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Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

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HEALTH EFFECTS ASSESSMENT FOR LINDANE

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with lindane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Hexachlorocyclohexane. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-054. NTIS PB81-117657.

U.S. EPA. 1985. Drinking Water Criteria Document for Lindane. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Lindane, given orally, produced an increase in liver tumors in mice in one study. Other animal bioassays (rats and mice) have been negative or equivocal. Data concerning the carcinogenicity of lindane to humans are not available. The U.S. EPA (1980a) used the mouse liver tumor data to calculate a carcinogenic potency factor for lindane. The q_1^* is 1.326 $(mg/kg/day)^{-1}$ No data are available to assess the potential carcinogenicity of lindane following inhalation exposure.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
LD_{50}	Median lethal dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of lindane, also known as γ-hexachlorocyclohexane (CAS No. 58-89-9), are as follows:

Chemical class:	pesticide
Molecular weight:	291 (Callahan et al., 1979)
Vapor pressure:	1.6×10^{-4} mm Hg (Mabey et al., 1981)
Water solubility:	7.8 mg/ℓ at 25°C (Horvath, 1982)
Log octanol/water partition coefficient:	3.85 (Veith et al., 1979)
Log BCF:	2.26-2.67 (Veith et al., 1979)
Half-life in	
Water:	>5-10 days (estimated)
Soil:	56 days in clay loam (Callahan et al., 1979) 378 days in sandy loam (Callahan et al., 1979)

The estimation of the half-life for lindane in aquatic media is based on the anaerobic microbial degradation half-life of this chemical in aquatic sediments as reported in Callahan et al. (1979).

No reported value for the half-life of lindane in the atmosphere could be located in the literature searched. Based on the reactions for chlorinated aliphatic hydrocarbons, lindane may undergo reaction with hydroxyl radicals in the atmosphere (Graedel, 1978). Unfortunately, the rate constant value for this reaction is not known. Based on the saturation vapor pressure data and the predictions of Cupitt (1980), lindane may not be sorbed onto particulate matter in the air. In air, the demonstrated removal mechanism for lindane appears to be rainout (IARC, 1979).

The average K_{oc} for lindane was determined to be 735 (McCall et al., 1980). This suggests that lindane may have a low soil mobility; however, lindane may leach from soil to groundwater, particularly from soils with low organic matter content (McCall et al., 1980). Page (1981) detected lindane in ~21% of groundwater samples collected from New Jersey during 1977-1979.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

Lindane (γ-HCH) is apparently rapidly absorbed from the gastro-intestinal tract; the rapidity may be enhanced by incorporation in lipid vehicles. The fact that lindane is unusually water soluble for an organo-chlorine insecticide may contribute to the rapidity of its absorption (Herbst and Bodenstein, 1972).

Chadwick et al. (1971, 1978) treated Fischer 344 rats with daily oral doses (number unspecified) of 2 mg [^{14}C]-labeled lindane. Only 2-5% of the total dose was recovered in the feces, indicating that ~95% of the dose was absorbed following oral administration.

2.2. INHALATION

Pertinent data regarding absorption of lindane following inhalation exposure could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Studies of toxicity due to lindane are complicated by the fact that five isomers of hexachlorocyclohexane, each with its own toxic effects on mammalian species, are often involved in mixtures of hexachlorocyclohexane tested for toxicity in laboratory animals. According to Deichmann (1981), commercially available hexachlorocyclohexane is a mixture of predominantly four of its five isomers. As an insecticide the γ-isomer, lindane, is the most effective.

Lindane is the most acutely toxic isomer of hexachlorocyclohexane and causes (as does the α-isomer) stimulation of the CNS. The ß- and δ-isomers generally cause CNS depression. Because lindane is more rapidly eliminated than other hexachlorocyclohexane isomers, it is the least chronically toxic isomer.

It has been demonstrated that young animals are more sensitive to the toxic effects of lindane than are adults of the same species (Radaleff and Bushland, 1960). The increased sensitivity among the young may be related to the inability of livers of young animals to produce, as rapidly as livers of adults, the enzymes that detoxify lindane (Fouts and Adamson, 1959). Diseased and distressed animals also show a similar sensitivity (Chen, 1968).

Although cases of acute toxicity associated with ingestion of lindane by humans have been reported, data regarding subchronic oral exposure of humans to lindane have not been located in the available literature.

An abstract of a study of the toxicity of technical grade hexachlorocyclohexane in rats was located (Barros and Saliba, 1978). Groups of 10, 60-day-old male Wistar rats were fed diets containing 0, 0.9 or 900 ppm

technical hexachlorocyclohexane for 90 days. The high-dose group experienced growth rate depression, an increase in relative liver weight and mild hyaline degeneration of the kidneys. Both treated groups exhibited degenerative liver changes including fatty accumulation.

In a range-finding experiment prior to a major carcinogenicity bioassay (NCI, 1977), groups of five male and five female Osborne-Mendel rats were fed diets containing 0, 160, 320, 640, 1280 or 2500 ppm lindane for 6 weeks, followed by a 2-week observation period. Dosage levels ≥1280 ppm were associated with increased mortality when compared with controls. A reduction in weight gain during the first 3 weeks was recorded for both male and female rats exposed to 320 or 640 ppm lindane. After cessation of exposure, weight gains of treated males approached those of controls.

Concurrently, groups of five male and five female $B6C3F_1$ mice were fed diets containing 0, 40, 80, 160, 320, 640 or 1280 ppm lindane for 6 weeks, followed by an observation period of 2 weeks. No effects on weight gain were recorded and no mortality occurred in groups of mice fed diets containing <160 ppm lindane. Mortality of one male and two females occurred in the 320 ppm groups and all mice exposed to the 640 ppm had succumbed by 5 weeks of treatment. Although these subchronic studies provide some information on mortality, the small group size and limited evaluation of toxicity criteria render these studies inadequate for use in risk assessment.

More recently, the histochemical and biochemical changes in rats fed diets containing hexachlorocyclohexane (grade and purity not specified) have been investigated (Shivanandappa and Krishnakumari, 1981). Groups of 28-day-old weanling male rats (number and strain not specified) were fed diets containing 0, 100, 250, 750, 1500 or 3000 ppm lindane for 90 days. Dosage levels ≥250 ppm resulted in progressive accumulation of lipids in the

periportal hepatocytes and adrenal cortex. At dosages of 750 and 1500 ppm, succinic dehydrogenase activity decreased and alkaline phosphatase activity increased in the bile canaliculi and kupfer cells of the liver, as determined histochemically. At "higher dietary levels," serum glutamic oxaloacetic transaminase and ß-glucuronidase were elevated, and lactate dehydrogenase and alkaline phosphatase activities were reduced. Hepatic microsomal protein was markedly elevated at all dietary levels. The authors concluded that the dietary level of 100 ppm hexachlorocyclohexane resulted in no significant histopathological, histochemical or biochemical changes when compared with controls. Therefore, in this study 100 ppm benzene hexachloride is designated a NOAEL.

Subsequently, Shivanandappa et al. (1982) fed diets containing 0, 100, 250, 750 or 1500 ppm hexachlorocyclohexane to groups of ten, 28-day-old male CFT-Wistar rats to investigate inhibition of adrenal steroidogenic activity associated with hexachlorocyclohexane. The hexachlorocyclohexane used in this experiment was reportedly 99% pure and consisted of 72% α-, 5% ß-, 13.5% γ-, 8% δ- and a trace of the ε-isomers. Following the 90-day treatment period, rats were killed and adrenal glands were collected and subjected to histological and histochemical evaluation. No significant changes associated with treatment were noted in adrenal glands from rats fed diets containing 100 or 250 ppm hexachlorocyclohexane. At dietary levels of 750 or 1500 ppm of hexachlorocyclohexane, marked hypertrophy of the adrenal glands was noted with cortical cells enlarged and showing vacuolization. Histochemical examination revealed accumulation of cholesterol-positive lipids and marked reduction in the activities of several steroidogenic enzymes.

Oesch et al. (1982) investigated the effects of lindane on liver weights and the activities of various hepatic enzymes in CF_1 and $B6C3F_1$ mice and Osborne-Mendel rats. Groups of three animals of each sex were allocated to control, low, medium or high dose diets. Diets fed to CF_1 mice contained 0 (control), 56 (low), 111 (medium) or 360 (high) ppm lindane. Diets fed to $B6C3F_1$ mice contained 0 (control), 56 (low), 170 (medium) or 270 (high) ppm lindane. Osborne-Mendel rats received diets containing 0 (control), 56 (low), 111 (medium) or 360 (high) ppm lindane. The lindane used in these studies was reportedly 99% pure. At the end of the 3-month treatment period, the animals were killed, livers were weighed and the activity of several hepatic enzymes was determined.

Liver weights were significantly increased in high dose group CF_1 mice ($p<0.01$) and Osborne-Mendel rats ($p<0.01$) when compared to controls. No high-dose group $B6C3F_1$ mice survived to 90 days. Female Osborne-Mendel rats in the middle dose group experienced a significant ($p<0.05$) increase in body weight compared with controls. Significant induction of several hepatic enzymes was observed in both strains of mice and Osborne-Mendel rats. The most marked examples were the induction of glutathione-S-transferase in all treated groups of female CF_1 mice ($p<0.01$) and the induction of epoxide hydrolase in all treated groups of Osborne-Mendel rats. Since minimal enzyme induction without hepatomegaly occurred at the lowest dose tested in both species of animal, this dietary concentration (56 ppm) is a NOAEL in this study. Assuming that rats and mice consume food equivalent to 5 and 13% of their body weight, respectively, daily intakes of 2.8 and 7.3 mg/kg/day, respectively, can be estimated.

3.1.2. Inhalation. Repeated inhalation of lindane by humans is most likely to result from occupational exposure and will be discussed in Section 3.2.2.

Rats exposed to 0.78 mg lindane/m³ for 7 hours/day, 5 days/week for 180 days showed "some hepatocellular enlargement." No other clinical symptoms of toxicity were noted (Heyroth, 1952).

3.2. CHRONIC

3.2.1. Oral. Reports of toxicity in humans associated with chronic oral exposure to lindane could not be located in the available literature.

According to Deichmann (1981), Lehman (1954) indicated that the highest tolerated no-effect dose of lindane in rats consume for $\geq$2 years is ~50 ppm in the diet, or 5 mg/kg bw, assuming that rats eat food equivalent to 10% of their body weight per day. Fitzhugh et al. (1950) suggested that rats can tolerate "long term" feeding of diets containing 50 ppm lindane, but experienced "changes of questionable significance" at that level. No changes were observed in rats exposed to diets containing 0.15, 10 or 30 ppm lindane (ACGIH, 1980).

Administration of 10 ppm lindane to the diets of rats for 1-2 years resulted in noxious effects to them and their offspring. Body weights were decreased after treatment for 5 months; increased urinary ascorbic acid and changes (unspecified) in blood levels of ascorbic acid were noted. Ascorbic acid content in both liver and adrenals was reduced (Petrescu et al., 1974).

Administration of 100 ppm lindane in the diet to male and female beagle dogs resulted in slightly enlarged livers without histopathological change (Rivett et al., 1978). In this study, dogs were fed diets containing 25, 50 or 100 ppm lindane for 104 weeks. Rivett et al. (1978) reported that the 50 ppm diet was a no-effect level.

An NCI (1977) carcinogenicity bioassay of lindane was performed using Osborne-Mendel rats and $B6C3F_1$ mice. Groups of 50 male and 50 female rats were allocated to high- and low-dose groups. Matched controls consisted of

10 rats of each sex. The dosage schedule for rats in this experiment is detailed in Table 3-1. Similar numbers of mice were allocated to matched control, low and high dose groups as indicated in Table 3-2.

Groups of treated rats exhibited no changes in body weights when compared with those of matched controls. Individual rats, however, did exhibit decreases in body weight occasionally. Applying the Tarone test for positive dose-related trends in mortality to the Kaplan and Meier probability of survival curves indicated no significant effect of treatment on survival. Clinical signs in all groups of treated rats included rough and discolored hair coats, pale mucous membranes and vaginal bleeding, particularly during the second year of the study.

Groups of treated mice exhibited no statistically significant changes in body weight when compared with that of matched controls. Low-dose female mice, however, consistently had body weights less than that of matched control or high-dose group female mice. Clinical signs in all groups of treated mice included rough hair coats, alopecia and abdominal distention (particularly in males) during the second year. Female mice appeared to be more excitable when handled and increased fighting was observed among male mice.

3.2.2. **Inhalation.** Toxicity to lindane by inhalation in the workplace has been reported by Sasinovich et al. (1974), who observed pathological changes in the livers of 55% of 59 female and 29 male workers exposed to hexachlorocyclohexane (composition not characterized) for 11-23 years. Chronic pancreatitis was observed in 5% of the workers; "biochemical abnormalities" were noted in 60% of these workers. No exposure data were reported in this study.

TABLE 3-1

Design of Lindane Chronic Feeding Studies in Rats[a]

Sex and Treatment Group	Initial No. of Animals[b]	Lindane in Diet[c] (ppm)	Time on Study		TWA
			Treated[d] (weeks)	Untreated[e] (weeks)	Average Dose[f] (ppm)
Male					
Matched control	10	0	NA	109	NA
Low-dose	50	320	38	NA	236
		160	42	NA	NA
		0	NA	30	NA
High-dose	50	640	38	NA	472
		320	42	NA	NA
		0	NA	30	NA
Female					
Matched control	10	0	NA	108-109	NA
Low-dose	50	320	2	NA	135
		160	49	NA	NA
		80	29	NA	NA
		0	NA	29-30	NA
High-dose	50	640	2	NA	270
		320	49	NA	NA
		160	29	NA	NA
		0	NA	30	NA

[a]Source: NCI, 1977

[b]All animals were 35 days of age when placed on study.

[c]Doses of lindane were lowered during the study, as indicated, due to deaths among the treated animals.

[d]All animals were started on study on the same day.

[e]When diets containing lindane were discontinued, treated rats and their matched controls were fed diets without corn oil for 15 weeks, then control diets (2% corn oil added) for an additional 15 weeks.

[f]$TWA = \frac{\Sigma(\text{dose in ppm x no. of weeks at that dose})}{\Sigma(\text{no. of weeks receiving each dose})}$

NA = Not applicable

TABLE 3-2

Design of Lindane Chronic Feeding Studies in Mice[a]

Sex and Treatment Group	Initial No. of Animals[b]	Lindane in Diet (ppm)	Time on Study	
			Treated[c] (weeks)	Untreated[d] (weeks)
Male				
Matched control	10	0	NA	90
Low-dose	50	80	80	NA
		0	NA	10
High-dose	50	160	80	NA
		0	NA	10
Female				
Matched control	10	0	NA	90
Low-dose	50	80	80	NA
		0	NA	10
High-dose	50	160	80	NA
		0	NA	10-11

[a]Source: NCI, 1977

[b]All animals were 35 days of age when placed on study.

[c]All animals were started on study on the same day.

[d]When diets containing lindane were discontinued, treated mice and their matched controls were fed control diets (2% corn oil added).

NA = Not applicable

The ACGIH (1980) reported that minor symptoms and signs (unspecified) of neurological disturbances were noted in 14/37 workers exposed to lindane over a 2-year period (Czegledi-Janko and Avar, 1970). Of these workers, three had "serious EEG disturbances." Blood levels of lindane ranged from 0.002-0.340 ppm; levels $\geq$0.02 ppm correlated with more severe evidence of neurological dysfunction. No exposure data from this study were reported.

Treon et al. (1951) reported "minimal pathology in several species of laboratory animals exposed 7 hours/day, 5 days/week for ~1 year at an average of 0.7 mg/m^3 lindane." Rats exposed continuously for 655 days to 0.19 mg lindane/m^3 exhibited no pathological lesions (Spear, 1952). No other toxicity parameters were reported.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. The teratogenic and fetotoxic effects of lindane were studied in four groups of rats (number and strain not reported) (Mametkuliev, 1978). Group 1 received 25 mg lindane/kg bw/day on days 1-20 of gestation. Group 2 received 25 mg lindane/kg bw/day on days 7-15 of gestation. Group 3 received 25 mg lindane/kg bw/day on days 1-7 of gestation. Group 4 received 12 mg lindane/kg bw/day on days 1-20 of gestation. A group of untreated controls was maintained; no vehicle control group was mentioned. Lindane was dissolved in corn oil (strength of solution not reported) and administered by gavage. All dams were killed and examined on day 20 of gestation. Terata were not reported in the offspring from any treated dams. Postimplantation fetal death was reported to be 13.2, 25.6, 11.2, 7.6 and 9.5% in the control group and groups 1-4, respectively. Statistical significance of the apparently high incidence of postimplantation fetal mortality in Group 1 rats was not reported. Palmer et al. (1978) obtained similar results with white rabbits.

A 4-generation study of the effects of lindane on reproductive performance of rats (strain not specified) was performed by Petrescu et al. (1974). According to the U.S. EPA (1980a), these authors reported that 5, 10 or 15 mg lindane/kg bw/day administered in the diet resulted in an increase in the average length of gestation from 21-22 days in control rats and 21-24 days in treated animals. A dose of 15 mg/kg/day was associated with a decrease in the number of births compared with the number of animals in the parental generation. Delayed sexual maturation and longer estrous cycle length were noted in F_2 and F_3 females from all treated dams. An increase in the number of stillbirths was also reported. Additionally, F_1 and F_2 offspring from all exposed dams exhibited a high incidence of spastic paraplegia.

Disturbed estrous cycles, lowered embryonic viability, reduced fertility and delayed sexual maturation were reported in female rats treated with 0.5 mg lindane/kg bw/day for 4 months. Rats treated with 0.05 mg/kg bw/day showed none of these effects (Shtenberg and Mametkuliev, 1976).

In beagle dogs, Earl et al. (1973) reported that oral doses of 7.5 and 15 mg lindane/kg bw/day from day 5 of gestation to delivery resulted in an increase in stillbirths.

Some parameters of reproductive performance in male rats exposed to lindane were investigated by Shivanandappa and Krishnakumari (1983). Groups of 10 male 28-day-old CFT Wistar rats were fed diets containing 0, 100, 750 or 1500 ppm technical hexachlorocyclohexane for 90 days. The technical hexachlorocyclohexane reportedly contained 72% α-, 5% β-, 13.6% γ-, 8% δ- and a trace of the ε-isomers. The dietary concentration of 1500 ppm was associated with decreased food consumption ($p<0.01$) and decreased growth rate ($p<0.05$) beginning at week 7. Also at this dietary level, a marked

decrease in testicular weight ($p<0.001$), diameter of the seminiferous tubule ($p<0.001$) and diameter of the nuclei of the Leydig cells ($p<0.001$) was noted. Total testicular lipid ($p<0.05$) and cholesterol ($p<0.02$) levels were increased. A marked decrease in the activity of several enzymes related to steroidogenesis was also seen (no statistical analysis). These investigators concluded that exposure to 1500 ppm lindane in the diet markedly reduced normal testicular maturation and function.

3.3.2. Inhalation. Pertinent data regarding teratogenicity, fetotoxicity or impaired reproductive performance associated with inhalation exposure to lindane in humans or animals could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Litterst and Miller (1975) determined that the daily treatment of beagle dogs with phenobarbital for 60 days prior to the intravenous administration of lindane resulted in reduced lindane concentrations in the brain compared with controls. The intravenous administration of 7.5 mg lindane/minute resulted in convulsions in nonphenobarbital-pretreated dogs within 27 minutes; infusion of lindane at this rate failed to trigger convulsions in phenobarbital-pretreated dogs after 60-70 mintues. These investigators concluded that phenobarbital may be protective against the ability of lindane to cause convulsions.

Pretreatment of Wistar rats with lindane was associated with a reduction of the teratogenic effects of a carbamate insecticide and of sodium acetylsalicylate (Shtenberg and Torchinskii, 1977).

The chlorination of water containing hexachlorocyclohexane (not further characterized) has been shown to decrease the subsequent LD_{50}s in mice and rats, presumably by conversion of these compounds to more toxic products (Shtannikov et al., 1977).

Lindane has been shown to increase the sensitivity of mice to the convulsion-producing effects of pentylenetetrazol (Hulth et al., 1976).

Ulmann (1972) reported that the toxic effects of lindane have been antagonized by various tranquilizers.

4. CARCINOGENICITY

4.1. HUMAN DATA

No epidemiological studies of cancer in humans associated with exposure to lindane have been reported. Several case histories link the development of aplastic anemia with exposure to hexachlorocyclohexane or lindane alone (Hans, 1976; Loge, 1965; West, 1967; Woodliff et al., 1966) or in combination with other compounds, particularly DDT (Hans, 1976; Woodliff et al., 1966). The concurrent development of acute paramyeloblastic leukemia in two cousins simultaneously exposed to lindane was reported by Jedlicka et al. (1958). Barthel (1976) reported an increased incidence of lung cancer in workers who had applied various pesticides, including lindane. These reports do not constitute sufficient weight of evidence to conclude that lindane is a human carcinogen.

4.2. BIOASSAYS

Several investigators have examined the potential carcinogenicity of lindane in laboratory animals. These studies are summarized in Table 4-1.

In male and female Wistar rats, Fitzhugh et al. (1950) observed no tumors following lifetime exposures of doses up to 800 ppm lindane in dry diet or 1600 ppm lindane in oil solution added to the diet. Dietary concentrations of 500 ppm lindane for 24 weeks failed to result in liver tumors in male dd mice (Nagasaki et al., 1972a; Ito et al., 1973a,b), but 660 ppm technical hexachlorocyclohexane for 24 weeks resulted in hepatomas in 20/20 mice (Nagasaki et al., 1971, 1972b). Hanada et al. (1973) produced hepatomas in both male and female dd mice fed diets containing 600 ppm lindane for 32 weeks. In male Wistar rats exposed to a dietary concentration of 500 ppm lindane, no hepatocellular carcinomas were observed after 24 or 48 weeks (Ito et al., 1975).

TABLE 4-1

Investigations of the Carcinogenicity of Lindane in Laboratory Animals by the Oral Route

Species/ Strain	Sex	Dose of Exposure (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)	Reference
Rat/ Wistar	M,F	1600	lifespan	lifespan	>98%	10% oil in diet	all organs	NA	0/10	Fitzhugh et al., 1950
		800	lifespan	lifespan	>98%	10% oil in diet	all organs	NA	0/10	
		400	lifespan	lifespan	>98%	10% oil in diet	all organs	NA	0/10	
		100	lifespan	lifespan	>98%	10% oil in diet	all organs	NA	0/10	
		50	lifespan	lifespan	>98%	10% oil in diet	all organs	NA	0/10	
		10	lifespan	lifespan	>98%	10% oil in diet	all organs	NA	0/10	
		5	lifespan	lifespan	>98%	10% oil in diet	all organs	NA	0/10	
		800	lifespan	lifespan	>98%	dry diet	all organs	NA	0/10	
		100	lifespan	lifespan	>98%	dry diet	all organs	NA	0/10	
		10	lifespan	lifespan	>98%	dry diet	all organs	NA	0/10	
		0	lifespan	lifespan	NA	dry diet	all organs	NA	0/10	
Mice/dd	M	660	24	24	technical	diet	liver	hepatoma	20/20	Nagasaki et al., 1971,1972b
		66.0	24	24	technical	diet	liver	hepatoma	0/20	
		6.6	24	24	technical	diet	liver	hepatoma	0/20	
		0	NA	24	NA	diet	liver	hepatoma	0/20	
Mice/dd	M	500	24	24	NR	diet	liver	hepatoma	0/20	Nagasaki et al., 1972a
		250	24	24	NR	diet	liver	hepatoma	0/20	
		100	24	24	NR	diet	liver	hepatoma	0/20	
		0	NA	24	NA	diet	liver	hepatoma	0/20	
Mice/dd	M	500	24	24	>99%	diet	liver	hepatocellular carcinoma	0/20	Ito et al., 1973a,b
		250	24	24	>99%	diet	liver	hepatocellular carcinoma	0/20	
		100	24	24	>99%	diet	liver	hepatocellular carcinoma	0/20	
		0	NA	24	NA	diet	liver	hepatocellular	0/20	
Mice/dd	M	600	32	37-38	NR	diet	liver	hepatoma	3/4	Hanada et al., 1973
		300	32	37-38	NR	diet	liver	hepatoma	0/9	
		100	32	37-38	NR	diet	liver	hepatoma	0/10	
		0	NA	37-38	NA	diet	liver	hepatoma	0/14	
Mice/dd	F	600	32	37-38	NR	diet	liver	hepatoma	1/3	Hanada et al., 1973
		300	32	37-38	NR	diet	liver	hepatoma	0/7	
		100	32	37-38	NR	diet	liver	hepatoma	0/8	
		0	NA	37-38	NA	diet	liver	hepatoma	0/15	

TABLE 4-1 (cont.)

Species/ Strain	Sex	Dose of Exposure (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)	Reference
Rat/ Wistar	M	500	48	48	<99%	diet	liver	hepatocellular carcinoma	0/8	Ito et al., 1975
		500	24	24	<99%	diet	liver	hepatocellular carcinoma	0/6	
		0	NA	72	NA	diet	liver	hepatocellular carcinoma	0/8	
Mice/ Chbi NMRI	M,F	50	80	80	NR	diet	liver	liver cell adenoma	2/100	Weisse and Herbst, 1977
							all other organs	NA	22/100	
		25	80	80	NR	diet	liver	liver cell adenoma	0/100	
							all other organs	NA	13/100	
		12.5	80	80	NR	diet	liver	liver cell adenoma	2/100	
								hemangioendo-thelioma	1/100	
							all other organs	NA	22/100	
		0	NA	80	NA	diet	liver	liver cell adenoma	5/200	
							all other organs	NA	41/200	
Mice/ CF_1	M	400	110	110	99.5%	diet	liver	total tumors[a]	27/28(96%)[b]	Thorpe and Walker, 1973
	F	400	110	110	99.5%	diet	liver	total tumors[a]	20/21(95%)[b]	
	M	0	NA	110	NA	diet	liver	total tumors[a]	11/45(24%)[b]	
	F	0	NA	110	NA	diet	liver	total tumors[a]	10/44(23%)[b]	
Rats/ Osborne-Mendel	M	472[c]	80	110	100%	diet	all organs	NA	NS	NCI, 1977
	M	236[c]	80	110	100%	diet	all organs	NA	NS	
	M	0 (matched controls)	NA	109	NA	diet	all organs	NA	NS	
	F	270[d]	80	110	100%	diet	all organs	NA	NS	
	F	135[d]	80	109-110	100%	diet	all organs	NA	NS	
	F	0 (matched controls)	NA	108-109	NA	diet	all organs	NA	NS	

TABLE 4-1 (cont.)

Species/ Strain	Sex	Dose of Exposure (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)	Reference
Mice/ $B6C3F_1$	M	160	80	90	100%	diet	liver	hepatocellular carcinomas	9/46 (NS)	
	M	80	80	90	100%	diet	liver	hepatocellular carcinomas	19/49 (p=0.001)	
	M	0 (matched controls)	NA	90	NA	diet	liver	hepatocellular carcinomas	2/10 (NS)	
	F	160	80	90-91	100%	diet	all organs	NA	NS	
	F	80	80	90	100%	diet	all organs	NA	NS	
	F	0 (matched controls)	NA	90	NA	diet	all organs	NA	NS	

[a]Includes neoplasia and hyperplastic nodules

[b]Based on numbers of animals alive subsequent to first tumor

[c]TWA dose reflecting 38 weeks of treatment at 640 or 320 ppm and 42 weeks of treatment at 320 or 160 ppm for the high dose-group or the low-dose group, respectively (dose lowered due to death among the treated rats).

[d]TWA dose reflecting 2 weeks of treatment at 640 or 320 ppm, 49 weeks of treatment at 320 or 160 ppm, and 29 weeks of treatment at 160 or 80 ppm for the high-dose group or the low-dose group, respectively (dose lowered due to death among the treated animals).

NA = Not applicable

NS = Not significant

NR = Not reported

Weisse and Herbst (1977) fed diets containing 12.5, 25 or 50 ppm lindane to groups of 100 male and female Chbi NMRI mice. Groups of 200 males and females were maintained as controls. The incidence of liver cell adenomas, after 80 weeks of treatment, was 5/200, 2/100, 0/100 and 2/100 in control, low-, mid- and high-dose groups, respectively. Tumor incidence was not reported by sex. The incidence of tumors in other organ sites was 41/200, 22/100, 13/100 and 22/100 in control, low-, mid- and high-dose groups, respectively.

The NCI (1977) published the results of an extensive bioassay in Osborne-Mendel rats and $B6C3F_1$ mice. The protocol of this study was described in Section 3.2.1. After 80 weeks of exposure and an additional 29-30 weeks of observation, no significantly exposure-related increase in the incidence of tumors was found in rats of either sex. Only in low-dose male $B6C3F_1$ mice was a significantly increased incidence of tumors (hepatocellular carcinomas) found ($p=0.001$, Fisher exact test). The incidence in the high-dose group was not significant and the Cochran-Armitage test for dose-related trend was not significant. Combining the incidence of neoplastic nodules with hepatocellular carcinomas did not increase the significance of the findings. No hepatic hyperplasia was observed in mice of either sex. These factors, coupled with a relatively high (23%) incidence of hepatocellular carcinoma combined with neoplastic nodules in control mice, led the NCI (1977) to conclude that "under the conditions of this bioassay lindane was not carcinogenic for Osborne-Mendel rats or $B6C3F_1$ mice."

Thorpe and Walker (1973) demonstrated a substantial increase in the incidence of malignant liver tumors in both male and female CF_1 mice fed

diets containing 400 ppm lindane for 110 weeks. Malignancies were observed in 16/29 treated males and 10/29 treated females compared to incidences of 2/45 and 0/44 in control male and female mice, respectively.

4.3. OTHER RELEVANT DATA

Mutagenicity of lindane has been studied by several investigators, predominantly with negative results. Buselmaier et al. (1972) reported that lindane had no effect on the reversion of Salmonella typhimurium G46 or Serratia marcescens a21 in a host-mediated assay. Schubert (1969) found no increased incidence of respiratory-deficient mutants in yeast (species unspecified) associated with lindane. Negative results in dominant lethal assays were reported in mice (U.S. EPA, 1973; NAS, 1977). No sex-linked recessive mutants were found in Drosophila melanogaster exposed to lindane (Benes and Sram, 1969). No unscheduled DNA synthesis was reported by Ahmed et al. (1977) in SV-40 transformed human fibroblasts (VA-4) exposed to lindane.

Chromosomal breaks and gaps in Chinese hamster fibroblasts were related to lindane exposure (Ishidate and Odashima, 1977), and alterations in mitotic activity were reported by Tsoneva-Maneva et al. (1971). A positive dominant lethal response in D. melanogaster related to lindane was observed only in the third and subsequent generations from adults fed food containing 20 ppm lindane (Sinha and Sinha, 1983). Technical grade hexachlorocyclohexane was also associated with a dominant lethal effect in Swiss mice when fed continuously to males at 500 ppm diet for 4, 6 or 8 months (Lakkad et al., 1982).

4.4. WEIGHT OF EVIDENCE

Although lindane has been associated with aplastic anemia, possibly a preneoplastic lesion (Hans, 1976; Loge, 1965; West, 1967; Woodliff et al.,

1966) and paramyeloblastic leukemia (Jedlicka et al., 1958), insufficient evidence exists to classify lindane as a human carcinogen. The carcinogenicity of lindane in the mouse has been clearly demonstrated by Thorpe and Walker (1973), who reported liver cancers in 55 and 34% of male and female mice, respectively, fed diets containing 400 ppm lindane for 110 weeks. The incidence in control males and females was 4 and 0%, respectively. Applying the criteria for weight of evidence proposed by the Carcinogen Assessment Group of the U.S. EPA, lindane is most appropriately classified a Group B2 - Probable Human Carcinogen (Federal Register, 1984).

5. REGULATORY STANDARDS AND CRITERIA

Based primarily on the work of Treon et al. (1951), who found minimal pathology in several species (unspecified) exposed to 0.7 mg lindane/m^3 for 7 hours/day, 5 days/week for ~1 year, and the work of Spear (1952), who reported "no pathology" in rats continuously exposed to 0.19 mg lindane/m^3 for 655 days, the ACGIH (1980) has recommended a TWA-TLV of 0.5 mg/m^3 and a STEL of 1.5 mg/m^3.

The FAO/WHO interim ADI is 1 μg/kg/day, which was revised downward from an original recommendation of 12.5 mg/kg/day made in 1972 (NAS, 1977). The U.S. EPA (1980a) reported a tolerance for lindane in animal fats of 7 ppm, and in milk of 0.3 ppm. The tolerance for most fruits and vegetables is 1 ppm. Finished drinking water should contain no more than 0.004 ppm (U.S. EPA, 1980a).

Based on the carcinogenic potency derived from the carcinogenicity assay data of Thorpe and Walker (1973), the U.S. EPA (1980a) has determined that an ambient water quality criteria of 186 and 625 ng/ℓ should be protective for the consumption of 2 ℓ water and 6.5 g fish and shellfish/day, or the consumption of fish and shellfish alone, respectively.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Lindane is a chemical that is a known carcinogen in mice, and for which data are sufficient for computing a q_1*. It is, therefore, inappropriate to calculate an oral or inhalation AIS for lindane.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Lindane is a chemical that is a known carcinogen in mice, and for which data are sufficient for computing a q_1*. It is, therefore, inappropriate to calculate an oral or inhalation AIC for lindane.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. The U.S. EPA (1980a) derived a q_1* of 1.326 $(mg/kg/day)^{-1}$ for human exposure to lindane based on the incidence of liver tumors that occurred in male CF_1 mice in the Thorpe and Walker (1973) study. This risk estimate reflects the lack of additional data between 1980 and the present. A q_1* of 1.326 $(mg/kg/day)^{-1}$ was also presented in U.S. EPA (1985). The complete data base from which this computation is made is presented in Appendix B.

6.3.2. Inhalation. Since no reports of cancers in either humans or animals exposed to lindane by inhalation have been found in the available literature, no q_1* for inhalation of lindane can be calculated.

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APPENDIX A

Summary Table for Lindane

Experimental Species	Dose/Exposure	Effect	q_1*	Reference
Inhalation				
AIS				ND
AIC				ND
Carcinogenic potency				ND
Oral				
AIS				ND
AIC				ND
Carcinogenic potency	mice	liver malignancies	1.326 $(mg/kg/day)^{-1}$	Thorpe and Walker, 1973

ND = Not derived

APPENDIX B

Cancer Data Sheet for Derivation of q_1*

Compound: Lindane

Reference: Thorpe and Walker (1973); U.S. EPA (1980a)

Species, Strain, Sex: mice, CF, male

Body weight: 0.03 kg (assumed)

Length of exposure (le) = 770 days

Length of experiment (Le) = 770 days

Lifespan of animal (L) = 770 days

Tumor site and type: liver, "malignant"

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm)	Transformed Dose (mg/kg/day)	Incidence: No. Responding/No. Tested or Examined
0	0	11/45
400	52	27/28

Unadjusted q_1* from study = 1.0×10^{-1} $(mg/kg/day)^{-1}$

Human q_1* = 1.326 $(mg/kg/day)^{-1}$