui et al., 1981a; Kutz et al., 1977). Lindane can be transferred to the fetus through the placenta and to the neonate through the mother's milk (Siddiqui et al., 1981b).

Data pertaining to the bioaccumulation and pharmacokinetics of lindane have been reviewed by U.S. EPA (1988). Kutz et al. (1991) have summarized numerous studies of lindane occurrence in human adipose tissue samples collected between 1972 and 1986. Average reported concentrations range from 0.002 ppm (Canada) to 7.2 ppm (Japan). Values reported for the U.S. general population averaged 0.02 ppm (geometric mean). Lindane was not reported in a recent survey of semivolatile organics in adipose tissue of the U.S. population and selected

subpopulations (Lordo et al., 1996). A recent report on organochlorine pesticides in adipose tissue of British Columbia residents gave an average for lindane of 2.03 ng/g lipid (range, 0.04-50.0) (Teschke et al., 1993). The occurrence of chlorinated hydrocarbons in adipose tissue of healthy children and tumor patients in Germany was evaluated by Teufel et al. (1990). For lindane in 183 healthy children the mean, standard deviation, and range were 0.038 ± 0.054 (0.002-0.324) mg/kg fat tissue. The corresponding values for total hexachlorocyclohexanes were 0.092 ± 0.108 (0.004-0.629) mg/kg fat tissue.

METABOLISM AND PHARMACOKINETICS

Absorption of lindane and related isomers following inhalation, oral, or dermal exposures has been inferred from human occupational or accidental exposures. Limited animal study data are available from the inhalation route. Lindane is well absorbed from the gastrointestinal tract in animals and humans and distribution is primarily to adipose tissue but also to brain, kidney, muscle, blood and other tissues. Metabolism of lindane occurs mainly in the liver and chlorophenol metabolites are mainly excreted via the urine.

Absorption

Humans absorb lindane vapor or dusts via inhalation as inferred from adverse effects seen in occupational studies such as hematological and neurological effects (ATSDR, 1998). No specific studies have quantified the rate and extent of inhalation absorption. A number of authors have reported accidental oral poisonings by lindane resulting in high blood concentrations. Studies in rodents show that lindane is readily absorbed following oral administration. Ahdaya et al. (1981) found that half of a dose of ^{14}C lindane administered by stomach tube to fasted mice was absorbed from the GI tract in about 14 minutes.

Feldman and Maibach (1974) dosed six human subjects with lindane intravenously (i.v.) and topically (to the forearm) and measured subsequent urinary excretion. Approximately 25% of the i.v. and 10% of the topical dose was measured in the urine after 120 hours of compound administration. This indicates that at least 10% of lindane topically applied to humans may be absorbed. No data were presented on other routes of excretion or on the amount deposited in body fat. An upper bound estimate of the fraction of lindane absorbed through the skin may be derived by the following method: First, assume that 100% of the lindane dose is absorbed when given intravenously. Using the data of Feldman and Maibach (1974) showing urinary excretion of 25% of an i.v. dose compared to only 10% of a topically applied dose, one can estimate the percent dermally absorbed as the ratio of these two values ($10\%/25\% = 40\%$). Dick et al. (1997) studied the percutaneous absorption and skin distribution of lindane in human volunteers. Doses of 3 mg/mL commercial formulation and 120 mg/mL of lindane in acetone were applied to 75 cm² areas of the forearms of four male Caucasian subjects (20-44 years, 62-78 kg). The exposure sites were washed at six hours to mimic a decontamination procedure. The peak plasma concentrations for the lower dose averaged 0.47 ± 0.14 ng/mL at 6.5 ± 1.6 hours. For the higher dose the peak value was 0.91 ± 0.08 at 3-45 hours respectively. The areas under the plasma lindane concentration x time curves (AUC) were 14.1 ± 4.0 and 46.8 ± 2.9 ng/mL hour, respectively.

Distribution

In rats orally dosed with lindane for 5, 10, or 15 days the distribution was greatest in fat, followed by brain, kidney, muscle, lungs, heart, spleen, liver, and blood (Srinivasan & Radhakrishnamurty, 1983b). Lindane has also been found in the adrenal glands of rats (Lahiri et al., 1990; Sulik et al., 1988). In a 12-day experiment, the accumulation of lindane in the brain of rats gavaged with 5 or 12 mg/kg-day began to decline after eight days. This reduction was not seen in rats gavaged with 20 mg/kg-day (Tusell et al., 1988). The distribution of lindane in humans is known largely through case reports of accidental poisonings. In a fatal case involving ingestion of an unknown amount by a young male, lindane was found in the cerebrospinal fluid (Davies et al., 1983). In another case involving topical application to an infant, lindane was found in the brain tissue.

Metabolism

In mice, urinary metabolites of a single i.p. injection of lindane accounted for 57% of the dose. The metabolites were mostly of glucuronide and sulfate conjugates of 2,4,6-trichlorophenol and 2,4-dichlorophenol. No mercapturic acid conjugates were detected (Kurihara & Nakajima, 1974). Metabolites found in the liver of rats following oral gavage or dietary administrations of lindane included di-, tri-, tetra-, and pentachlorobenzenes, pentachlorocyclohexanes, and pentachloro-2-cyclohexen-1-ol. (Chadwick & Freal, 1972; Kujawa et al., 1977). Metabolites found in blood of these rats included di-, tri-, and pentachlorophenols and pentachloro-2-cyclohexen-1-ol (Kujawa et al., 1977). Di-, tri-, and tetrachlorophenols, pentachlorocyclohexenes, and pentachloro-2-cyclohexen-1-ol have been found in samples of kidney, spleen, heart, and brain tissue from rats fed lindane (Kujawa et al., 1977). Metabolites found in urine included tri-, tetra-, and pentachlorophenol, pentachloro-2-cyclohexen-1-ol, and isomers of tetrachloro-2-cyclohexen-1-ol (Chadwick & Freal, 1972, Chadwick et al., 1978c; Kujawa et al., 1977). The metabolism of lindane appears to be dependent on the cytochrome P-450 oxidative system. Pretreatment of rats with phenobarbital accelerated the rate of excretion of lindane and α -HCH (Koransky et al., 1964). Lindane exhibited greater toxicity in DBA/2 mice than in C57BL/6 mice, the former being unresponsive to microsomal enzyme induction by lindane (Liu & Morgan, 1986).

Angerer et al. (1983) showed that chlorophenols were the primary urinary metabolites of lindane excreted by workers involved in lindane production. The metabolites 2,3,5-, 2,4,6-, and 2,4,5-trichlorophenol accounted for 58% of the lindane metabolites identified. Other metabolites included other trichlorophenols, dichlorophenols, tetrachlorophenols, and dihydroxychlorobenzenes. Pentachlorophenol has also been identified as a urinary metabolite following occupational lindane exposure (Engst et al., 1979). In vitro human liver microsomes convert lindane via dechlorination, dehydrogenation, dehydrochlorination, and hydroxylation to five primary metabolites: 3,6/4,5-hexachlorocyclohexane, pentachlorocyclohexane, 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol, and pentachlorobenzene (Fitzloff et al., 1982). In vitro studies have demonstrated that an epoxide forms during the metabolism of pentachlorocyclohexene. This stable halogenated epoxide metabolite may be involved in the mutagenic and carcinogenic effects of lindane (Fitzloff & Pan, 1984).

Excretion

When single doses of ³⁶Cl-labelled α-HCH or lindane were given i.p. to rats at 200 mg/kg and 40 mg/kg, respectively, about 80% of the total radioactivity was excreted in the urine and 20% in the feces (Koransky et al., 1964). Bosch (1987a) treated male rats dermally with radiolabelled doses of lindane (20% emulsifiable concentrate) on 4.9 cm² shaved dorsal area. Doses of 0.06, 0.6, and 6.0 mg/cm²/kg of radiolabelled lindane resulted in 0.28%, 0.08%, and 0.02% of the applied radiolabel in urine after four hours, respectively. After 24 hours, 4.4%, 3.2%, and 0.6% were excreted. In male rabbits similarly dosed with 0.005, 0.05, and 0.5 mg/cm²/kg in a 28.3 cm² shaved dorsal area the four hours urinary excretion was 3.8%, 2.6%, and 1.3%, respectively. After 24 hours, 25.5%, 11.6%, and 6.8% of radiolabel was excreted in urine (Bosch, 1987b; ATSDR, 1998).

Physiologically Based Pharmacokinetic (PBPK) Model

DeJong & Blaauboer (1997) have developed a PBPK model for oral or i.p. intake of lindane in the rat. The model has four perfused compartments: fat, brain, liver, and other tissue. Oral and i.p. uptake is via the liver compartment. Biotransformation of lindane also occurs in the liver compartment. Both uptake and biotransformation are modeled as first order processes. The model simulations generally agree with experimental data. An indication for gender differences in lindane metabolism was observed in the simulations of male and female rats. Elimination of lindane from the tissues of the male rats is simulated quite well. By contrast, the simulations of lindane concentrations in both brain and fat compartments of female rats overestimated the experimental data. Simulations of lindane brain levels after multiple oral doses indicate a possible nonlinear relationship between simulated and experimental tissue concentrations over a dose range of 1-10 mg/kg-day. A dose-dependent uptake or metabolism of lindane cannot be excluded and could result from saturation of biotransformation, auto-induction of metabolism or concentration-dependent uptake of lindane from the oil vehicle in the GI tract. Simulations of single i.p. doses were adequate at 10 mg/kg and 60 mg/kg.

TOXICOLOGY

Toxicological Effects in Animals and Plants

Acute Toxicity

ATSDR (1998) has summarized a number of studies dealing with acute exposures of lindane in experimental animals. Median lethal doses (LD₅₀) were obtained with 88 mg/kg in male and 91 mg/kg in female Sherman rats. A 14-day ad libitum administration of lindane in feed to Wistar rats gave a LOAEL of 72 mg/kg-day for increased kidney weight. A 10-day study with a single daily oil gavage administration of lindane to B6C3F₁ mice gave a LOAEL of 10 mg/kg-day for decreased bone marrow progenitor cell numbers. A NOAEL of 10 mg/kg-day for these effects was observed in mice exposed for only three days (Hong & Boorman, 1993). The most sensitive

effects for lindane exposure were neurological. Single doses of lindane in oil gavage gave a LOAEL of 5 mg/kg-day in Long-Evans rats that exhibited myoclonic jerks and a single clonic seizure. In Sprague-Dawley rats dosed daily by oil gavage for four days a NOAEL was observed at 1 mg/kg-day and LOAELs at 3 mg/kg-day for increased kindling acquisition and 10 mg/kg-day for seizures. The steepness of the dose-response relation for lindane was indicated by a single oil gavage dose NOAEL of 15 mg/kg in Wistar rats which showed convulsions at 20 mg/kg-day (Vendrell et al., 1992).

Subchronic Toxicity

Zoecon (1983; U.S. EPA, 1998) administered 0, 0.2, 0.8, 4, 20, or 100 ppm lindane (99.85%) in the diet to 20 male and 20 female Wistar KFM-Han SPF rats/treatment group. After 12 weeks, 15 animals/sex/group were sacrificed. The remaining rats were fed the control diet for an additional six weeks before sacrifice. No treatment-related effects were noted on mortality, hematology, clinical chemistry, or urinalysis. Rats receiving 20 or 100 ppm lindane were observed to have greater-than-control incidence of the following: liver hypertrophy, kidney tubular degeneration, hyaline droplets, tubular distension, interstitial nephritis, and basophilic tubules. Since these effects were mild and/or rare in animals receiving 4 ppm, this dose was identified as the study NOAEL. The study doses were estimated to be 0.29 mg/kg-day for males and 0.33 mg/kg-day for females based on measured feed intake. U.S. EPA (1998) used this study and an uncertainty factor of 1,000 to derive an oral RfD of 0.0003 mg/kg-day for lindane.

Chadwick et al. (1988) observed a LOAEL/frank effect level (2/12 deaths) of 20 mg/kg-day in female Fischer 344 rats administered lindane once daily by oil gavage for 15 weeks. Suter (1983) administered lindane in feed ad libitum to Wistar rats and observed NOAELs/LOAELs of 0.3/1.0 mg/kg-day for liver and kidney effects, centrilobular hypertrophy and necrosis, tubular distension, and basophilic tubules, respectively. Lower LOAELs were identified by Meera et al. (1992) for immunological effects in Swiss mice administered lindane ad libitum in their feed for 24 weeks. At 0.012 mg/kg-day biphasic changes were seen in the cell- and humoral-mediated immune system. At a much higher dose of 1.2 mg/kg-day, necrosis of the thymus was seen. ATSDR (1998) used the LOAEL of 0.012 mg/kg-day and applied an uncertainty factor (UF) of 1,000 to derive a Minimum Risk Level (MRL) of 1×10^{-5} mg/kg-day for lindane.

Videla et al. (1995) studied parameters related to hepatic oxidative stress, cell injury, phagocytic activity, and liver histology in rats administered triiodothyronine (T3) and /or lindane as well as control animals. The joint administration of lindane and T3 elicited a marked elevation in serum GOT and glutamate pyruvate transaminase (GPT) concomitant with extensive liver necrosis and the presence of granulomas containing lymphocytes, Kupffer cells and polymorphonuclear leukocytes (PMN). The authors concluded that hyperthyroidism increases the susceptibility of the liver to the toxic effects of lindane.

Genetic Toxicity

Lindane and its isomers have some genotoxic potential but the evidence is not conclusive. The Genetic Activity Profile (Version 4.01) data base lists positive results with lindane for 5 out of 22 systems tested. Lindane was not genotoxic in bacterial assays for gene mutation with or without exogenous microsomal activation, did not produce DNA damage (without activation), and was not mutagenic in yeast or algae (ATSDR, 1998). Lindane has been reported as negative for cytogenetic effects in Chinese hamster ovary cells (NTP, 1984; Murli, 1990) and inactive in

inducing unscheduled DNA synthesis in primary rat hepatocytes in vitro (Cifone, 1990). Lindane and α -HCH were reported to bind to calf thymus DNA in vitro with metabolic activation and to mouse liver in vivo at a low rate (Iverson et al., 1984). The incidence of chromosome aberrations in mouse bone marrow cells was increased by exposure to 1.6 mg/kg-day for seven days (Kumar et al., 1995). Bhunya and Jena (1992) observed a significant increase in chromosome aberrations in chicks administered 100 mg/kg lindane. Significant increases in micronuclei in bone marrow cells were induced at all three doses of 50, 75, and 100 mg/kg of lindane administered either intraperitoneally or orally. Lindane was clearly genotoxic in this in vivo chick system.

Perocco et al. (1995) found that lindane was able to induce BALB/c 3T3 cell transformation in vitro with and without exogenous microsomal activation. This result suggests a possible tumor promoting role of lindane in multistep oncogenesis. Guan & Ruch (1996) studied the mechanism of lindane-induced loss of gap junction intercellular communication (GJIC) in WB-F344 rat liver epithelial cells treated with lindane. Immunochemical and biochemical data strongly indicate that the loss of gap junction plaques and of Connexin43-P2 in treated WB-F344 cells were due to endocytosis of the plaques and degradation of Cx43-P2 in lysosomes. Several non-genotoxic rodent carcinogens such as phthalate esters, barbiturates, peroxides, PCBs, and PBBs inhibit GJIC. Because of the involvement of GJIC in growth and regulation, inhibition of GJIC may play an important role in their ability to enhance neoplastic transformation.

Biochemical Toxicity

Lindane exposure is known to affect the activities of a number of liver enzymes that could influence the toxicity of lindane and other xenobiotics. Krechniak et al. (1994) found that lindane treatment of rats for three days at 11, 22, or 44 mg/kg increased the activity of 4-*O*-demethylase and aniline 4-hydroxylase significantly ($p < 0.05$) at all dose levels in a dose-dependent manner. In an in vitro study of the induction of reactive oxygen species by polyhalogenated cyclic hydrocarbons, Bagchi & Stohs (1992) found that lindane clearly induced superoxide anion production following incubation with macrophages, hepatic mitochondria, and hepatic microsomes. Similar results were seen with endrin but much less activity with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The effect of lindane on hepatic lipogenic enzymes and serum lipids was investigated by Boll et al. (1995). Male Wistar rats were administered 50-350 ppm (0.17-1.19 μ mole/kg chow) in the feed for 12 days. The liver enzyme activities measured were: fatty acid synthase (FAS; EC 2.3.1.85); citrate cleavage enzyme (CCE; EC 4.1.3.8); malic enzyme (ME; EC 1.1.1.40); glucose-6-phosphate dehydrogenase (G6PDH; EC 1.1.1.49); and 6-phosphogluconate dehydrogenase (PGDH; EC 1.1.1.44). Serum lipids were also measured. Lindane at 150 ppm caused a substantial decline in all enzyme activities during the first 24 hours of lindane administration. The recovery of activity was faster for ME, G6PDH, and PGDH (70-80% of controls in four days) than for CCE and FAS (50-60% of controls at 11 days). Polychlorinated biphenyls (PCBs) in the diet caused opposite changes of the activities of the lipogenic enzymes. Co-administration of lindane and PCBs resulted in an apparent cancellation of effects, suggesting that lindane and PCBs affect fatty acid synthesis at opposite points. Levels of serum triglycerides were significantly increased by lindane feeding, while serum cholesterol and phospholipid levels were only slightly elevated.

Endocrine Effects

A number of environmental xenobiotics such as the organochlorines have been shown to exert estrogenic or anti-estrogenic effects at cellular and organismal levels. Such agents have been implicated in the incidence of hormonally-related cancers, estrogenic and antiestrogenic effects, and infertility in humans and animals (Ratnasabapathy et al., 1997). In *in vivo* studies, lindane has been reported to inhibit steroidogenesis (Sircar & Lahiri, 1990). Zisterer et al. (1996) studied the inhibition of steroidogenesis in a mouse Y1 adrenocortical cell line. They observed that lindane, but not α - and δ -HCH, was a potent and selective inhibitor of ligand binding to the peripheral-type benzodiazepine binding site which, in turn, is reported to regulate the rate-limiting step in steroidogenesis. A 50% reduction of pregnenolone production was seen at a lindane concentration of 50 μ M. In a peripheral-type benzodiazepine site binding assay in Y1 cells with 5 nM [³H]PK 11195, a displacement curve was generated assuming mutually exclusive binding by lindane and PK 11195. The mean K_i value of 1.8 ± 0.7 μ M was obtained for lindane from triplicate determinations. Petit et al. (1997) conducted two complementary bioassays for screening the estrogenic potency of xenobiotics: recombinant yeast for trout estrogen receptor and trout hepatocyte cultures. The first assay uses recombinant yeast expressing rainbow trout estrogen receptor (rtER). The rtER, constitutively and permanently expressed in yeast, can induce the *lacZ* gene transcription in the presence of estrogens. The reporter gene 2ERE-CYC1-*lacZ* is the *E. coli* gene for β -galactosidase which is integrated in the yeast genome. This combination in yeast provides a screening test for estrogenic potential of various xenobiotics. A dose-dependent induction of *lacZ* gene was observed with lindane and a number of other xenobiotics. The effective dose range was 10^{-6} to 10^{-4} M compared to estradiol at 10^{-9} to 10^{-8} M. A second assay involved the use of hepatocyte cultures in which the vitellogenin gene whose expression is principally dependent upon estradiol was used as a biomarker. Only four of the active estrogenic compounds from the yeast system were inactive in the hepatocyte cultures. Lindane was more active in this second system, giving 100% of control activity compared to 50% of control at the same concentration in yeast.

In contrast to the results summarized above, lindane was found not to be estrogenic in the E-SCREEN system (Soto et al., 1995). Ratnasabapathy et al. (1997) found that lindane exhibited neither estrogenic nor anti-estrogenic activity based on the estrogen-mediated stabilization of apolipoprotein II (apoII) mRNA in avian liver. Laws et al. (1994) found that lindane did not alter the estrogen receptor or estrogen-dependent induction of progesterone receptors in sexually immature or ovariectomized adult rats. Lindane was administered to 21 day-old female Long Evans at 40 mg/kg-day for seven days or to adult ovariectomized rats at 10, 20, or 40 mg/kg-day for five days. Lindane was not found to alter serum estradiol concentrations, to change the estrogen receptor number, or to change the estrogen-dependent induction of progesterone in the hypothalamus, pituitary, or uterus. The authors suggest that effects of lindane on the female reproductive system may be mediated through the GABA-nergic system or via altered growth factors.

Developmental and Reproductive Toxicity

A dose-related increase in the incidence of fetuses with an extra 14th rib was reported in CFY rats exposed to 5, 10, or 20 mg/kg lindane by gavage during gestation days 6-15; only the 20 mg/kg group was statistically significant (Palmer et al., 1978a). The incidence of fetuses with an extra 13th rib was significantly increased in rabbits given 20 mg/kg lindane by gavage during

gestation days 6-18 (Palmer et al., 1978a). In rats treated with a single dose of 20 mg/kg lindane, Rivera et al. (1991) interpreted regional changes in brain noradrenaline and serotonin levels as developmental effects.

Uphouse & Williams (1989) observed increased length of estrous cycle and decreased sexual receptivity in female rats treated with a single 33 mg/kg dose of lindane given by gavage. Tezak et al. (1992) reported inhibition of the formation of estradiol-receptor complex in the uterus cytosol of female rats administered 30 mg/kg-day by gavage for seven days. Mouse dams given 5 mg/kg lindane during various times of the gestation period had increased numbers of fetuses resorbed (Sircar & Lahiri, 1989). Anti-estrogenic effects of lindane were observed in female rats given 20 mg/kg-day by gavage for 15 weeks but not in another group given 5 mg/kg-day (Chadwick et al., 1988). Laws et al. (1994) observed that ovariectomized rats and sexually immature female rats given 40 mg/kg-day for five days showed no effect on estrogen receptor number. The authors concluded that lindane's anti-estrogenic effect is not due to direct action on estrogen receptors. In male rats fed 75 mg/kg-day lindane for 90 days, Shivanandappa & Krishnakumari (1983) observed testicular atrophy, degeneration of seminiferous tubules, and disruption of spermatogenesis. Rats exposed to 10 mg/kg-day for four generations showed no adverse reproductive effects (Palmer et al., 1978b). Dalsenter et al. (1996) orally dosed male rats (10/group) with either six mg/kg for five days or a single dose of 30 mg/kg of lindane and evaluated effects on the reproductive system. The number of spermatids in the testes two weeks after dosing was significantly reduced at both doses compared to control animals ($p < 0.05$). Reductions in epididymal sperm concentration were also seen but were significantly reduced only at the 30 mg/kg dose. Lindane concentrations in adipose tissue, liver, brain and testes two weeks after the single 30 mg/kg dose were: 5,542; 476; 92; and 163 ng/g, respectively. At the lower dose regimen the testes lindane concentration was 41 ng/g after two weeks.

Alm et al. (1996) evaluated the effect of lindane on the development of eight-cell mouse embryos in vitro. Lindane showed a dose-dependent decrease in blastocyst hatching over the concentration range of 3.6-29 $\mu\text{g/mL}$. At 3.625 $\mu\text{g/mL}$ lindane caused a significant decrease in the number of nuclei in preimplantation mouse embryos. Significant toxicity of lindane has been shown not only during the first cleavage stages but also in the early embryogenesis stage. Direct exposure of gestational day 10 rat conceptus to lindane in the culture medium resulted in dose- and time-dependent increases in mortality and decreased growth parameters. A lindane concentration of 14.5 $\mu\text{g/mL}$ had a significant effect on the organogenesis-stage rat conceptus (McNutt et al., 1994). Lindane and related HCH isomers are not currently listed as chemicals known to the State to cause reproductive toxicity under Proposition 65 (Safe Drinking Water and Toxic Enforcement Act of 1986) (OEHHA, 1996).

Immunotoxicity

Immunosuppression, as indicated by decreases in serum agglutinin titers against *Salmonella typhi* and *Salmonella paratyphi*, was reported in rats gavaged with 6.25 or 25 mg/kg-day lindane for five weeks (Dewan et al., 1980) and in rabbits given capsules five times per week with 1.5, 6, and 12 mg/kg-day for five to six weeks (Desi et al., 1978).

Meera et al. (1992) observed a biphasic dose-dependent and time-dependent immunological effect of lindane on cell- and humoral-mediated immunity of initial stimulation followed by suppression in groups of six female Swiss mice at doses of 0.012, 0.12, and 1.2 mg/kg-day for 24 weeks. Histological examinations revealed decreased lymphocyte populations in the thymus and lymph nodes and a reduction in cellularity in the spleen. A LOAEL for immunotoxicity of

0.012 mg/kg-day was identified (see additional discussion below in the section on Dose Response). Banerjee et al. (1996) also observed that lindane suppressed both primary and secondary humoral immune responses to sheep red blood cells in albino mice administered lindane in the diet at 0, 10, 30, or 50 ppm for periods up to 12 weeks (10-14 animals/group). The suppression was seen at 30 and 50 ppm, was found to increase in a dose-time dependent pattern, and was in general more pronounced in secondary antibody response than primary.

Saha & Banerjee (1993) studied the effect of subchronic lindane exposure on humoral and cell-mediated immunity in albino rats. Lindane (97%) was administered in feed to four groups of Wistar male albino rats (10-12/group) at 0, 5, 20, or 30 ppm in the diet for periods of 8 to 22 weeks. Half of the animals were immunized s.c. with tetanus toxoid. Rats (10-12/group) were randomly selected from each group at 8, 12, 18, and 22 weeks of exposure. Blood samples, peritoneal macrophages, liver, spleen, and thymus were collected. Serum antibody titer to tetanus toxoid was estimated by indirect hemagglutination technique, quantitation of serum immunoglobulin (IgM and IgG) was carried out by single radial immunodiffusion, serum albumin, and globulin fractions were studied by electrophoresis, and leucocyte and macrophage migration inhibition were assayed in vitro by a capillary method.

Exposure to 5-30 ppm dietary lindane for 8-22 weeks produced no overt toxicity as indicated by mortality, growth rate, and food intake versus control rats. No significant alterations of spleen or thymus weights were observed. Serum albumin and globulin concentrations were consistent and unaffected by lindane exposure. However, the effect of tetanus toxoid injection in humoral response was readily observed from an increased globulin level (decreased A/G ratio) in stimulated animals. The A/G ratio was significantly decreased in the 30 ppm group at 18 weeks and in the 20 and 30 ppm groups at 22 weeks. Rats exposed to 20 or 30 ppm lindane for 12-22 weeks showed significant decreases ($p < 0.05-0.01$) in serum antibody titer to tetanus toxoid. Decreases were noted at 5 ppm at 12-22 weeks. The effect of lindane on IgM and IgG production was to lower the response of these immune elements to tetanus toxoid immunization. The response was significantly lower in rats exposed to 20 ppm lindane for 22 weeks or 30 ppm lindane for 18-22 weeks. The effect of lindane on cell-mediated immune response was demonstrated by macrophage and leucocyte migration inhibition tests (MMI, LMI). Rats exposed to 20 ppm lindane for 12-22 weeks or 30 ppm for 8-22 weeks showed significant MMI and LMI responses. Dose-time dependent inhibitions were found when both the ability to produce MMI and LMI were evaluated. While significant effects were not found at 5 ppm (0.5 mg/kg-day) over the limited course of this study, the time as well as dose dependence of the immunotoxic effects noted, and the apparent trends in dose-time response seem to indicate that this is a LOAEL rather than a NOAEL.

It appears from these studies that the immune system is a sensitive target of lindane toxicity. Immunotoxicity of lindane in rats and mice was observed at exposure levels well below reported NOELs for other toxic endpoints (e.g., WHO, 1991; ATSDR, 1998). The effects of lindane are dose-and-time dependent and suggest a threshold(s) for immunological effects. Such a threshold(s) would depend on the method of testing, the test species, the endocrine and nutritional status of the host and the type of antigen causing the response (Saha & Banerjee, 1993). A number of possible mechanisms have been advanced to explain these effects including alteration of normal plasma membrane bound functions resulting from lindane's lipophilicity, the estrogenic activities of lindane, estrogen being known to modulate the immune system, possible depression of hematopoiesis in bone marrow and impairment of helper cell functions and/or the deletion of the suppressor cell activity (Meera et al., 1992). Subsequently,

Meera et al. (1993) demonstrated that the uptake of ^{45}Ca by spleen cells was enhanced during the initial stimulatory phase of lindane action and decreased during the immunosuppression phase. Lymphocyte proliferation was inhibited during both phases of immune response by verapamil, a calcium channel blocker, and by trifluoperazine, a calmodulin inhibitor. From this study the authors concluded that prolonged exposure to lindane produced a time dependent biphasic immunomodulation by altering the slow calcium channel activity in lymphocytes.

Neurotoxicity

Neurotoxic effects of lindane have been reported in several species of animals (ATSDR, 1998). Seizures have been reported following a single intragastric dose of 30-60 mg/kg in rats. Less serious effects in rats included increased anxiety following a single gavage dose of 20 mg/kg (Llorens et al., 1990) and increased spontaneous motor behavior at 10 mg/kg (Llorens et al., 1989). Increased rates of acquisition of kindled seizures were seen in rats exposed to 3-10 mg/kg-day lindane for four days (Joy et al., 1982). Kindling refers to the development of behavioral seizures with repeated application of initially subthreshold electrical or chemical stimuli. Gilbert administered 0 or 10 mg/kg-day lindane, p.o. for 30 days, or three times/week for 10 weeks. Enhanced behavioral responsiveness to lindane (myoclonic jerks, clonic seizures) emerged over the course of dosing and persisted two to four weeks after the last dose. Electrical kindling of the amygdala, beginning four to six weeks after the final dose, was facilitated. The data indicate that repeated exposure to subconvulsant doses of lindane produces a persistent alteration in the central nervous system (CNS) as evidenced by an enhanced susceptibility to kindled seizures. Significantly altered Skinner box behavior (operant conditioning) was found in rats exposed to 2.5 mg/kg-day lindane for 40 days (Desi, 1974), and significantly reduced nerve conduction velocity in rats exposed to 25 mg/kg-day for 30 days (Muller et al., 1981). The mechanism(s) of lindane neurotoxicity has been investigated in a number of cell culture systems. Pomes et al. (1994) studied the effects of lindane and other organochlorine pesticides on GABA-dependent Cl^- fluxes in primary mouse embryo neuronal cultures. In this system cyclodienes inhibited GABA-induced $^{36}\text{Cl}^-$ uptake with similar potencies to those described using brain synaptoneurosomes whereas lindane showed greater potency than that described using other *in vitro* systems. In all cases statistically significant ($p < 0.01$) inhibition of GABA-induced $^{36}\text{Cl}^-$ uptake was observed, with α -endosulfan and dieldrin showing the greatest inhibition followed by aldrin and lindane. Lindane had no effect on GABA-independent $^{36}\text{Cl}^-$ uptake. Rosa et al. (1997) studied the cytotoxic action of lindane and δ -HCH as well as their ability to induce changes in intracellular Ca^{+2} homeostasis in cultured rat cerebellar granule neurons. Both δ - and γ -HCH induced an increase in $[\text{Ca}^{+2}]_i$ which was most pronounced in the case of the δ -HCH. Both isomers stimulated Ca^{+2} influx through voltage-gated Ca^{+2} channels but only the γ -isomer affected a Ca^{+2} -dependent, dantrolene-sensitive pool. Alternatively, δ -HCH affected mainly Ca^{+2} -dependent, dantrolene-insensitive pool. The toxic action of lindane may be primarily related to release of Ca^{+2} from the dantrolene-sensitive stores.

Chronic Toxicity

Fitzhugh (1950) fed 10 Wistar rats/sex /group 5, 10, 50, 100, 400, 800, or 1,600 ppm lindane for two years. Slight liver and kidney damage and increased liver weights were noted at the 100 ppm dose level. Based on a feed intake of 5% body weight, a NOAEL of 2.5 mg/kg-day (50 ppm) was derived for this study by U.S. EPA (U.S. EPA, 1998). In another two-year bioassay,

four beagle dogs/sex/group were administered 0, 25, 50, or 100 ppm lindane in the diet (Rivett et al., 1978). Treatment-related effects noted in dogs of the 100 ppm group were increased serum alkaline phosphatase and enlarged dark friable livers. The NOAEL was determined to be 50 ppm (1.6 mg/kg-day) (U.S. EPA, 1998).

Amyes (1990) administered lindane to Wistar rats ad libitum in feed for two years. The author identified NOAELs/LOAELs of 0.7/7.0 mg/kg-day for liver and kidney effects, peri-acinar hepatocytic hypertrophy and increased kidney weight, urinary volume, urea, and creatinine excretions, respectively.

Carcinogenicity

Fitzhugh et al. (1950), Ortega et al. (1957) and Ito et al. (1975) conducted studies in which lindane was administered to rats by the oral route. These studies are of limited value for determining carcinogenicity due to several factors including poor animal survival, small number of animals, inadequate study duration, and/or a limited number of animals submitted to pathological evaluation. An additional oral study, conducted with Osborne-Mendel rats, was reported by the National Cancer Institute (NCI, 1977). This study was limited by poor survival rates in all groups, inadequate evidence that the dose given to males corresponded to the maximum tolerated dose, and a small number of matched controls. NCI found that the incidences of tumors at any site in the treated animals were not statistically significant when compared to concurrent controls. However, when compared to historical control data compiled from NCI/NTP reports by DHS, there was an increase in the incidence of liver neoplastic nodules among treated rats. For male rats, the incidence of liver neoplastic nodules in historical controls was 2/692 compared to 3/45 and 2/45 for the low dose and high dose groups, respectively ($p=0.002$). For female rats, the incidence of liver neoplastic nodules in historical controls was 18/698 compared to 4/48 and 2/45 for the low dose and high dose groups, respectively ($p=0.047$). There were no incidences of liver neoplastic nodules in any of the concurrent control animals. It is interesting to note that the incidence of liver nodular hyperplasia was significantly increased in rats exposed to the *a* isomer of hexachlorocyclohexane (Ito et al., 1975). It is apparent that the effects of lindane exposure in rats have not been adequately studied.

In mice, several studies have been conducted in which lindane was administered by the oral route (Goto et al., 1972; Hanada et al., 1973; Ito et al., 1973; Thorpe and Walker, 1973; Weisse and Herbst, 1977; NCI, 1977; and Wolff et al., 1987). In addition, studies of lindane administered by subcutaneous implantation, dermal application, and intraperitoneal injection have also been conducted, but these routes of exposure are not appropriate for this risk assessment. Of the oral studies, the one by Thorpe and Walker (1973) is the most appropriate for estimating risks for the purposes of setting a PHG. It is the most appropriate study for potency evaluation due to the experimental design and thorough reporting of the data. Wolff et al. (1987) reported increased incidences of tumors in two of three different phenotypic classes of YSxVY-F₁ hybrid female mice. The Wolff study was not selected for the potency calculation because, although it was a well conducted study, the strain of mice chosen was unusual and less sensitive to lindane carcinogenicity than the male CF1 mice used in the Thorpe and Walker study. In Wistar rats fed 0.05-20 mg lindane/kg-day in the diet for 104 weeks (Amyes, 1990), no statistically significant increases in endocrine, thyroid, pituitary, adrenal gland, liver, or ovary tumors were observed; however, poor survival rates limit the significance of these results. The remaining studies are

limited by the following: inadequate reporting (Goto et al., 1972), short duration of experiment (Hanada et al., 1973; Ito et al., 1973), small experimental and/or control groups (Hanada et al., 1973; NCI, 1977), and low experimental doses (Weisse and Herbst, 1977; NCI, 1977). Lindane and other HCH isomers are listed among chemicals known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) (OEHHA, 1996). The potency and CSF estimates derived from the study by Thorpe and Walker (1973) are given below.

Thorpe and Walker (1973)

Groups of 30 male and 30 female Carworth Farm No. 1 (CF1) mice were fed diet containing 400 ppm lindane continuously for 110 weeks. The control groups, comprising 45 animals of each sex, were maintained on diet without lindane. Survival was significantly reduced in treated versus control animals: 3% of females and 17% of males fed lindane survived the duration of the experiment while 32% of females and 44% of males fed control diet survived the duration of the experiment. Significant increases in the incidences of liver tumors with increasing dose in male and female mice were reported. Lung metastases were also reported in lindane-treated male and female animals. Results in male mice which were used in the potency calculation are reported in Table 3.

Table 3. Incidence of Liver Tumors in Male CF1 Mice Treated with Lindane¹

Administered Dose (ppm)	Average Dose (mg/kg-day)	Tumor Incidence	Statistical Significance ²
0	0	11/45	-----
400	48	27/29	p < 0.0001

Notes: 1. Thorpe and Walker, 1973; 2. Results of pairwise comparison using the Fisher exact test.

Toxicological Effects in Humans

Acute Toxicity

Mucous membrane irritation of the nose and throat was reported after acute exposure from the use of an overheated lindane vaporizer (ATSDR, 1998). Hematological effects have been reported in humans following acute or chronic inhalation exposure to lindane. Hypochromic anemia was reported in a 2.5-year-old male exposed to lindane in a home where a vaporizer was used. Air lindane concentrations in the basement and living room of the house were 2.4-5.5 µg/m³; it is uncertain to what concentrations the child was exposed (ATSDR, 1998). Aplastic anemia was reported in a boy exposed to lindane used in the home and a man exposed at work. The anemia was reversible and was not observed in other family members (Rugman & Cosstick, 1990). Human deaths (usually children) have been reported following ingestion of lindane tablets for use in vaporizers. Suicide with lindane has also been reported (ATSDR, 1998). Decreased appetite, vomiting, nausea, and diarrhea have been observed in humans following lindane ingestion. Widespread striatal muscle necrosis was seen in a woman who died 11 days

after ingesting 8 ounces of a 20% lindane solution. Progressive renal failure was also seen and was the ultimate cause of death (Sunder Ram Rao et al., 1988). An acute dermal poisoning of a two-month-old infant who had received a whole body application of 1% lindane lotion resulted in death. The autopsy findings were minimal but showed epicardial petechiae (Davies et al., 1983).

Subchronic Toxicity

Hematological abnormalities including leukopenia, leukocytosis, granulocytopenia, granulocytosis, eosinophilia, monocytosis, and thrombocytopenia have been reported following occupational exposures to lindane (ATSDR, 1998). Granulocytopenia, aplastic anemia, paramyeloblastic leukemia, and pancytopenia have been reported in case reports of individuals exposed to lindane and other pesticides in the home or in occupational settings. Due to poor exposure information and concomitant exposure to other pesticides, definitive causal conclusions with respect to lindane hematotoxicity in humans cannot be made.

Parent-Massin et al. (1994) evaluated lindane hematotoxicity in vitro in cultures of hematopoietic progenitors, Colony Forming Unit-Granulocyte and Macrophage (CFU-GM). Lindane was tested at concentrations of 0.2, 2, 20 and 200 µg/mL. With 0.2 µg/mL, CFU-GM showed a growth percentage of 56% and 51% after 7 and 10 days of culture respectively. Both results were highly significant reductions ($p < 0.001$) compared to the control cultures in nine replicates. All the higher lindane doses killed the cell cultures. The results indicate that human progenitors are about 1,000-fold more sensitive to lindane than similar rat cell cultures conducted in parallel.

Genetic Toxicity

Pool-Zobel et al. (1994) studied the genotoxic effects of lindane and other agents in human gastric (GM) and nasal (NM) mucosal cells isolated from biopsy samples. Viable cell suspensions of $2-8 \times 10^6$ GM and $5-10 \times 10^5$ NM cells were incubated for one hour in vitro with lindane at concentrations of 0.125, 0.25, 0.5, and 1.0 µmole/mL. DNA damage was determined microscopically after lysing cells and subjecting the preparations to electrophoresis and ethidium bromide staining of liberated DNA ("Comet Assay"). Lindane was found to be genotoxic in three out of four rat GM but not in human GM cells (0.5-1.0 µmole/mL), whereas it was genotoxic in both rat and human NM cells.

Developmental and Reproductive Toxicity

No studies were located with respect to lindane induced developmental or reproductive toxicity in humans.

Immunotoxicity

No studies were located with respect to lindane induced immunotoxicity in humans. Information on human dermal exposure to lindane in pharmaceutical products was considered inadequate to assess the risk of immunotoxicity from chronic oral exposures.

Neurotoxicity

Abnormal electroencephalographic (EEG) patterns were reported in 16 of 37 workers following occupational exposure to lindane for 0.5-2 years (Czegledi-Janko & Avar, 1970). The EEG effects were found to correlate with blood concentrations of lindane. Fonseca et al. (1993) reported weakness of limbs, dysarthria, and dysphagia in an agricultural worker exposed to lindane and several other organochlorine pesticides. There have been several reports of human intoxication involving convulsions in children following excessive dermal application of lindane (ATSDR, 1998). Solomon et al. (1995) have reported an apparent increased neurotoxicity of lindane in an HIV-seropositive patient.

Chronic Toxicity

No studies were identified with respect to chronic toxicity of lindane in humans.

Carcinogenicity

Case reports of the effects of lindane on humans have been reviewed by the International Agency for Research on Cancer (IARC, 1979, 1987). None of these reports is suitable for risk assessment. IARC (1987) summarized the only epidemiological studies which reported exposure to lindane as follows:

"Exposure to γ -hexachlorocyclohexane (lindane) was recorded in case-control studies of soft-tissue sarcoma and of lymphomas (Eriksson, 1981; Hardell, 1981), but was insufficiently frequent for any conclusion to be drawn. An increase in lung cancer mortality was observed in agricultural workers who had used hexachlorocyclohexane (unspecified) and a variety of other pesticides and herbicides (SMR, 180, 95% C.I. 140-240) (Barthel, 1981)."

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The key study for noncarcinogenic endpoints is that of Meera et al. (1992). These authors fed lindane (97% purity) in the diet to groups of six female Swiss albino mice/dose at 0.012, 0.12, and 1.2 mg/kg-day for 24 weeks. Both cell-mediated and humoral components of the immune system were evaluated at 4, 8, 12, 16, 20, and 24 weeks. These evaluations included: delayed-type hypersensitivity (DTH) to sheep red blood cells (SRBC); lymphocyte transformation to mitogens; mixed lymphocyte reaction (MLR); hemolytic plaque forming cell assay; and macrophage phagocytic activity.

DTH response to SRBC was observed by measuring the induration in foot pads of presensitized mice 24 hours after being given a challenging dose intradermally. Foot pad skin was also examined for histological changes. Lymphocytic transformation was measured by ³H-thymidine incorporation in the last 24 hours of 72-hour splenocyte cultures stimulated with Con A and lipopolysaccharide (LPS). The results were expressed as a "stimulation index" calculated by dividing radioactive counts from mitogen treated culture/control culture. The antibody response to T-dependent and T-independent antigens was measured by a hemolytic plaque forming cell

assay. Both T-dependent (SRBC) and T-independent antigen (LPS-coated SRBC) were mixed with a spleen cell suspension (5×10^5 cells) obtained from mice immunized five days earlier, incubated in a monolayer suspension, and examined microscopically for plaques. The number of plaque forming cells were expressed / 10^6 lymphocytes. For the MLR assay, stimulator splenocytes were collected from a BALB/c mouse treated with mitomycin C, and were incubated with responder splenocytes from control or lindane treated mice. The cells were pulsed with ^3H -thymidine, harvested, and measured for radioactivity. The stimulation index in this case was the mean radioactivity of the BALB/c stimulated cultures/mean radioactivity of the Swiss albino stimulated cultures. The bactericidal activity of peritoneal macrophages was studied by incubating them with *Staphylococcus aureus* at a 1:100 ratio for 30 min and measuring bacterial survival.

Neither the MLR assay nor the macrophage phagocytic activity test showed effects due to lindane exposure. However, in the other tests both cell mediated and humoral responses in lindane treated animals showed a biphasic effect characterized by an initial stimulation followed by a suppression that was both dose and time dependent. The results at 24 weeks are summarized in Table 4. The initial increase in the lymphoid follicle activity together with the packed medullary cords with plasma cells during the first 12 weeks correlated well with the enhanced immune response observed. Thereafter, marked depletion of cellular population in thymus, lymph node, and spleen was observed with evidence of cytotoxicity, which was in line with the observed suppression of immune response associated with more prolonged lindane exposures. Despite the limited numbers of animals used in this study the continuous nature of the data obtained with replicate analyses on five separate but related endpoints adds strength to the study.

Table 4. Summary of 24 Week Data from Meera et al. (1992) on Lindane Fed Female Mice

Endpoint	Control	0.012 mg/kg-day	0.12 mg/kg-day	1.2 mg/kg-day
DTH (a)	0.67 ± 0.007	0.575 ± 0.003	0.505 ± 0.003	0.51 ± 0.007
Lymphoproliferation to Con A (b)	15.25 ± 0.8	8.0 ± 0.47	3.7 ± 0.14	5.66 ± 0.15
Plaque formation /SRBC (c)	422.3 ± 4.0	322.0 ± 23.76	197.6 ± 28.2	98.2 ± 16.6
Plaque formation/ LPS-SRBC (d)	$1,896 \pm 10.19$	700 ± 16.5	622 ± 58.9	436 ± 32.2
Lymphoproliferation to LPS (e)	13.5 ± 0.19	6.15 ± 0.47	1.6 ± 0.24	4.0 ± 0.009

Note: a = values are diameters of induration in mouse foot pad in cm (mean \pm SEM), all values are $p < 0.001$ vs. Control; b = values are stimulatory indices (mean \pm SEM), $p < 0.05-0.001$; c = values are number of PFC/ 10^6 lymphocytes (mean \pm SEM), $p < 0.05-0.001$; d = values as in c but all $p < 0.001$; e = values are stimulatory indices (mean \pm SEM), $p < 0.005-0.001$.

The lowest dose tested of 0.012 mg/kg-day gave significant reductions in the five immunological responses noted in Table 4, suggesting that lower doses and/or longer exposures would also give lower values compared to controls. The average reduction compared to control values for a 24-week exposure was over 40%, whereas 10% reductions appeared statistically significant. Table 5 below gives some estimates of ED₁₀ values based on simple linear extrapolation from the low dose or on extrapolation of logarithmic regressions of individual and pooled-normalized data (table gives slope, intercept and correlation coefficient for logarithmic regressions). These values indicate an ED₁₀ based LOAEL of about 0.005 mg/kg-day or less for lindane induced immunotoxicity in mice.

Table 5. Estimates of ED₁₀ Values for Immunological Effects of Dietary Lindane in Female Swiss Albino Mice (based on data of Meera et al., 1992).

Endpoint, Exposure duration	Linear ED ₁₀ mg/kg-day	Log regres. intercept ^a	Log regres. slope ^b	Log regres. corr. coeff., r ²	Log regres. ED ₁₀ mg/kg-day
DTH 16 wk		0.594	-0.010	0.75	ND
20 wk		0.519	-0.013	0.87	ND
24 wk	0.008	0.50	-0.014	0.693	0.0006
Lymphoproliferation to Con A					
16 wk		7.66	-0.979	1.0	0.002
20 wk		6.03	-0.982	0.924	0.0025
24 wk	0.0025	4.7	-0.508	0.295	ND
Plaque formation to SRBC					
16 wk		334.9	-5.36	0.992	0.0001
20 wk		217.1	-42.29	0.961	0.008
24 wk	0.005	98.6	-49.77	0.998	0.0035
Plaque formation to LPS-SRBC					
20 wk		833.0	-8.25	0.027	ND
24 wk	0.002	464.2	-57.4	0.946	0.00012
Lymphoproliferation to LPS					
16 wk		5.03	-1.66	0.923	0.01
20 wk		4.40	-0.436	0.993	<0.0001
24 wk	0.0022	2.94	-0.463	0.219	ND
Mean of 24 wk	0.004				

Endpoint, Exposure duration	Linear ED ₁₀ mg/kg-day	Log regres. intercept ^a	Log regres. slope ^b	Log regres. corr. coeff., r ²	Log regres. ED ₁₀ mg/kg-day
values above					

Note: Logarithmic regression, $y = a + b \ln x$, where x is the lindane dose in mg/kg-day, y is the response in Table 4 or Meera et al., 1992, Tables 1 through 5. ED₁₀ values are estimates of the dose required to reduce the control values by 10% determined by linear extrapolation from the LOAEL or by logarithmic regression.

Carcinogenic Effects

Chadwick et al. (1987) investigated the metabolism of lindane in the three phenotypic classes of hybrid (YSxVY)F₁ mice used by Wolff et al. (1987). Chadwick et al. reported that after 24 months of lindane exposure there were distinct differences in lindane metabolism among the three phenotypic groups (the obese yellow, lean pseudoagouti, and lean black). The authors concluded that the bioaccumulation of lindane is greater in the obese yellow mice than in the pseudoagouti and lean black mice or Sprague-Dawley rats, and that lindane bioaccumulation is associated with increased incidence of tumors. Although we have limited data on the bioaccumulation of lindane in humans (see Tissue Residues above), humans bioaccumulate organochlorine compounds to a greater extent than do rodents (Poiger and Schlatter, 1986; Bowman et al., 1988).

The most appropriate study of sufficient quality was that reported by Thorpe and Walker (1973) for male CF1 mice. This study was used as the basis of the risk specific intake level of 0.7 µg/day and potency of 1.1 (mg/kg-day)⁻¹ for Proposition 65 (DHS, 1991). The value chosen by U.S. EPA was 1.33 rather than 1.1 (mg/kg-day)⁻¹ due to different assumptions about daily feed consumption of the laboratory mice. In addition, U.S. EPA used 28 as the original number of lindane-treated animals instead of 29 as reported in the Thorpe and Walker paper. For this risk assessment the human potency of 1.1 (mg/kg-day)⁻¹ will be used.

CALCULATION OF THE PHG

Noncarcinogenic effects

Calculation of a public health-protective concentration (C, in mg/L) for lindane in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{\text{NOAEL/LOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{L/day}}$$

where,

NOAEL/LOAEL = No-observed-adverse-effect-level or lowest-observed-adverse-effect-level

BW = Adult body weight (a default of 70 kg for male or 60 kg for female)

RSC	=	Relative source contribution (a default of 20% or 80%) to account for drinking water contribution to total lindane intake
UF	=	Uncertainty factors (10 to account for inter-species extrapolation, 10 for LOAEL to NOAEL extrapolation, and 10 for potentially sensitive human subpopulations or inter-individual differences)
L/day	=	Adult daily water consumption rate (a default of 2 L/day)

For this calculation the LOAEL from the immunotoxicity study of Meera et al. (1992) is used as the relevant toxic endpoint for chronic exposure to lindane via drinking water.

This was a 24-week study in mice that were fed 0, 0.012, 0.12 and 1.2 mg lindane kg body weight per day. Both cell mediated and humoral components of immunity showed stimulation followed by suppressions in a dose response manner.

The specific endpoints showing effects at the LOAEL of 0.012 µg/kg-day were: decreases in delayed type hypersensitive reaction to sheep red blood cells; decreases in lymphoproliferation to Con A; decreases in IgM plaque formation to sheep red blood cells; decreases in plaque formation to lipopolysaccharide-sheep red blood cells; and decreases in lymphoproliferative responses to lipopolysaccharide in mice

$$C = \frac{0.012 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{1,000 \times 2 \text{ L/day}} = 8.4 \times 10^{-5} \text{ mg/L}$$

$$C = 0.08 \text{ ppb}$$

In this calculation the uncertainty factors employed are:

- 10 for LOAEL to NOAEL. In this case it appears that lower LOAELs could have been observed due to the logarithmic nature of the dose responses for the various immunotoxicity endpoints studied. For extrapolation from a LOAEL to a NOAEL a 10-fold UF is commonly used.
- 10 for interspecies differences. For interspecies extrapolation of toxic effects seen in experimental animals to what might occur in exposed humans an UF of up to 10-fold is generally recommended. This is usually considered as consisting of two parts: one that accounts for metabolic or pharmacokinetic differences between the species; and another that addresses pharmacodynamic differences, i.e., differences between the response of human and animal tissues to the chemical exposure.
- 10 for interindividual differences. Exposed humans are known to vary considerably in their response to toxic chemical and drug exposures due to age, disease states, and genetic makeup, particularly in genetic polymorphisms for enzymes (isozymes) for detoxifying chemicals. The use of a 10-fold uncertainty factor seems prudent for lindane in view of reported body burdens.

The combined UF of 1,000 reflects the uncertainty in the identification of the NOAEL for immunotoxic effects in animals and their extrapolation to potentially sensitive human subjects. The use of 20% as the relative source contribution seems justified in view of potential food sources and human body burdens including human breast milk.

Carcinogenic Effects

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C) for lindane in drinking water (in mg/L):

$$C = \frac{BW \times R}{q_1^* \times L/\text{day}} = \text{mg/L}$$

where,

BW = Adult body weight (a default of 70 kg)

R = De minimis level for lifetime excess individual cancer risk (default of 10^{-6})

q_1^* = The q_1^* is the upper 95% confidence limit on the cancer potency slope calculated by the LMS model. The potency estimate is converted to human equivalent [in $(\text{mg}/\text{kg}\text{-day})^{-1}$] using $BW^{2/3}$ scaling.

L/day = Daily volume of water consumed by an adult (a default of 2 L/day).

For lindane, using the q_1^* derived from the Thorpe and Walker (1973) data set in CF1 mice described above, the drinking water concentration associated with negligible lifetime extra cancer risk, C is calculated as follows:

$$C = \frac{70\text{kg} \times 10^{-6}}{1.1 (\text{mg}/\text{kg}\text{-day})^{-1} \times 2 \text{ L/day}} = 3.2 \times 10^{-5} \text{ mg/L}$$

$$C = 0.032 \text{ ppb or } 32 \text{ ppt.}$$

Since the value of C based on the carcinogenic effects in mice is lower than the corresponding concentration based on immunotoxicity, **the PHG is 3.2×10^{-5} mg/L (32 ppt) based on carcinogenicity, which is assumed to be protective of any adverse health effect from lindane contamination in drinking water.**

RISK CHARACTERIZATION

The following factors are considered significant in characterizing the risk of chronic lindane exposure via drinking water.

- Like other organochlorine pesticides and related xenobiotics, the use and human exposure to lindane would appear to be declining.

- Due to its persistence in the environment and ability to bioaccumulate there still are some human exposures via fish, milk, etc., and there are human body burdens in adipose tissue and breast milk.
- The history of lindane's drug and insecticide uses and accidental/suicidal exposures have largely involved acute neurotoxicity, occasionally resulting in convulsions and death.
- Like other organochlorine insecticides lindane induces tumors in mouse liver and marginal oncogenic effects in rat liver. Lindane was classified as a Group C carcinogen by U.S. EPA. IARC found limited evidence for lindane's carcinogenicity in animals and inadequate evidence in humans. They classified the HCH isomers including lindane as Group 2B. Lindane is listed as a carcinogen under Proposition 65.
- Lindane has exhibited adverse endocrine effects in some tests and lack of effects in others. Presently the significance of these results is uncertain with respect to developmental, reproductive, or endocrine toxicity in humans.
- Lindane exhibits immunotoxicity in rodents and rabbits similar to DDT. The effects in rodents show dose and time dependence and occur at doses indicating negligible effect levels in humans well below other previously described toxic endpoints including rodent liver carcinogenicity. The mechanism(s) of these effects is unknown but may be related to a disruption of calcium homeostasis in lymphocytes chronically exposed to lindane. While this process most likely has a threshold below which no immune response impairment would be expected to occur, the demonstration of such threshold(s) is currently lacking. Also the implications for human populations exposed to lindane, possessing lindane burdens in adipose tissue, and possibly suffering immune system impairment from concurrent disease states are unknown.
- Lindane toxicity may be potentiated by concurrent exposure to other chemicals or existence of disease states e.g., hyperthyroidism, synergy with malathion.
- Lindane has been associated with various hematological effects in humans and some confirmatory evidence has been found in human blood cell progenitors in vitro. These studies indicate that humans may be up to 1,000 times more sensitive to lindane induced hematotoxicity than rodents.
- Lindane genotoxicity in microbial and animal systems is inconclusive although lindane has been observed to induce BALB/c 3T3 cell transformation and to induce DNA damage in human nasal mucosal cells and rat gastric and nasal mucosal cells in vitro.
- Lindane exhibited some developmental toxicity in animals at relatively high applied doses.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using uncertainty factors (UFs), body weights and water consumption rates (L/day) and the RSC, respectively. The RSC range is 20% to 80% (0.2 to 0.8) depending on the scientific evidence.

U.S. EPA follows a general procedure in promulgating MCLGs:

1. if Group A and B carcinogens (i.e., strong evidence of carcinogenicity) MCLGs are set to zero,
2. if Group C (i.e., limited evidence of carcinogenicity), either an RfD approach is used (as with a noncarcinogen) but an additional UF of 1 to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range,
3. if Group D (i.e., inadequate or no animal evidence) an RfD approach is used to promulgate the MCLG.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in an RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions. In developing PHGs, OEHHA has generally employed the assumption that RSCs should not be factored in for carcinogens subject to linear low-dose extrapolation. This is an area of uncertainty and scientific debate and in some cases it may be suitable to consider the use of a relative source contribution for carcinogens in drinking water and OEHHA will evaluate these on a case by case basis..

OTHER REGULATORY STANDARDS

U.S. EPA (1998) has assigned an oral reference dose (RfD) of 3.0×10^{-4} mg/kg-day for lindane based on liver and kidney toxicity in a subchronic oral study in rats and a 1,000 uncertainty factor. U.S. EPA has established a National Primary Drinking Water Regulation or Maximum Contaminant Level (MCL) of 0.0002 mg/L (0.2 ppb) for lindane. The MCL goal (MCLG) is also 0.0002 mg/L. One-day, 10-day and longer-term Health Advisories (HAs) of 1, 1, and 0.03 mg/L respectively, for a 10 kg child, have been set by U.S. EPA. For a 70 kg adult the longer-term and lifetime HAs are 0.1 and 0.0002 mg/L, respectively. U.S. EPA has classified lindane as a "C" or possible human carcinogen and has not provided a quantitative risk assessment (U.S. EPA, 1996).

The State of California has adopted a drinking water MCL of 0.0002 mg/L. Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) OEHHA has identified lindane (and other HCH isomers) as a carcinogen and established a risk specific intake level of 0.7 µg/day (DHS, 1991).

Tolerances are established for lindane in or on raw agricultural commodities: 7 ppm in or on the fat of meat from cattle, goats, horses, and sheep; 4 ppm in or on the fat of meat from hogs; 3 ppm in or on cucumbers, lettuce, melons, pumpkin, squash, summer squash, and tomatoes; and 1 ppm in or on apples and apricots (U.S. EPA, 40 CFR 180.133).

The IARC has classified lindane and other HCH isomers as Group 2B: possible human carcinogens (IARC, 1987).

The World Health Organization (WHO) has set a drinking water guideline of 0.003 mg/L for lindane (ATSDR, 1998).

The Food and Drug Administration (FDA) has set the permissible level of lindane in bottled water at 0.004 mg/L (21 CFR 103.35).

The Food and Agriculture Organization and WHO (FAO/WHO) has established an Allowable Daily Intake (ADI) of 0.0-0.1 mg/kg for lindane/HCH (WHO, 1978).

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