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Environmental Health Criteria 34

CHLORDANE

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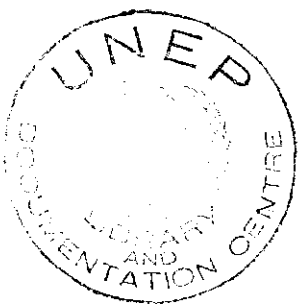

World Health Organization
Geneva, 1984

The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 988400 - 985850).

ENVIRONMENTAL HEALTH CRITERIA FOR CHLORDANE

Following the recommendations of the United Nations Conference on the Human Environment held in Stockholm in 1972, and in response to a number of World Health Resolutions (WHA23.60, WHA24.47, WHA25.58, WHA26.68), and the recommendation of the Governing Council of the United Nations Environment Programme, (UNEP/GC/10, 3 July 1973), a programme on the integrated assessment of the health effects of environmental pollution was initiated in 1973. The programme, known as the WHO Environmental Health Criteria Programme, has been implemented with the support of the Environment Fund of the United Nations Environment Programme. In 1980, the Environmental Health Criteria Programme was incorporated into the International Programme on Chemical Safety (IPCS). The result of the Environmental Health Criteria Programme is a series of criteria documents.

A WHO Task Group on Environmental Health Criteria for Organochlorine Pesticides other than DDT met in Geneva from 28 November - 2 December, 1984. Dr K.W. Jager opened the meeting on behalf of the Director-General. The Task Group reviewed and revised the draft criteria document on chlordane and made an evaluation of the health risks of exposure to chlordane.

The first drafts of the document were prepared by Dr D.C. Villeneuve of Canada and Dr S. Dobson of the United Kingdom.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

Partial financial support for the publication of this criteria document was kindly provided by the United States Department of Health and Human Services, through a contract from the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA - a WHO Collaborating Centre for Environmental Health Effects.

1. SUMMARY AND RECOMMENDATIONS

1.1 Summary

1.1.1 Identity and analytical methods

Chlordane is a viscous, light yellow to amber-coloured liquid. Technical chlordane is a mixture of at least 26 different components and up to 14 distinct chromatographic components have been described. Its main components are α- and γ-chlordane.

Analysis is difficult because of the complex nature of chlordane. The principal method for its qualitative and quantitative determination is gas-liquid chromatography with electron capture detection.

1.1.2 Use and sources of exposure

Chlordane has been used for more than 35 years as a broad-spectrum contact insecticide, mainly on non-agricultural crops and on animals. In its country of origin, the USA, its use is now restricted to underground termite control. In several other countries, approved uses have been gradually withdrawn.

The main source of exposure of the general population is through residues in food. This is not a significant problem since chlordane is not normally used on food crops, and residues in food of animal origin are usually below accepted residue levels in various countries. Under normal circumstances, chlordane intake from air and water is insignificant. Chlordane has, however, been detected in the air of buildings where the compound has been used for termite and other insect control.

Under occupational exposure conditions, both inhalation and skin contact are relevant, if adequate preventive and protection measures are lacking.

1.1.3 Environmental concentrations, exposures, and effects

Chlordane is stable to light under normal conditions. It is readily adsorbed on soil particles and therefore there is no significant migration through the soil profile or leaching into ground water. Some volatilisation into air from treated soils, and some run-off into surface waters can take place.

Chlordane is fairly persistent in soil and sediments, especially in the form of its α- and γ-isomers, which are, to a certain extent, translocated into crops grown on the soil.

Limited bioaccumulation in the adipose tissue of terrestrial and aquatic organisms can take place. In general, concentration factors in mammals are less than 1.

Chlordane is highly toxic to earthworms, which may present its greatest long-term hazard for the environment.

1.1.4 Kinetics and metabolism

In experimental animals, chlordane is readily absorbed via the skin and through oral ingestion, and probably also following inhalation. It is readily distributed in the body, the highest levels being found in adipose tissue, followed by the liver. The distribution was found to be similar in the rat and the rabbit. The metabolism of chlordane, which is a complex mixture, has been largely elucidated. Several metabolites have been identified and species differences have been found. Oxychlordane is the most relevant animal metabolite, being more persistant and toxic than the parent compound.

Following a single, oral dose, elimination of chlordane was almost complete after 7 days in the rat. After long-term exposure, elimination from the body was slower.

1.1.5 Studies on experimental animals

Chlordane is moderately toxic according to the scale of Hodge & Sterner (1956) (acute oral LD_{50} for rat: 200 - 590 mg/kg body weight). WHO (1984) classified the technical product as moderately hazardous. Most of its metabolites are slightly to moderately toxic, with the exception of oxychlordane, which is highly toxic (acute oral LD_{50} for rat: 19.1 mg/kg body weight).

Signs of poisoning in various animal species are neurotoxic manifestations such as disorientation, tremors, and convulsions. Death may follow respiratory failure. On continuous exposure, a certain degree of accumulation may occur in the body, mainly in adipose tissue and to a lesser extent in the liver. The induction of hepatic microsomal enzyme activity is one of the most sensitive parameters for long-term, low-level chlordane exposure. At higher levels, liver hypertrophy with histopathological and functional changes may occur.

At high dosages (50 - 320 mg/kg diet), chlordane decreased the fertility of rats and mice and the viability of the offspring.

There were no indications for teratogenicity.

Chlordane is not generally active in short-term tests for genetic activity.

It induces hepatocellular carcinomas in mice.

1.1.6 Effects on man

Cases of accidental and suicidal poisoning with chlordane have been reported. With the exception of suicide cases, recovery was generally complete. The acute lethal dose for man is estimated to be 25 - 50 mg/kg body weight. No adverse effects have been reported in occupationally-exposed workers. Epidemiological data are insufficient to judge the potential carcinogenicity of chlordane for man.

1.2 Recommendations

(a) Figures relating to the current production and use of chlordane should be made available;

(b) More information on human exposure from sources other than food, such as its used in termite control, are required;

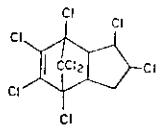
(c) Further research is required in order to better assess the significance for man of the carcinogenic findings in mice;

(d) Epidemiological studies on workers who, in the past, have been exposed to chlordane, should continue.

2. IDENTITY, PROPERTIES AND ANALYTICAL METHODS

2.1 Identity

Chemical structure:



Molecular formula: $C_{10}H_6Cl_8$

CAS chemical name: 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene

Common trade names: Aspon, Belt, CD 68, Chlorindan, Chlorkil, Chlordane, Corodan, Cortilan-neu, Dowchlor, HCS 3260, Kypchlor, M140, Niran, Octachlor, Octaterr, Ortho-Klor, Synklor, Tat Chlor 4, Topichlor, Toxichlor, Velsicol-1068

CAS registry number: 57-47-9

Relative molecular mass: 409.8

2.2 Properties and Analytical Methods

2.2.1 Physical and chemical properties

Chlordane is a viscous, light yellow to amber-coloured liquid (IARC, 1979) with a melting point of 106 - 107 °C for the α-isomer and 104-105 °C for the γ-isomer. It has a density of 1.59 - 1.63 g/ml and a vapour pressure of $1 \cdot 10^{-5}$ mm Hg at 25 °C. It is insoluble in water but soluble in most organic solvents.

The major isomers of chlordane have the endo-endo-configuration on the carbon skeleton (US EPA, 1976a,b). However, the term chlordane actually refers to a complex mixture of chlordane isomers, other chlorinated hydrocarbons and by-products. According to the Canada National Research Council (1974), the technical product is described as follows:

> "Technical chlordane is a mixture of insecticidal components, including chlorinated addition and substi-

tution derivatives of 4,7-methano-3a,4,7,7a-tetrahydroindane. The chlorine content is 64-67%. The principal components are α (alpha)- and γ (gamma)-chlordane ($C_{10}H_6 \cdot Cl_8$), heptachlor ($C_{10}H_5Cl_7$) and nonachlor ($C_{10}H_5Cl_9$). Technical chlordane conforms to the biological, chemical and physical properties of reference technical chlordane".

The production of technical chlordane is strictly controlled and its composition varies within narrow limits (Canada, National Research Council, 1974). Technical chlordane is a mixture of at least 26 different components, mainly however α- and γ-chlordane. Up to 14 distinct chromatographic components have been described (Cochrane et al., 1975; Cochrane & Greenhalgh, 1976; US EPA, 1976a,b; Gaeb et al., 1977; Sovocool et al., 1977; Kadam et al., 1978; Parlar et al., 1979). The composition has been essentially, but not completely, worked out. Chlordane is available in the USA in five basic formulations (von Rumker et al., 1974, IARC, 1979), including 5% granules, oil solutions containing chlordane at 2 - 200 g/litre, and emulsifiable concentrates containing chlordane at 400 - 800 g/litre.

2.2.2 Analytical methods

Determination of chlordane residues is difficult because of the complex nature of the components and the fact that each component degrades independently. Resulting residues may bear little relation to the proportions in the technical product (Council for Agriculture Science and Technology, 1975). Separation from interfering materials can be carried out by thin-layer chromatography or other partition and clean-up methods (US EPA, 1976a,b). Extraction from crops, other plant products, dairy products, plants, and oils was achieved with an 80 - 110% efficiency using acetonitrile for extraction, petroleum ether for partitioning, and clean-up on a Florisil column (Canada, National Research Council, 1974). Gel-permeation chromatography can also be used for clean-up, particularly with human adipose tissue (Wright et al., 1978).

The principal method for the qualitative and quantitative estimation of chlordane isomers is gas-liquid chromatography with electron capture detection (US EPA, 1976a,b). This method has a high sensitivity and specificity (Canada, National Research Council, 1974; Cochrane et al., 1975). According to Atallah et al. (1977), the highly sensitive electron capture detector can, however, lead to the incorrect identification of residues of chlordane and its metabolites. Confirmation of gas-chromatographic analysis can be carried out with GLC-Mass spectrometry, a method that can also give a

better determination of some of the components such as heptachlorepoxide (US EPA, 1976a,b). Other methods of detection include bioassay, carbon-skeleton chromatography, colorimetric, and total chlorine methods (US EPA, 1976a,b).

Analysis for total organically-bound chlorine (Canada, National Research Council, 1974) remains the preferred method for the determination of technical chlordane and the active ingredient (chlordane) in formulations.

3. SOURCES OF ENVIRONMENTAL POLLUTION, ENVIRONMENTAL TRANSPORT AND DISTRIBUTION

3.1 Sources of Environmental Pollution

3.1.1 Industrial production and uses

Chlordane was first prepared in the 1940s by exhaustive chlorination of the cyclopentadiene-hexachlorocyclopentadiene adduct (IARC, 1979). It was first described as an insecticide in 1945 by Kearns (Spencer, 1973).

Chlordane is produced commercially by reacting hexachlorocyclopentadiene with cyclopentadiene to form chlordene, which is then chlorinated to produce chlordane (IARC, 1979). Chlordane was first produced commercially in the USA in 1947 (IARC, 1979). Production in the USA, in 1974, amounted to 9.5 million kg (IARC, 1979). Chlordane is not produced in Europe nor has it ever been manufactured in Japan (IARC, 1979). In Japan, the only permitted use of the compound is for the control of termites. It is also used against wood-boring beetles and in ant baits. Both the amounts of chlordane produced and used have decreased considerably in recent years (WHO, 1982).

Chlordane has been used as an insecticide for more than 35 years. It is a versatile, broad spectrum, contact insecticide and is used mainly for non-agricultural purposes (primarily for the protection of structures, but also on lawn and turf, ornamental trees, and drainage ditches) (von Rumker et al., 1974). Furthermore, it is used on corn, potatoes, and livestock. In 1978, a US EPA cancellation proceeding led to a settlement on contested uses. This settlement allowed for limited usage by crop, location, amount allowed, and maximum time interval for use.

Since 1 July 1983, the only use of chlordane approved in the USA is for the control of underground termites (IARC, 1979). In Canada, the use of chlordane is controlled under the Pest Control Products Act and it is used for the protection of structures, ornamental plants, lawns, and various crops. Accepted uses vary from province to provide (Canada, National Research Council, 1974).

3.2 Environmental Transport and Distribution

3.2.1 Air

Entry into the atmosphere occurs mainly through aerial applications of dusts and sprays, soil erosion by the wind,

and volatilization from soil and water (Canada, National Research Council, 1974).

3.2.2 Water

Few data are available on the routes of entry or the behaviour and fate of chlordane in aquatic systems. It can be assumed that not much originates from ground water since there is little leaching of chlordane. One possible source is surface run-off, but no studies have tested the extent of this assumption. Another source is rain; however, in two studies, chlordane levels did not exceed 2 - 3 ng/litre rain water (Bevenue et al., 1972a; US EPA, 1976a,b).

One important aspect of chlordane residues is that they accumulate in sediment. The fate and behaviour of chlordane was investigated in an isolated fresh water lake, previously free from pesticide residues (Oloffs et al., 1978). The lake was treated with technical chlordane at 10 µg/litre, and sediment samples were analysed for chlordane residues 7, 24, 52, 279, and 421 days after treatment. It was found that water residue concentrations declined rapidly. After 7 days, only 46.1% of the chlordane residue remained. After 421 days, residues were still detectable, but all levels were below 0.01% of the initial concentration. It was observed that chlordane residues moved quickly to the bottom sediment and persisted there. Mean residue levels in sediment were 35.29 µg/kg wet weight after 7 days and 10.31 µg/kg after 421 days.

3.2.3 Soil

Chlordane is used almost exclusively as a soil insecticide to control soil pests such as termites (Canada, National Research Council, 1974). Thus, residues of chlordane are mainly present in this environmental compartment. In most temperate climates, only the two chlordane isomers generally persist (Canada, National Research Council, 1974). For example, in Nova Scotia, chlordane was applied at 5 kg/ha per year to sandy loam soil for 3 years. Fifteen years later, approximately 15% of the residues remained, the alpha and gammma isomers being the major components (US EPA, 1976a,b).

The components of technical chlordane are relatively insoluble in water and are readily adsorbed onto soil particles. As a result, one of the characteristics of soil residues is that they do not migrate readily through the soil profile (Canada, National Research Council, 1974; von Rumker et al., 1974). In general, not more than 15% of the residues migrate below the cultivated layer (Canada, National Research Council, 1974). As a result, residues are not likely to

become a serious contaminant of the lower soil strata or deep water sources (Canada, National Research Council, 1974). The organic matter and moisture contents of the soil can affect the volatilization of chlordane components (Stauffer, 1977). The organic matter causes greater adsorption and thus reduces volatilization while soil moisture increases volatilization (Stauffer, 1977). Also, liquid formulations are more volatile than granular (Atallah et al., 1979).

3.2.4 Abiotic degradation

Chlordane is stable to light under normal conditions. When it is exposed to photosensitizers such as rotenone or benzophenone and short irradiation exposure at wavelengths above 300 nm, some components will isomerize (Canada, National Research Council, 1974). No detectable degradation products were formed on plant foliage in the absence of a photosensitizer (Ivie et al., 1972).

3.2.5 Biodegradation

Three conversion products of γ-chlordane were found in white cabbage and carrots, 4 weeks after application. One of the two metabolites isolated from white cabbage (35% of the total), was given the chlordene chlorohydrin structure. The other isolated metabolite (15% of the total) was assigned the dihydroxy-β-dihydroheptachlor structure. The third metabolite was not identified. 1,2-Dichlorochlordene, oxychlordane, and photo-α-chlordane, as well as the parent chlordane compounds, were found in alfalfa after treatment of the soil with chlordane (Canada, National Research Council, 1974).

Oxychlordane (or 1,2-dichlorochlordene epoxide) is the common metabolite derived from both α- and γ-chlordane. It has been found in the fat of pigs fed either of the isomers and in the milk and cheese from cows fed alfalfa treated with technical chlordane. According to some authors, α- and γ-chlordane give rise to oxychlordane via the intermediate 1,2-dichlorochlordene (Canada, National Research Council, 1974).

4. ENVIRONMENTAL LEVELS AND EXPOSURES

4.1 Environmental Levels

4.1.1 Air

Generally, atmospheric concentrations of chlordane appear to be insignificant. However, chlordane has been detected in the air of buildings where the compound has been used for termite or other insect control (US EPA, 1976a,b). Insufficient information is available on this.

4.1.2 Water

Data from several studies indicate that contamination of water with chlordane is not a widespread problem (US EPA, 1976a,b), and that, generally, water residue levels are non-measureable or very low (Canada, National Research Council, 1974).

In a study of the bottom material of 26 tributary streams in San Fransisco Bay, chlordane was found to be ubiquitous at concentrations ranging from a trace to 800 µg/kg (Oloffs et al., 1978).

No chlordane was detected in 188 samples of surface water from southern Florida but it was detected in 30% of 214 sediment samples (Mattraw, 1975). In a study in Hawaii in 1970-71 (Bevenue et al.,.1972b), chlordane was found in drinking-water in 9% of samples at a mean level of 1.0 ng/litre. Chlordane was detected in non-potable waters from canals at levels ranging from 3.7 - 9.1 ng/litre. Again, sediments showed much higher levels of 190 - 378 µg/kg. Chlordane was found to occur in the lower Mississippi river almost continuously throughout 1974 at values ranging from 1.3 to 2.9 ng/litre (Brodtmann, 1976). In a study in the lower Mississippi (Barthel et al., 1969), during 1964-67, chlordane residues ranged from 0.80 to 2.80 mg/kg in river bed material samples. In tributaries of the river, values ranged from 0.56 - 6.44 mg/kg, in 13 out of 348 samples. No chlordane was detected in any water or sediment samples taken from the upper Great Lakes in 1974 (Glooschenko et al., 1976). In one study in 1976 (Harrington et al., 1978), chlordane contamination of a municipal water system was reported, concentrations of chlordane accidently rising to 1.2 g/litre.

4.1.3 Soil

One study has shown that the α- and γ-isomers of chlordane are less persistent in mineral sand soil than in

organic mucky soil (Harris & Sans, 1976). Data from the National Soils Monitoring Program in 1970 showed that chlordane occurred in 0.07% of 1346 sites in 35 States. The range of residues was 0.01 - 13.34 mg/kg dry weight with a mean of 0.08 mg/kg (Crockett et al., 1974). Monitoring of the corn belt region in the USA (12 States) in 1970 showed chlordane to be one of the most commonly detected insecticides with values of ND - 0.20 mg/kg (Carey et al., 1973). Data from 9 States in 1971 detected chlordane in one soil sample at 0.04 mg/kg dry weight (Gowen et al., 1976). Monitoring in 1973 showed residues ranging from 0.001 - 0.020 mg/kg with generally higher values in urban areas. When urban soils were tested in 14 cities in the USA in 1970, values ranged from 0.01 - 1.27 mg/kg. In the Atlantic provinces of Canada, chlordane was detected in less than 10% of agricultural lands at concentrations below 1 mg/kg dry weight (Duffy & Wong, 1967). In another study on chlordane in Saskatchewan soils (Saha & Sumner, 1971), 7 out of 41 samples contained chlordane with residue values ranging from 0.01 to 3.91 mg/kg dry weight. The duration of soil contamination has been studied by several investigators. Using bioassay techniques, it was found in one study that 15% of active ingredients remained in turf soils in Wisconsin after 12 years (Lichtenstein & Poliuka, 1959). In a study in 1970 (Lichtenstein, 1970), it was found that 10 years after application of chlordane at 8.5 kg /ha, approximately 18 - 20% remained.

4.1.4 Crops and wildlife

Since chlordane residues are present predominantly in the soil, translocation into plants is an important factor. In most temperate climates, α- and γ-chlordane are the principal plant residues. In the Canadian climate, the composition of plant residues resembles that of technical chlordane (Canada, National Research Council, 1974). In a field study on soil/plant relationships, it was found that the relationship between residues in soil and those in crops was not consistent and consequently not predictable (Boyd, 1971).

In a three-year study, Onsager et al. (1970) monitored chlordane residues in sugar beets cultivated on loam soil treated once at 6 different application rates ranging from 1.4 - 22.4 kg/ha. In the first growing season, only sugar beets treated at the two lowest rates (1.4 and 2.8 mg/kg) showed residues below 0.3 mg/kg dry weight. In the last two seasons, beets from soil treated at all rates contained residues below this value. In another study, uptake by root crops was shown to be related to the soil type (Stewart, 1975). When chlordane was applied to sandy loam soil with 12%

clay at 15 kg/ha, residues in beets, carrots, parsnips, potatoes, and rutabagas were 0.03, 0.26, 0.24, 0.04, and 0.01 mg/kg, respectively. In sandy loam containing 28% clay, values were 0.01, 0.07, 0.12, 0.15, and 0.01 mg/kg, respectively. A study of residues in alfalfa following applications of high purity chlordane showed that during the first 4 months following treatment, oxychlordane and photo-α-chlordane accounted for 16% and 17% of the residues, respectively (Wilson & Oloffs, 1973a).

Generally, no detectable residues of chlordane were found in wildlife such as birds (Canada, National Research Council, 1974; Fitzhugh & Fairchild, 1976; Clark & Krynitsky, 1978). However, in one study (Clark & Prouty, 1976), mean total residues of oxychlordane ranging from 0.11 to 6.63 µg found in the carcasses of bats from Maryland and Virginia were attributed to chlordane use.

In extensive surveys, residues in fish have generally been low. In 1976, residues in several species from Lake Erie and Lake Saint Claire in Canada were found to range from non-detectable to 0.046 mg/kg fresh weight (Frank et al., 1978a,b). Residues in Canadian commercially caught fish in 1970 were not detectable (Reinke et al., 1972). The National Pesticide Monitoring Program from 1967-68 found chlordane residues in 128 out of 590 fish samples at levels generally less than 0.5 mg/kg (Wilson & Oloffs, 1973b). From 1972-76, chlordane residues were found in only 3% of the samples of estuarine fish in the USA (Butler & Schutzmann, 1978). Chlordane residues were also not detectable in fish and fishery products from the Northwestern Atlantic (Meith-Avcin et al., 1973; Sims et al., 1977).

4.1.5 Food

There have been many studies in Canada, Great Britain, the USA, and other countries on the occurrence of pesticide residues in food. Generally, the results of these studies showed that residues of chlordane seldom occur and uptake by man is negligible (Canada, National Research Council, 1974). Residue tolerances for chlordane have been established at the following levels: Belgium, Luxembourg, and the Netherlands, 0.1 mg/kg, Canada, 0.3 mg/kg, European Economic Community, 0.2 mg/kg and the USA, 0.3 mg/kg. These levels are for a wide variety of foods (US EPA, 1976a,b). A temporary acceptable daily intake (ADI) for human beings for the sum of the α- and γ-isomers of chlordane and oxychlordane of 0 - 0.001 mg/kg body weight was advised by the Joint Meeting on Pesticide Residues (FAO/WHO, 1983). Chlordane is rarely present in market basket surveys, and then only at low levels. It is not among the top 10 chlorinated pesticides

usually found as residues in food (US EPA, 1976a,b). For example, in a survey in the USA from 1963 to 1969, chlordane residues were found in less than 1% of the samples and ranged from 1 - 5 µg/kg.

It has already been shown that crops will translocate chlordane residues from the soil. Generally, the amounts in crops are low. Residues tend to accumulate in the crude oils of oil-seed crops at levels higher than those in the original seed and in the oil-seed meal. However, these levels are reduced by refining processes. Chlordane residues were found in meat, milk, and eggs. Residues in feed crops or from direct applications to cattle and poultry were shown to result in significant residues in milk, meat, and eggs (US EPA, 1976a,b). In a study on eggs in Canada, γ-chlordane was found in 78% of the samples with a mean value of 2 µg/kg fresh weight and α-chlordane in 81% of the eggs with a mean value of 1 µg/kg (Mes et al., 1974). In another study (Herrick et al., 1969), no residues were found in the eggs of chickens fed chlordane in their diet at 0.08 mg/kg for a week.

In a study on samples of cow's milk analysed in the USA, 87% were positive for chlordane with levels ranging from 0.02 to 0.06 mg/litre (IARC, 1979). In another study (US EPA, 1976a,b), the milk of cows grazing on pastures with chlordane applied at 0.55 kg/ha contained an average chlordane concentration of 0.03 mg/litre. No residues were found at lower treatment levels. Chlordane was also found in Canadian meat samples at levels ranging from 0 to 106 µg/kg in beef, 0 to 32 µg/kg in pork, and 0 to 70 µg/kg in fowl (Saschenbrecker, 1976).

4.1.6 Human milk

Several studies on pesticide residues in human breast milk did not reveal any residues of chlordane, but oxychlordane, transnonachlor, and heptachlor epoxide were found, which may be related to chlordane exposure. In a study on 54 women in Arkansas and Mississippi from 1973-74, breast milk contained oxychlordane at 0.005 mg/litre, heptachlor epoxide at 0.004 mg/litre, and trans-nonachlor at 0.001 mg/litre (Strassman & Kutz, 1977). In another study on 34 samples of breast milk in Northern Mississippi from 1973-75, oxychlordane levels were found of 0.005 mg/litre in high-pesticide-usage areas and 0.002 mg/litre in low-usage areas (Barnett et al., 1979). In a survey involving 1436 lactating mothers in the USA, the mean levels of oxychlordane in the milk ranged from 75.4 - 116 µg/litre on an adjusted fat basis (Savage, 1976). In a study of Canadian human milk samples in 1974, oxychlordane was found in 77% of the samples, trans-nonachlor in 68%, and

heptachlor epoxide in 69%, each at a mean level of 1 mg/litre whole milk (Mes & Davies, 1978).

Jensen (1983) recently reviewed the levels of chlordane and oxychlordane in human milk, and his data, including the above-mentioned studies as well as more recent data, are reproduced in Table 1.

4.2 General Population Exposure

Oxychlordane was found together with other organochlorine pesticides in human fat samples at levels ranging from 0.03 to 0.4 mg/kg wet weight (mean 0.14 mg/kg) in residents of the USA (Biros & Enos, 1973). Sovocool & Lewis (1975) also reported the identification of oxychlordane in human fat. As indicated by Biros & Enos (1973), the occurrence of oxychlordane residues in human adipose tissue in the general population may reflect previous exposure to chlordane and/or oxychlordane. This organochlorine compound is included in the human tissue residue monitoring program (Kutz et al., 1976).

4.3 Occupational Exposure

Permissible levels of exposure to chlordane in the workplace air have been adopted in different countries (ILO, 1980). Examples include: 0.5 mg/m^3 as a time-weighted average concentration in Belgium, Finland, Japan, the Netherlands, and the USA (both OSHA and ACGIH), 0.3 mg/m^3 as a time-weighted average and 0.6 mg/m^3 as a ceiling concentration in Romania, and 0.01 mg/m^3 as maximum allowable concentration in the USSR.

People primarily exposed are those employed in the application of chlordane for the control of insects and pests (IARC, 1979). Chlordane has been found in household dust in the homes of farmers (mean level 5.79 mg/kg air-dried dust) and pesticide formulators (mean level 23.11 mg/kg) (Starr et al., 1974).

Table 1. Chlordane and oxychlordane in human milk[a]

Area, year	No. of samples (% positive)	Fat % (mean)	Oxychlordane and chlordane content in[b] Whole milk (mg/litre)	Milk fat (mg/kg)	References
Canada (1975)	100	2.2	1 (< 2)	-	Mes & Davies (1978)
Japan					
Tokyo (1978)	11	-	0.5 (0.1 - 1.0)	-	Miyazaki et al. (1980)
Tokyo (1979)	12	-	0.5 (0.3 - 1.1)	-	Miyazaki et al. (1980)
Mexico (1976)	620	-	-	0.40 (median)	FAO/WHO (1981)
Spain (1979)	45 (17.8%)	-	0.3[c]	0.026[c] (0 - 0.72)	Lora et al. (1979)
USA					
Arkansas/Mississippi (1973-4)	57 (46%)	3.0	12/10 (0 - 20)	-	Strassman & Kutz (1977); FAO/WHO (1981)

Table 1 (contd).

Area, year	No. of samples (% positive)	Fat % (mean)	Oxychlordane and chlordane content in[b] Whole milk (mg/litre)	Milk fat (mg/kg)	References
Hawaii (1979-80)	50 (100%)	3.2	-	0.059 (0.01 - 0.16)	Takahashi et al. (1981)
Mississippi (1973-5) (pesticide area)	34 (100%)	-	5 (1 - 22)	0.13 (0.03 - 0.70)	Barnett et al. (1979)
Mississippi (1973-5) (non-pesticide area)	6 (68%)	-	2 (0 - 4)	0.05 (0 - 0.12)	Barnett et al. (1979)
USA-NE (1975)	233	-	-	0.08 ± 0.05	Savage (1976); Savage et al. (1981)
USA-SE (1975)	288	-	-	0.12 ± 0.15	Savage (1976); Savage et al. (1981)
USA-MW (1975)	378	-	-	0.08 ± 0.05	Savage (1976); Savage et al. (1981)
USA-SW (1975)	388	-	-	0.11 ± 0.35	Savage (1976); Savage et al. (1981)
USA-NW (1975)	149	-	-	0.08 ± 0.05	Savage (1976); Savage et al. (1981)
USA (total) (1975)	1 436 (74%)	-	2 (median)	0.096 ± 0.195 (0.013 - 0.57)	Savage (1976); Savage et al. (1981) FAO/WHO (1981)

[a] From: Jensen (1983).
[b] Results are expressed as means ± S.D. Ranges are listed in parentheses below.
[c] Chlordane.

5. KINETICS AND METABOLISM

5.1 Absorption

In studies on 4 male rabbits, a combination of ^{14}C-α and γ-chlordane (approximately 1700 mg of each, administered orally in 4 doses at 4-day intervals), was well absorbed (Balba & Saha, 1978). Brief exposure of dogs to topically applied chlordane solutions (3.2 g/litre) resulted in a significant and long-lasting decrease in the biological half-life of orally-administered warfarin (Bachmann & Burkman, 1974).

5.2 Distribution and Storage

Studies using radio-labelled chlordane showed that after oral administration, the radioactivity was well distributed in tissues of rats (Barnett & Dorough, 1974) and rabbits (Balba & Saha, 1978). Rats, whether being treated with single oral doses of chlordane or fed diets containing this compound, retained the highest levels of residues in adipose tissue, followed by the liver, kidney, brain, and muscle. More of the γ-isomers was retained than of the α-isomer. Residues in the fat of rats fed radiolabelled chlordane (3:1 α- and γ-chlordane) at 1, 5, and 25 mg/kg diet for 56 days were approximately 3 times higher than those in the diets. Oxychlordane was the most persistent residue in the tissues of these rats after chlordane was removed from the diet (Barnett & Dorough, 1974). The tissue distribution of chlordane in rabbits was found to be similar to that in rats (Poonawalla & Korte, 1971; Balba & Saha, 1978).

5.3 Biotransformation

Poonawalla & Korte (1971) showed that 70% of γ-chlordane fed to rabbits was excreted in the urine in the form of metabolities, a.o., γ-1-hydroxy-2-chlorodihydrochlordene and 1,2-dihydroxydichlordene.

Oxychlordane has been isolated from the fat of dogs, rats (Polen et al., 1971), pigs (Schwemmer et al., 1970), and cattle (Lawrence et al., 1970). It has also been isolated from human fat (Biros & Enos, 1973). Barnett & Dorough (1974) indicated that the faecal extracts of rats fed ^{14}C-chlordane showed the presence of eight radioactive areas on the TLC plate. Although the structures of the metabolites were not fully elucidated, they were tentatively identified as mono-, di-, and tri-hydroxylated products of chlordane.

The major route of metabolism for both α- and γ-chlordane was via dichlorochlordene and oxychlordane (Tashiro & Matsumura, 1977). The results of these studies were in general agreement with the proposal of Street & Blau (1972) and the results of in vitro metabolism studies of Brimfield et al. (1978). Tashiro & Matsumura (1977) were able to isolate 1-exo-hydroxy-2-endo-chloro-2,3-exoepoxychlordene, and found another major metabolic route for α-chlordane that involved a more direct hydroxylation reaction to form 1-exo-hydroxy-dihydrochlordenes and 1,2-γ-dihydroxydihydrochlordene. Both Brimfield et al. (1978) and Tashiro & Matsumura (1977) indicated that oxychlordane and, to a lesser extent, heptachlor were metabolites of chlordane. However, they did not agree as to whether these two metabolites would be terminal residues or intermediates in the metabolic pathways of chlordane. Recent investigations have indicated that other metabolites were present in the urine of rabbits fed chlordane. Thus, α-chlordane gave rise to 1-hydroxy-2-chlorochlordene, 1-hydroxychlordene, and γ-chlordene chlorhydrin. Administration of the γ-isomer resulted in excretion in the urine of the rabbits of 1,2-dichlorochlordene, 1-hydroxy-2-chlorochlordene, γ-chlordene chlorhydrin, and 3-hydroxychlordane (Balba & Saha, 1978).

In vitro metabolism studies have been summarized by Brimfield & Street (1979). By incubation of α- and γ-chlordane with rat liver postmitochondrial supernatant, dichlorchlordene and oxychlordane were isolated, a result that was similar to those from in vivo studies. Hart et al. (1963) and Hart & Fouts (1965) reported that chlordane induced non-specific microsomal enzyme activity in the rat, resembling, from this point of view, phenobarbital.

5.4 Elimination and Excretion

Elimination of radiolabelled chlordane (3:1 α- and γ-chlordane) and the individual isomers was studied in rats. Single oral doses of 0.05, 0.2, and 1 mg/kg body weight in corn oil were almost completely eliminated after 7 days; 24 h after administration, 70% of α-chlordane and 60% of the γ-isomer were excreted. Female rats excreted more of the dose in the urine than the males (Barnett & Dorough, 1974).

6. STUDIES ON EXPERIMENTAL ANIMALS

The toxicity and the residue data on chlordane including some unpublished studies have been reviewed several times by international bodies such as FAO/WHO (1968, 1973, 1978, 1981, 1983), CEC (1981), and IARC (1979). For their conclusions, refer to section 9.

6.1 Short-term Exposures

6.1.1 Oral exposure

The acute toxicity of chlordane in several animal species is shown in Table 2.

The signs associated with acute chlordane poisoning include ataxia, convulsions, respiratory failure, and cyanosis followed by death (US EPA, 1976a,b). Correlation between respiratory difficulty and EEG patterns suggest that respiratory failure is a contributing factor in chlordane-induced mortality (Hyde & Falkenberg, 1976). Pathological manifestations include haemorrhage in the gastrointestinal tract, kidneys, lung, and heart as well as pulmonary congestion and oedema, and degenerative changes in the central nervous system (US EPA, 1976a,b).

Seven dogs were given chlordane in single oral doses ranging from 200-700 mg/kg body weight. Convulsions were seen in one dog at 200 mg/kg (lowest dose) but 700 mg/kg (highest dose) did not induce any effects (Batte & Turk, 1948). Four groups of 2 - 4 dogs were given chlordane orally in doses of 5 - 200 mg/kg body weight. All of the dogs died within 25 days to 93 weeks (Lehman, 1952b).

Chlordane administered by stomach-tube to sheep at 500 mg/kg body weight induced toxic symptoms (incoordination, partial blindness). Full recovery occurred in 5 - 6 days. A dose of 1000 mg/kg body weight induced severe respiratory and nervous symptoms 16 h after treatment and death after 48 h (Welch, 1948).

When a diet containing 1000 mg chlordane/kg was fed to 12 male rats, all of them died within 10 days (Stohlman et al., 1950). At 500 mg/kg all 12 died within 70 days and, at 300 mg/kg, 9 animals out of 12 were alive after 100 days. Daily oral doses of 6.25 - 25 mg/kg body weight administered to 5 rats for 15 days did not induce tremors or convulsions, but daily doses of 50 mg/kg body weight induced toxic symptoms, and 2 of the animals died (Ambrose et al., 1953). Cytoplasmic bodies in the liver cells were observed in all groups and were dose-related.

Table 2. Acute toxicity of chlordane in experimental animals

Species	Sex	Route	Vehicle	LD_{50} (mg/kg)	Reference
Rat	F	dermal	xylene	530	Gaines (1969)
Rat	M	dermal	xylene	205	Gaines (1969a)
Rabbit	NS	dermal	"early" chlordane	< 780	Ingle (1965b)
Rabbit	NS	dermal	"later" chlordane (more purified)	1100 - 1200	Ingle (1965b)
Rat	M	oral	peanut oil	335	Gaines (1969)
Rat	F	oral	peanut oil	430	Gaines (1969)
Rat	NS	oral	variety	200 - 590[a]	Ambrose et al. (1953); Ingle (1965a)
Rat	NS	oral	NS	283	Buck et al. (1973)
Rat	NS	oral	NS	350	Truhaut et al. (1974)
Rabbit	NS	oral	NS	100 - 300[a]	Stohlman et al. (1950)
Rabbit	NS	oral	NS	20 - 40[a]	Ingle (unpublished data, 1955)
Hamster	NS	oral	NS	1720	Truhaut et al. (1974)
Goat	NS	oral	NS	180	Welch (1948)
Sheep	NS	oral	NS	500 - 1000	Welch (1948)
Chicken	NS	oral	NS	220 - 230	FAO/WHO (1968)
Mallard	NS	oral	NS	1200	Buck et al. (1973)
Cow	NS	oral	NS	25 - 90	Buck et al. (1973)

[a] The wide range is explained by the use of different solvents and the fact that chlordane produced before 1950 contained a considerable amount of hexachlorocyclopentadiene.

NS - Not specified.

6.1.2 Dermal exposure

The single-dose dermal LD_{50} of "early" chlordane in rabbits was reported to be less than 780 mg/kg body weight (Ingle, 1965b), and it was noted that this concentration caused severe skin irritation, tremors, and convulsions (Lehman, 1952a). The dermal LD_{50} of the later, more purified chlordane was 1100 - 1200 mg/kg (Ingle, 1965b).

6.1.3 Parenteral exposure

Male gerbils were dosed intramuscularly with chlordane at 2.5 mg/kg body weight every 3 days for 45 days. Treatment induced hyperproteinemia, hyperglycemia, and enhanced serum alkaline and acid phosphatase activities (Karel & Saxena, 1976).

6.2 Long-term Exposures

6.2.1 Oral exposure

Groups of 4 - 7 male and 4 - 7 female dogs were fed dietary levels of 0, 0.3, 3, 15, or 30 mg chlordane/kg for 2 years. Abnormalities in the results of clinical liver function tests were seen in the 15 and 30 mg/kg groups. In animals selected for necropsy at the end of the first year, increased relative liver weights and associated hepatocellular changes were found at 30 mg/kg; at the end of two years, dose-related increases in relative liver weights were found at 15 and 30 mg/kg, with non-dose-related hepatocellular changes. There was no difference between the severity of the liver lesions of the 30 mg/kg animals and those of four animals withdrawn from 30 mg/kg treatment for eight months prior to sacrifice. Liver biopsies on two animals of the 30 mg/kg group at 1, 3, and 6 months showed hepatocellular changes at 6 months but not at 1 or 3 months. No adverse effects were seen on behaviour, appearance, survival, weight gain, blood picture, or the results of periodic physical examinations, at any level (Wazeter, 1967).

Twenty-four rats, 12 of each sex, were fed dietary levels of 2.5, 25, or 75 mg chlordane/kg for 2 years (Lehman, 1952b). The two higher levels caused moderate to severe signs of toxicity. The lowest level caused histological liver changes. Rats were fed technical chlordane (early production) for two years at levels in the diet of 0, 5, 10, 30, 150 or 300 mg/kg (Ingle, 1952; 1965a). Convulsions and tremors were observed in animals receiving 150 mg/kg or more. Hepatocellular alterations consisting of hypertrophy, cytoplasmic oxyphilia and hyalinization, karyorrhexis, karyolysis, and

cell necrosis were obvious at 150 and 300 mg/kg, slight at 30 mg/kg, minimal at 10 mg/kg and absent at 5 mg/kg. Growth was retarded and liver weight and mortality rate increased at 150 and 300 mg/kg. In a subsequent study on rats (Ingle, 1965a), technical chlordane of later production containing fewer by-products was administered at levels of 2.5 - 300 mg/kg diet for 2 years. Changes in food consumption, growth, and mortality rate were seen only at the highest dose. Cellular alterations were seen at 50 mg/kg and higher.

Rats were fed chlordane at levels ranging from 10 to 1280 mg/kg diet for 407 days (Ambrose et al., 1953). The animals in the two highest dose groups died early; liver weight was increased at 320 mg/kg; fatty infiltration and cytoplasmic margination were seen in the liver parenchymatous cells in males at 40 mg/kg and above, and in females at 80 mg/kg and above.

Groups, each comprising 20 male and 20 female rats, were fed dietary levels of 0, 5, 15, 25, or 35 mg/kg of α-chlordane, 15, 25, 35, or 75 mg/kg of γ-chlordane or 5, 15, 25, 35 or 50 mg/kg of a 1:1 mixture of α- and γ-chlordane (Ingle, 1969). In the group fed α-chlordane, growth retardation became apparent in the rats fed 35 mg/kg after 4 months in males and after 5 months in females; with γ-chlordane, the 75 mg/kg group of males only displayed growth retardation after 8 months. With the mixture, growth retardation was evident in both sexes fed 50 mg/kg, beginning earlier in males than in females. Growth retardation was not evident in any group fed lower doses of either isomer. Food consumption bore a relationship to growth. Increased mortality rates for both sexes became significant in the groups fed α-chlordane at 35 mg/kg, γ-chlordane at 75 mg/kg, or the α-γ mixture at 50 mg/kg. Haematocrit was normal for all test groups. Autopsy did not reveal any gross pathological lesions. There was no evidence of tumours. Histological examination did not show any changes from feeding chlordane in any organ except the liver. Compression of sinusoids due to slight hepatic cell hypertrophy in the centrolobular region and minimal bile duct proliferation were evident with administration of α-chlordane at 35 mg/kg. The same changes were noted, but were minimal with the same isomer at 25 mg/kg. Slight to moderate cytoplasmic homogeneity of the hepatic cells in the centrolobular region, minimal cytoplasmic margination, and minimal cell hypertrophy with compressed sinusoids were noted with administration of γ-chlordane at 75 mg/kg. Slight cytoplasmic homogeneity of hepatic cells in the centrolobular region and occasional cytoplasmic margination were observed with the α-γ mixture at 50 mg/kg. The above alterations were minimal with the same

mixture at 35 mg/kg. No liver changes were evident after feeding lower levels of the chlordane isomers.

Groups of 6 female and 6 male rats were fed 2.5 mg or 25 mg of a sample of technical chlordane containing 60 - 75% chlordane and 25 - 40% unrelated products per kg diet for up to 9 months (Ortega et al., 1957). Centrolobular cell hypertrophy, cytoplasmic margination, and cytoplasmic bodies were observed in the liver in 1 male fed 2.5 mg/kg and in 5 males fed 25 mg/kg. No changes were seen in females.

In a two-year feeding study, pure-bred male and female beagle dogs were fed chlordane at levels of 0, 0.3, 3.0, 15, or 30 mg/kg diet. No adverse treatment-related alterations were observed in behaviour, appearance, eye examination, body weight, food consumption, haematology, or plasma biochemistry. Some liver enzyme activities were altered throughout the study at the 15 and 30 mg/kg levels. Relative liver weights were slightly increased after two years in the two highest groups. Treatment-related microscopic changes, observed in dogs fed the two highest levels, consisted of enlargement of centrolobular hepatocytes with margination of coarse cytoplasmic granules (IRDC, 1967).

The Joint Meeting on Pesticide Residues (JMPR) reviewed the toxicity data on chlordane at its 1977 meeting (FAO/WHO 1978) and decided on the following "no-observed-adverse-effect levels":

- rat: 5 mg/kg in the diet, equivalent to 0.25 mg/kg body weight; and

- dog: 3 mg/kg in the diet, equivalent to 0.075 mg/kg body weight.

These "no-observed-adverse-effect levels" were confirmed by the 1982 JMPR (FAO/WHO, 1983).

6.2.2 Dermal exposure

When male guinea-pigs were exposed to chlordane at 67 mg/kg body weight/day, through dermal painting for 90 days, mild degenerative changes in the skin and testis were evident (Datta et al., 1975).

The ninety-day repeated daily dose LD_{50} for rabbits was reported in the paper by Lehman (1952a) (section 6.1.2) to be from 20 - 40 mg/kg body weight. Ingle (1965b) reviewed the dermal toxicity of chlordane and attributed the toxicity of early technical chlordane to the significant content of hexachlorocyclopentadiene (HCPD). A more pure product, which did not contain significant quantities of HCPD, was only half

as toxic to rabbits as the earlier chlordane and did not cause any skin irritation or damage to mucous membranes.

6.3 Reproduction Studies and Teratogenicity

Rats, maintained from weaning on a diet containing a chlordane level of 320 mg/kg, showed reduced rates of mating, of viable litters, and an increased rate of death of progeny prior to weaning. It was concluded that, at this dosage, chlordane interfered with both fertility and litter survival (Ambrose et al., 1953). Groups of 10 male and 20 female rats were used in a 3-generation study at dietary levels of technical chlordane of 0, 0.3, 3, 15, 30, and 60 mg/kg (Ingle, unpublished data, 1967). Two litters in each filial generation were studied. Levels up to and including 30 mg/kg did not have any effect on fertility, number of offspring, or weight, growth, or mortality rate of the young animals to weaning age. Autopsy of animals after weaning did not reveal any gross or microscopic differences between the groups. At 60 mg/kg, there was a high (10.6%) mortality rate in the second F_3 generation litters during the latter part of the nursing period; these animals showed gross and microscopic pathological changes, comparable with those characteristic for chlordane intoxication. However, survivors of this generation did not show any tissue changes at all. A third set of F_3 litters at 60 mg/kg suffered 17% mortality during the nursing period, with symptomatology and gross and microscopic tissue changes characteristic of chlordane intoxication. Third F_3 generation litters from dams removed from the 60 mg/kg group and placed on chlordane-free diets for 30 days prior to remating showed no differences in any respect from control litters. No evidence of teratogenicity was found in this study.

Hens and cocks fed up to 0.3 mg chlordane/kg diet did not show any toxic symptoms or any adverse effects on egg weight, hatchability, or growth of chicks (Biotox, unpublished data, 1969).

Mice fed diets containing chlordane at 25 - 100 mg/kg for 6 generations showed decreased viability in the first and second generations at 100 mg/kg; in the third generation at this level, no offspring were produced (Keplinger et al., 1968). At 50 mg/kg, viability was reduced in the fourth and fifth generations, and at 25 mg/kg no statistically significant effects were observed, even after 6 generations.

Chlordane was administered to rabbits orally at levels of 1.0, 5.0, and 15 mg/kg body weight per day on the 6th - 18th days of gestation. A control group and a positive control group were used. No changes were seen in behaviour, appearance, or body weight. Miscarriages were seen in 3

rabbits at the 1.0 mg/kg level and one rabbit at 15 mg/kg dose level. No effects on any of the maternal or fetal parameters were noted. No teratogenic effects were noted (IRDC, 1972).

6.4 Mutagenicity

α-Chlordane, γ-chlordane, and chlordene were tested in the Ames Salmonella microsome assay and were not mutagenic (Simmon et al., 1977). Chlordane was not mutagenic when tested using 5 different strains of Salmonella typhimurium in the Ames assay (Ercegovich & Rashid, 1977). Chlordane was shown to enhance the number of ouabain-resistant mutants in Chinese hamster V79 cells and was considered weakly mutagenic (Ahmed et al., 1977b).

Chlordane induced unscheduled DNA synthesis in SV-40 human cells in culture without activation (Ahmed et al., 1977a). It was established that chlordane-treated cells did not (for the most part) re-enter mitosis. They were, instead, arrested somewhere between the G_1 and G_2 phases of the cell cycle. Studies involving DNA synthesis were undertaken to determine more precisely at which phase (G_1, S, G_2) the cells are blocked. The data showed that the treated cells were as competant in DNA replication as the control cells. In both control and treated cultures, 25 - 30% of total DNA persisted as light-density material indicating that some of the pre-existing DNA never engaged in DNA synthesis. Either a large fraction of cells failed to complete DNA synthesis or 25 - 30% of the cells did not enter phase S. In any case, treated and control cells behaved the same in terms of DNA synthesis, indicating that treatment of the cells with chlordane blocked the cells at the G_2 stage of the cell cycle (Brubaker et al., 1970).

Chlordane induced gene conversions in Saccharomyces cerevisiae strain D4 (Chambers & Dutta, 1976).

Neither α-chlordane (42, 58, and 290 mg/kg body weight single ip doses or 5 daily oral doses of 75 mg/kg body weight) nor the γ-isomer (5 daily oral doses of 50 mg/kg body weight) had a significant effect in a dominant lethal assay on mice (Epstein et al., 1972). Technical chlordane at dose levels of 50 or 100 mg/kg body weight in a dominant lethal study using mice failed to induce any dominant lethal changes (Arnold et al., 1977).

More recent studies on animal and human cells in culture have shown that chlordane is not mutagenic or is only weakly mutagenic (Williams, 1979; Maslansky & Williams, 1981; Tong et al., 1981). Further work by Telang et al. (1982) showed that chlordane was not mutagenic to an adult rat liver cell line but inhibited cell to cell communication in a rat liver 6-thioguanine resistant/sensitive cell line. Telang et al.

proposed that chlordane was exhibiting properties exerted by many promoting agents.

6.5 Carcinogenicity

Epstein (1976) reported a previously unpublished study by the International Research and Development Corporation, carried out in 1973, in which groups of 100 male and 100 female Charles River CD-1 mice, 6 weeks of age, were fed technical-grade chlordane (purity not given) at 5, 25, and 50 mg/kg diet, for 18 months. Excluding 10 animals sacrificed from each group for interim study at 6 months, mortality rates at 18 months ranged from 27 - 49%, except in males and females receiving the 50 mg/kg diet, in which the mortality rates were 86 and 75%, respectively. A relatively large number of the deceased animals was lost due to autolysis. A dose-related increased incidence of liver hyperplastic nodules was reported in the 25 and 50 mg/kg diet test groups and a dose-related increased incidence of liver cell hypertrophy was found in all test groups. A significant incidence of hepatocellular carcinomas compared with controls was also reported. In the males receiving chlordane at 0, 5, 25, or 50 mg/kg diet, hepatocellular carcinomas were found in 3/33, 5/55, 41/52, and 32/39 animals, respectively; in females, the respective incidences were 0/45, 0/61, 32/50, and 26/37.

Groups of 50 male and 50 female B6C3F1 hybrid mice, 5 weeks of age, were fed analytical-grade chlordane, consisting of 94.8% chlordane (71.7% α-chlordane and 23.1% γ-chlordane), 0.3% heptachlor, 0.6% nonachlor, 1.1% hexachlorocyclopentadiene, 0.25% chlordene isomers, and other chlorinated compounds for 80 weeks (NCI, 1977). Males received initial levels of 20 or 40 mg/kg diet, and females 40 and 80 mg/kg diet; time-weighted average dietary concentrations were 30 and 56 mg/kg for males and 30 and 64 mg/kg diet for females. There were 20 male and 10 female matched controls and 100 male and 80 female pooled controls. Survival in all groups was relatively high, i.e., over 60% in treated males, over 80% in treated females, and over 90% in male and female controls. A dose-related increase in the incidence of hepatocellular carcinomas was found in males and females. The incidences were 43/49 and 34/49 in high-dose males and females, respectively, and 16/48 and 3/47 in low-dose males and females, respectively, compared with 2/18 and 0/19 in male and female matched controls, respectively.

Groups of 50 male and 50 female, 5-week-old Osborne-Mendel rats were given analytical-grade chlordane in the diet for 80 weeks, at initial levels of 400 and 800 mg/kg for males and 200 and 400 mg/kg for females (NCI, 1977). The levels had to be reduced during the study because of adverse toxic effects;

the time-weighted average dietary concentrations were 407 and 203 mg/kg for males and 241 and 121 mg/kg for females. There were 10 male and 10 female matched controls and 60 male and 60 female pooled controls. Survivors were killed at 80 weeks, at which time approximately 50% of treated and control males and 60% of treated females and 90% of control females were still alive. In all treated animals combined, there was an excess incidence of follicular-cell thyroid neoplasms (10/75 in treated females and 7/65 in treated males versus 0/10, 3/58, 0/6, and 4/51 in matched and pooled female and male controls); there was an excess of malignant fibrous histiocytomas in the treated male groups (8/88 versus 0/8 and 2/58 in matched and pooled male controls).

A committee of the National Academy of Sciences (NAS) in the USA was asked to review all available carcinogenicity data on chlordane as part of the cancellation hearings. Chlordane was not found to be carcinogenic in rats and the only target organ site for carcinogenic response in certain strains of mice was the liver. The committee concluded that "there are no adequate data to show that these compounds are carcinogenic in humans, but because of their carcinogenicity in certain mouse strains and the extensive similarity of the carcinogenic action of chemicals in animals and in humans, the committee concluded that chlordane, heptachlor and/or their metabolites may be carcinogenic in humans. Although the magnitude of risk is greater than if no carcinogenicity had been found in certain mouse strains, in the opinion of the committee the magnitude of risk cannot be reliably estimated because of the uncertainties in the available data and in the extrapolation of carcinogenicity data from laboratory animals to humans" (US NAS, 1977).

IARC (1979), in its evaluation of the carcinogenic risk of chlordane, concluded: "There is sufficient evidence that chlordane is carcinogenic in mice." In 1982, another IARC Working Group reviewed existing data on chlordane and concluded that there was limited evidence for the carcinogenicity of chlordane for experimental animals (IARC, 1982). The group of Williams (Telang et al., 1982) suggested that chlordane had the properties of many promoting agents.

6.6 Behavioural Studies

Offspring of chlordane-treated mice (1 or 2.5 mg/kg body weight for 7 consecutive days) made fewer conditioned avoidance responses than controls (Al-Hachim & Al-Baker, 1973). In addition, progeny of mothers receiving the higher dose were more active than the controls.

6.7 Other Studies

Chlordane induces hepatic mixed-function oxidase enzymes in rats (Fouts, 1963; Hart et al., 1963; Hart & Fouts, 1965; Villeneuve et al., 1972; den Tonkelaar et al., 1974; Madhukar & Matsumura, 1979) and enhances estrone metabolism in rats and mice (Welch et al., 1971). Chlordane has been shown to inhibit skin 7-ethoxycoumarin de-ethylase activity (7-EC) (EC 1.14.13) in mice at doses which induced hepatic 7-EC activity (Pohl & Fouts, 1977). Several studies were carried out in which rats were fed chlordane at levels of 2, 5, 10, 20, or 50 mg/kg diet during two weeks (den Tonkelaar et al., 1974). At the end of this period, the liver microsomal enzymes hexobarbital oxidase (EC 1.1), aminopyrine demethylase (EC 1.5.3), and aniline hydroxylase (EC 1.14.14) were determined. A no-observed-adverse-effect level of 5 mg/kg was found for chlordane. Chlordane inhibition of rat brain ATPase activity (Folmar, 1978) and bovine carbonic anhydrase (EC 4.2.1.1) (Maguire & Watkin, 1975) has been demonstrated in in vitro systems. The in vivo inhibition of rat brain ATPase has also been reported (Drummond et al., 1980).

Three female and 3 male baboons were fed atherogenic diets to which chlordane was added at 0.1 or 1 mg/kg body weight per day for two years. At the higher dose level, chlordane increased cytochrome P-450 activity significantly, otherwise no adverse effects on general health or on any major organ systems were found (McGill, 1979).

Acute intramuscular doses (50 mg/kg body weight) of chlordane have been shown to increase the alkaline phosphatase (EC 3.1.3.1) activity in gerbils temporarily (Karel, 1976) and stimulate gluconeogenetic enzymes in the liver and kidney cortex of rats (Kacew & Singhal, 1973a). Oral administration of 200 mg α-chlordane/kg body weight to mature Wistar rats also induced elevated serum levels of glucose and urea with a concomitant decrease in liver glycogen at sacrifice, 1 h later (Kacew & Singhal, 1973b). The chlordane-induced alterations have been attributed to the enhanced ability of these organs to synthesize cyclic AMP (Kacew & Singhal, 1973b, 1974; Singhal & Kacew, 1973, 1976; Kraybill, 1977).

Rats were administered chlordane ip daily for 42 days at levels of 0.15, 1.75, or 25.0 mg/kg body weight. Results revealed "dose-dependent alterations of brain potentials without behavioural signs of chronic toxicity" (Hyde & Falkenberg, 1976, Hyde et al., 1978). Chlordane has also been shown to influence brain biogenic amines including acetylcholine (Hrdina et al., 1973).

Prenatal exposure to 0.16 mg chlordane/kg body weight, in peanut butter, on each day of gestation, resulted in increased plasma corticosterone levels in adult male mice (Cranmer et

al., 1978). When neonatal mice were treated with 0.075 mg α- or γ-chlordane on days 2 - 4 after birth, growth rates were depressed and eye and vaginal opening were delayed (Talamantes & Jang, 1977).

Female Balb C mice were mated and treated with chlordane at 0.16 or 8 mg/kg body weight throughout gestation. Decreased cell-mediated immune competence was found in offspring of high-dose-treated females, at 101 days of age, challenged with oxazolone (Spyker-Cranmer et al., 1982).

Chlordane added to the medium at a concentration of 1 mg/kg inhibited the growth of Streptococcus viridans in vitro by more than 50%. Total growth inhibition occurred at a chlordane concentration of 3 mg/kg (Goes et al., 1978).

6.8 Factors Influencing Toxicity

Metabolites

The acute oral toxicity of chlordane isomers and their metabolites is summarized in Table 3.

Table 3. Toxicity of chlordane isomers and metabolites

Compound	Species (sex)	LD_{50} (mg/kg body weight)	Reference
α-chlordane	rat (M)	392	Wazeter et al. (1968)
γ-chlordane	rat (M)	327	Wazeter et al. (1968)
α + γ-chlordane (1:1 ratio)	rat (M)	371	Wazeter et al. (1968)
oxychlordane	rat (M,F)	19.1	Mastri et al. (1969a)
chlordene	rat (M,F)	over 4600	Mastri et al. (1969b)
3-chlorchlordene	rat (M,F)	over 4600	Mastri et al. (1969b)
1-hydroxychlordene	rat (M,F)	over 4600	Mastri et al. (1969b)
chlordene epoxide	rat (M,F)	over 4600	Mastri et al. (1969c)
1-hydroxy, 2,3-epoxy chlordene	rat (F)	over 4600	Mastri et al. (1969c)
2-chlorchlordene	rat (F)	over 10 200	Mastri et al. (1969c)

Only oxychlordane was more toxic than the parent compounds. Two male and 2 female rats were given the chlordane metabolite oxychlordane in their diet, at a level of 2.0 mg/kg body weight (Plank et al., 1970). Following 90 days feeding, the surviving animals were sacrificed. Body-weight gain, food consumption, behaviour, mortality rate, organ weights and organ to body weight ratios, and the results of haematological and blood chemistry tests and urological studies were considered to be within the normal range for the strain of rat used. No gross pathological abnormalities were evident, and no histopathological lesions could be attributed to oxychlordane.

Groups of 25 male and 25 female rats were fed dietary levels of 1-hydroxychlordene of 0, 100, 250, 500, 1000, and 2000 mg/kg for up to 224 days (Ingle, 1965a). After 110 days, 3 females from each feeding level were mated with males at all levels. The mortality rate in all groups was low, and no statistically significant differences existed. No gross abnormalities were revealed at autopsy after 224 days. The histopathological study of the visceral organs did not show any pathological effects. Slight to moderate hyperplasia of the smooth endoplasmatic reticulum and cytoplasmic margination of a few liver cells were noted at the 1000 and 2000 mg/kg levels.

Interactions

Chlordane has been shown to exert a protective effect against several organophosphorous and carbamate insecticides (Williams et al., 1967; Street et al., 1969; Williams & Casterline, 1970; US EPA, 1976a,b).

Protein deficiency has been shown to double the acute toxicity of chlordane in rats (Boyd, 1972).

Chlordane has also been shown to increase the hepatotoxic effects of carbon tetrachloride in the rat (Stenger et al., 1975; Mahon, 1977; Mahon & Oloffs, 1979; Mahon et al., 1979).

7. EFFECTS ON MAN: EPIDEMIOLOGICAL AND CLINICAL STUDIES

7.1 Poisoning Incidents

A 15-month-old girl ingested a mouthful of chlordane suspension and, after 3 h, displayed tremors and incoordination (Lensky & Evans, 1952). Repeated seizures developed and she was treated with ethyl chloride, amobarbital, and gastric lavage with magnesium sulfate. The child recovered completely and ataxia and excitability disappeared after 2 - 3 weeks. At 26 years of age, she was in excellent health and appeared not to suffer any consequences from the childhood episode (Taylor et al., 1979).

A 2-year-old child had drunk an unknown amount of a 74% formulation of chlordane (Curley & Garrettson, 1969). Vomiting preceeded convulsions, which were controlled by phenobarbital; the EEG pattern was normal within 40 h and the child recovered.

A similar poisoning incident was observed with a 4-year-old child (Aldrich & Holmes, 1969). Convulsions were treated with phenobarbital. As with the previous case, the individual recovered.

Two other cases of chlordane poisoning were reported in 1955 (Derbes et al., 1955). One was caused by the absorption of accidentally-spilled chlordane and the other was a suicide attempt where the individual (female) swallowed 6 g of chlordane (104 mg/kg body weight) and died 9 1/2 days after the incident (Derbes et al., 1955).

When a section of a municipal water system in Chattanooga, Tennessee, USA was contaminated with chlordane in concentrations of up to 1.2 g/litre in 1976, 13 persons showed gastrointestinal and/or neurological symptoms (Harrington et al., 1978).

7.2 Occupational and Epidemiological Studies

No deleterious effects associated with occupational exposure to chlordane have been reported. Twenty-two men, who had been occupationally exposed to chlordane during its manufacture for periods of 1 - 3 years, did not show any evidence of intoxication (Princi & Spurbeck, 1951). Other clinical studies have been reported on men engaged in the manufacture of chlordane (Alvarez & Hyman, 1953; Fishbein et al., 1964; Morgan & Roan, 1969).

Infante et al. (1978) reviewed 25 previously reported cases of blood dyscrasia together with a small number of newly identified cases of aplastic anaemia, leukaemia, or neuroblastoma in children in relation to their possible

association with pre- and post-natal chlordane or heptachlor exposure and reported an anecdotal relationship. However, in a case-control study, no association was found between blood dyscrasias and occupational exposure to a number of pesticides including chlordane (Wang & Gruffenman, 1981).

Wang & MacMahon (1979 a,b) studied a cohort of workers engaged in the manufacture of chlordane, heptachlor, and endrin and another cohort of 16 000 pesticide-spraying personnel, including termite-control workers. Both studies showed a deficit of deaths from all cancers and slight excesses of lung, skin, or bladder cancer that were not statistically significant.

In 1982, an IARC Working Group concluded that the above studies were inadequate to evaluate the carcinogenicity of chlordane for human beings (IARC, 1982).

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

In a retrospective cohort study of workers involved in the production of chlorinated hydrocarbon pesticides, Ditraglia et al. (1981) studied the workers in a chlordane-manufacturing plant; the same workers were also studied by Wang & MacMahon (1979a). SMRs for all cancer deaths were lower than expected; a slight excess of stomach cancer (3 vs 0.99 expected), which was observed, was not statistically significant. The number of workers studied was small and further follow-up of the cohort was recommended by the authors.

MacMahon & Wang (1982) carried out a second follow-up study of mortality rates in a cohort of workers employed in spraying pesticides, including termite-control workers. Among 540 deaths for which the cause was ascertainable, small excesses of bladder cancer in termite-control operators and of skin and lung cancer in other operators were observed, but these were not statistically significant.

7.3 Treatment of Poisoning

In case of overexposure, medical advice should be sought immediately.

Treatment before person is seen by a physician

The person should stop work immediately, remove contaminated clothing and wash the affected skin with soap and water, if available, flushing the area with large quantities of water. If swallowed, vomiting should be induced, if the person is conscious (FAO/WHO, 1978).

Medical Treatment

If the pesticide has been ingested, gastric lavage should be performed with 2 - 4 litres of water, followed by saline purgatives. Barbiturates (preferably phenobarbitone or pentobarbitone) or diazepam should be given intramuscularly or intravenously in sufficient dosage to control restlessness or convulsions. Mechanical respiratory assistance with oxygen may be required. Calcium gluconate, 10% in 10 ml, injected intramuscularly at 4-h intervals, may be helpful. Contraindicated are oily purgatives, epinephrine, and other adrenergic drugs and central stimulants of all types (FAO/WHO, 1978).

8. EFFECTS ON THE ENVIRONMENT

8.1 Toxicity for Aquatic Organisms

Data on the toxicity of chlordane for aquatic organisms are given in Table 4. A more comprehensive table, listing different conditions and exposure times, is available on request from IRPTC, Geneva, Switzerland. It is of importance for the interpretation of these data to note that a change in the purity of technical chlordane occurred in the early 1950s.

Studies of the effects of chlordane on fish began with the application of the original material to rainbow trout by Cope et al. (1947). They determined minimum disabling 24-h doses of chlordane in a xylene emulsion, an acetone solution, a fuel oil solution, and a Velsicol AR-50 solution, and found this to be higher than 6 mg chlordane/litre. An application of 1.12 kg/ha of a field formulation of chlordane to a small pond killed 87% of bluegills present (Surber, 1948), application of 0.56 kg/ha killed some bluegills whilst at 0.28 kg/ha all fish survived (Linduska & Surber, 1948). In a study by Lawrence (1950) on bluegill fingerlings, large-mouth black bass fingerlings, and juvenile goldfish in aquaria, no deaths occurred at 100 µg chlordane/litre (original formulation), whilst at 200 µg/litre, a 30-h exposure killed bass, and an 87-h exposure killed bluegills; goldfish were not affected. In earthen ponds, large-mouth black bass fingerlings were killed by a concentration of 200 µg/litre, but bluegills and fingerlings and juvenile goldfish survived.

Studies using the current formulation of chlordane are summarised in Table 4. A definite temperature effect demonstrated by Macek et al. (1969) during acute exposures, i.e., fish showed a greater susceptibility at higher temperatures, was not present in 96-h exposure studies. Temperature effects were also noted in toxicity tests on tubificid worms, Branchuria sowerbyi (Naqvi, 1973). In static tests, 500 µg chlordane/litre caused 100% mortality at 4.4° and 32 °C, but no mortality at 21 °C. Nutrition has been shown to affect chlordane toxicity in rainbow trout, with 96-h LC_{50}s ranging from 8.2 to 47 µg/litre, depending on the composition of the diet given to the fish (Merhle et al., 1974).

Recent in vitro studies on bluegills (Koch et al., 1971) and on rainbow trout (Davis et al., 1972) have shown that chlordane acts as an inhibitor of ATPase systems.

8.2 Toxicity for Terrestrial Organisms

Studies of the effects of chlordane on soil microfauna have been limited to work on nematodes. Populations of plant-feeding nematodes were reduced by an insecticide mixture

Table 4. Toxicity of chlordane for aquatic organisms

Organism	Age/ size	Temp (° C)	pH	Flow/ stat	Grade	Hardness (mg/litre)	alk (mg/litre)	sal °/00	End point	Parameter	Concentration (µg/litre)	Reference
Eastern oyster (Crassostrea virginica)	29-53 mm	31.6		flow	tech			27.3	% reduction shell deposition	96-h EC_{50}	6.2	Parrish et al. (1976)
Annelid (Nereis virens)				stat				sea water		288-h LC_{50}	220	McLeese et al. (1982)
Scud (Hyalella azteca)	5 mm juv.	16.7	7.9	flow	tech	148	152		immobilisation	168-h EC_{50}	97.1	Cardwell et al. (1977)
Cladoceran (Daphnia pulex)	1st instar	15.5	7.4-7.8	stat					immobilisation	48-h EC_{50}	29	Sanders & Cope (1966)
Pink shrimp (Penaeus duorarum)	50-65 mm	28.4		flow	tech			21.8		96-h LC_{50}	0.4	Parrish et al. (1976)
Dungeness crab (Cancer magister)	adult zoeal	13 13		stat stat	tech tech			25 25	immohilisation	96-h LC_{50} 96-h EC_{50}	220 1.3	Caldwell (1977)
Backswimmer (Notonecta) sp	5-6 mm	18-24		stat	25% EM					168-h LC_{50}	0.79	Konar (1968)
Water scorpion (Nepa) sp	24-28 mm	18-24		stat	25% EM					168-h LC_{50}	182	Konar (1968)
Bluegill (Lepomis macrochirus)	38-84 mm	25	7.1	flow	100%	20	18			96-h LC_{50}	22	Henderson et al. (1959)

Table 4 (contd).

Organism	Age/ size	Temp (° C)	pH	Flow/ stat	Grade	Hardness (mg/litre)	alk (mg/litre)	sal °/00	End point	Parameter	Concentration (µg/litre)	Reference
Fathead minnow (Pimephales promelas)	1 day	21/25	7.7	flow	tech	156	166		major chronic effects	11-mo lowest dose life cycle tests		Cardwell et. al. (1977)
	38-84 mm	25	7.1	flow	100%	20	18			96-h LC_{50}	52	Henderson et al. (1959)
	38-84 mm	25	7.1	flow	75% EM	20	18			96-h LC_{50}	170	Henderson et al. (1959)
Rainbow trout (Salmo gairdneri)	0.9 g	13			tech					96-h LC_{50}	7.8	Cope (1965)
Murrel (Channa punctatus)	24-26 mm	18-24		stat	25% EM					168-h LC_{50}	0.51	Konar (1968)
	48-50 mm	18-24		stat	25% EM					168-h LC_{50}	3	Konar (1968)
	100-105 mm	18-24		stat	25% EM					168-h LC_{50}	25.5	Konar (1968)
Tropical fish	juv	18-24		stat	25% EM					168-h LC_{50}	0.7-3.7	Konar (1968)
Channel catfish (Ictalurus punctatus)	finger ling	25		stat	tech					96-h LC_{50}	500	Clemens & Sneed (1959)
Common toad (Bufo bufo)	tad-pole	18-20		stat						48-h LC_{50}	2000	Ludemann & Neumann (1962)

containing chlordane (as well as DDT, diazinon, and zinophos) in July, following application in March, but at no other time during the study period (Corbett & Webb, 1968). Nematodes are generally unaffected by most soil insecticides (Edwards, 1965a).

Soil fauna populations (mainly arthropods with a small percentage of earthworms and nematodes) were reduced to very low levels by the normal application rate (112 kg/ha per year) of a commercial formulation of chlordane (Gould & Hampstead, 1951). However, Long et al. (1967) did not find any significant reductions in most soil arthropod populations following application of technical chlordane to sugar cane at 2.24 kg/ha, although numbers of Diplura and Pauropoda were reduced. In a summary of the effects of pesticides on soil invertebrates, Edwards (1965b) stated that chlordane caused a large reduction in the numbers of Coleoptera, Diptera, hemiedaphic Collembola, and non-predatory mites, but little reduction in the numbers of edaphic Collembola or predatory mites at application rates of 1.12 - 2.24 kg/ha. He also stated that chlordane was lethal for fly and beetle larvae. Fox (1958) produced a few data indicating that carabid and staphylinid beetle populations returned to normal 3 years after a field application of chlordane (as a 40% wettable powder) at 8.96 or 11.2 kg/ha.

Chlordane is toxic both to earthworms and to enchytraeid worms at application rates well within the range of normal usage (Hopkins & Kirk, 1957; Doane, 1962). The toxicity of chlordane for earthworms is given in Table 5. Legg (1968) made a single application of 25% EC chlordane at 9.0, 13.4, or 20.2 kg/ha on closely-mown turf and counted worm casts for up to 13 months. After 19 days, there were reductions of 52, 72, and 98%, respectively, for the 3 doses compared with control plots; after 13 months, the reductions were 89, 95, and 97%, respectively. Long et al. (1967) reported a significant reduction in earthworm populations, 6 - 11 months after an application of chlordane at 2.2 kg/ha. A reduction in worm casts to zero, 1 year after an application of chlordane at 11.2 kg/ha, either as granules or in spray formulation was shown by Doane (1962). Lidgate (1966) applied chlordane, either as 20% granules or 75% EC diluted with water, at rates between 13.4 and 35.2 kg/ha, to a putting green and measured worm activity by the number of worm casts. The first count of casts, 18 days after treatment, showed that worm activity was significantly depressed by granular applications of 17.6 and 35.2 kg/ha but not by spray formulations of 13.4 or 26.4 kg/ha. Activity became depressed on sprayed plots about 8 weeks after treatment. There were still significantly fewer worm casts on treated plots, 5 years later.

Table 5. Toxicity of chlordane for earthworms

Organism	Grade	Application method	Concentration (kg/ha)	Effect	Reference
Earthworm (Lumbricus terrestris)	25% EC	spray	9	52% reduction in worm casts at 19 days	Legg (1968)
	25% EC	spray	13.4	72% reduction in worm casts at 19 days	Legg (1968)
	25% EC	spray	20.2	98% reduction in worm casts at 19 days	Legg (1968)
	25% EC	spray	9	89% reduction in worm casts at 1 year	Legg (1968)
	25% EC	spray	13.4	95% reduction in worm casts at 1 year	Legg (1968)
	25% EC	spray	20.2	97% reduction in worm casts at 1 year	Legg (1968)
Red earthworm (Eisenia sp)	5% dust	soil incorporation	35	0% mortality in 4 days	Hopkins & Kirk (1957)
	5% dust	soil incorporatioin	70	46% mortality in 4 days	Hopkins & Kirk (1957)
	5% dust	soil incorporation	141	40% mortality in 4 days	Hopkins & Kirk (1957)
	5% dust	soil incorporation	282	79% mortality in 4 days	Hopkins & Kirk (1957)
	5% dust	soil incorporation	100	96-h LC_{50}	Hopkins & Kirk (1957)

The toxicity of chlordane for birds, when given in the diet, is summarised in Table 6. LC_{50} values as mg/kg diet ranged from 170 to 858 in studies where chlordane was given for between 5 days and 100 weeks. When chlordane was applied to marshland at 1.12 kg/ha, the fecundity of marsh birds was affected (Hanson, 1952); blue-winged teal and shovelers did not produce any young, and coot and redwinged-blackbirds produced 60% fewer young. It was postulated that chlordane had caused disruption in food cycles in the marsh and that this was the probable cause of reproductive failure in the birds.

8.3 Toxicity for Microorganisms

Some effects of chlordane on microorganisms are summarised in Table 7. Its effects may be due, at least in part, to inhibition of enzyme activity (Nakas, 1977). Some work has been reported on the effects of chlordane on soil microorganisms. Gram-positive bacteria appear to be more sensitive to chlordane than gram-negative bacteria, since the growth of gram-positives was inhibited whilst that of gram-negatives was unaffected (Trudgill et al., 1971). When Bacillus subtilis cultures were treated with technical chlordane at 20 mg/litre, they ceased to grow. Viable count and respiration rate fell to zero after about 3 h of exposure. The actual concentration experienced by the bacteria is not known, but it is likely to be less than the 20 mg/litre added because of the poor solubility of chlordane in aqueous solution. Langlois & Sides (1972) investigated the effects of constituents of technical chlordane on the growth of Staphylococcus aureus. The viability of the culture, the length of the lag-phase, and the generation time were affected by the amount of chlordane and γ-chlordane applied.

8.4 Bioaccumulation and Biomagnification

Grimes & Morrison (1975) examined the uptake of chlordane by 13 types of bacteria and found that although the uptake of α- and β-isomers of chlordane was the same for any one species, the concentration factors (CF) differed greatly between species. The CFs ranged from a few hundred to several thousand, with 3 species giving much higher values. The highest CF was 53 000 for Caulobacter vibrioides. Caulobacter cells were found to contain 4 distinct lipid-containing materials, and this was offered as an explanation of the high CF. Sanborn et al. (1976) used unlabelled chlordane and labelled ^{14}C-chlordane on filamentous Oedogonium alga and obtained CFs of 49 500 and 98 386. The lower figure may be due to uncertainties in determining chlordane in solution and

Table 6. Toxicity of chlordane for birds

Species	Age	Route	Parameter	Concentration[a] (mg/kg)	Reference
Mallard	4 - 5 mo	oral	acute LD_{50}	1200	Tucker & Crabtree (1970)
	10 days	diet	5-day LC_{50} [b]	858	Hill et al. (1975)
Bobwhite quail	14 weeks	diet	10-week LC_0	10	Ludke (1976)
	17 days	diet	5-day LC_{50} [b]	331	Hill et al. (1975)
	young	diet	100-day LC_{50}	100	DeWitt et al. (1963)
	young	diet	10-day LC_{50}	250	DeWitt et al. (1963)
	adult	diet	100-day LC_{50}	250	DeWitt et al. (1963)
Japanese quail	7 days	diet	5-day LC_{50} [b]	350	Hill et al. (1975)
Ring-necked pheasant	15 days	diet	5-day LC_{50} [b]	430	Hill et al. (1975)
	young	diet	10-day LC_{50}	500	DeWitt et al. (1963)
	young	diet	100-day LC_{50}	50	DeWitt et al. (1963)
	adult	diet	100-day LC_{50}	200	DeWitt et al. (1963)
Cowbird	adult	diet	30-week LC_{50}	500	DeWitt et al. (1963)

[a] Concentration in mg/kg body weight for oral dosing; concentration in mg/kg diet for dietary dosing.
[b] 5 days of treated diet followed by 3 days of clean diet. Mortality rate determined on day 8.

Table 7. Toxicity of chlordane for microorganisms

Organism	F/M/S	Temp (° C)	Grade	Solvent	Endpoint	Time	Concentration (µg/litre)[a]	Reference
Scenedesmus quadricauda	F	23	tech	acetone	stimulation of cell division	5 - 7 days	0.1 - 100	Glooschenko & Lott (1977)
	F	23	tech	acetone	inhibition of photosynthesis	1 - 5 days	50 & 100	Glooschenko & Lott (1977)
Chlamydomonas sp.	S	23	tech	acetone	stimulation of cell division	7 - 11 days	0.1 - 50	Glooschenko & Lott (1977)
	S	23	tech	acetone	stimulation of respiration	3 - 4 h	0.1 - 100	Glooschenko & Lott (1977)
	S	23	tech	acetone	inhibition of cell division	7 - 11 days	100	Glooschenko & Lott (1977)
	F	23 - 25	60%	acetone	50% reduction ATPase activity; no effect on cell density	3 days	100 000	Clegg & Koevenig (1974)
Volvox sp. Pandorina sp. Closterium sp.	F	18 - 24	20% EM	none	100% mortality	7 days	1	Konar (1968)

Table 7 (contd).

Organism	F/M/S	Temp (° C)	Grade	Solvent	Endpoint	Time	Concentration (µg/litre)[a]	Reference
Chlorella ellipsoidea Euglena elastica	F	23 - 25	60%	acetone	reduced ATPase levels; no effect on cell density	3 days	100 000	Clegg & Koevenig (1974)
Exuviella baltica	M		60%	methanol	virtual cessation of growth	7 days	50	Magnani et al. al. (1978)
Natural estuarine phytoplankton	M		60%	acetone	94% decrease in productivity	4 h	1000	Butler (1963)
Estuarine	M	7 - 14	60%	methanol	no effect	5 days	5	Biggs et al.
phytoplankton	M	7 - 14	60%	methanol	growth and ^{14}C uptake reduced in laboratory	5 days	10	(1978)
Bacillus subtilis	S		tech	acetone	growth ceased; decline in viable count; respiration to zero	3 h	20 000	Trudgill et al. (1971)

[a] Solubility of chlordane: 6 - 9 µg/litre.
F = freshwater; M = marine; S = soil.

in the alga. Moore et al. (1977), using the planktonic alga Ankistrodesmus amalloides, obtained a very much lower CF of 5560, but even this species shows accumulation potential.

Accumulation of α- and and γ-isomers of chlordane and nonachlor, and chlordenes was studied by Cardwell et al. (1977) in 3 species of freshwater invertebrates. Chironomus larvae did not show any detectable accumulation. After one week's exposure to 1.7 - 21.6 µg/litre, Daphnia magna gave CFs ranging from 15 000 to 175 000. After 65 days of exposure to 1.4 - 11.5 µ/litre, Hyallela azteca showed CFs ranging from 41 000 to 144 000. After a 24-h exposure to 0.5 µg α- and γ-chlordane/litre, Daphnia pulex gave a CF of 24 000 (Moore et al., 1977). Sanborn et al. (1976) found a CF of 6132 for insect larvae. A fresh-water gastropod Physa sp., concentrated chlordane 132 613 times (Sanborn et al., 1976). Little bioaccumulation has been observed in the marine invertebrate species studied. Wilson (1965) exposed oysters to 0.01 mg chlordane/litre and determined a CF of 7300, which is considerably lower than that for fresh-water gastropods. Water and oyster samples from Galveston Bay, Texas were analysed following an extensive mosquito-control programme (Casper, 1967). Oysters sampled did not contain any detectable chlordane and only 2 out of 9 water samples gave a positive result of less than 0.001 mg/litre. Chlordane was detected by Bugg et al. (1967) in 20 out of 133 oyster samples taken from the South Atlantic and the Gulf of Mexico, but 19 of these gave values of less than 0.01 mg/kg drained weight. Clams, which were living in water containing chlordane at 0.01 µg/litre for 106 days, showed CFs of 1000 or less (Godsil & Johnson, 1968). Parrish et al. (1976) reported that chlordane was concentrated in the tissues of the estuarine pink and grass shrimps at 1000 - 2300 times levels measured in water.

Few data are available on soil invertebrates. One report on earthworms has been published by Gish (1970), who measured the levels of γ-chlordane in the soil and earthworms. CFs of 0.37, 7.1, 10.6, and 152 were obtained for 4 worms in agricultural soils.

Several studies are available on fresh-water fish. Henderson et al. (1969) found that fish from Atlantic-coast streams, which gave positive samples, contained between 0.1 and 7.29 mg chlordane/kg (whole fish wet weight), fish from the Great Lake drainage areas contained between 0.01 and 0.39 mg/kg, and fish from the Mississippi River system contained between 0.01 and 0.72 mg/kg. Fish from other systems (Hudson Bay, Colorado River, Interior basins, Californian streams, Columbia River, Pacific coast and Alaskan streams) contained less than 0.01 mg/kg. A further study by Henderson et al. (1971) yielded 16 positive samples out of 666 fish taken from 50 sites, giving chlordane levels of between 0.09 and

13.5 mg/kg (whole fish wet weight). Working on chlordane accumulation in sucker-fish, Roberts et al. (1977) showed that accumulation from food was directly proportional to the lipid levels of the fish. Chlordane was given to the northern redhorse sucker, Moxostoma macrolepidotum, in the feed at 45 g/kg dry feed for 5 consecutive days and to the white sucker, Catostomus commersoni, directly to the stomach in a single dose of 340 µg in corn oil. Both tests gave CF values of less than, or equal, to 0.52. CF values obtained in fish by uptake from the food were lower than those obtained by uptake from water (goldfish at a CF of 162 with chlordane in diet (Moore et al., 1977); mosquito fish at a CF of 8258 with chlordane in diet and in water (Sanborn et al., 1976)). This suggests that chlordane is taken up directly from water (bioaccumulated) more than it is from ingested food (biomagnified).

Schimmel et al. (1976a,b) reported that CFs for two species of marine fish were similar to those found in fresh-water species. Spot and sheepshead minnow concentrated γ-chlordane 3700 - 14 800 and 9000 - 16 800 times, respectively, in 4 days, and 3300 - 5100 and 10 300 times, respectively, in 24 days. Veith et al. (1979) exposed fathead minnows to 5.9 µg chlordane/litre for 32 days and obtained a CF of 37 800 for the whole body. Parrish et al. (1978) similarly reported 16 000 for whole body in the sheepshead minnow after exposure for 189 days. They also determined the CF after only 28 days exposure and found a comparable whole-body value of 15 300. A range of CFs between 9000 and 16 786 was reported by Schimmel et al. (1976a) when sheepshead minnows were exposed to γ-chlordane (in technical heptachlor) at 1.1 - 2.8 µg/litre for 96 h. In a field study, long-term exposure (209 days or less) of large-mouth bass to between 0.01 and 0.1 µg/litre chlordane gave concentration factors of between 157 and 3308 (Godsil & Johnson, 1968).

Food chain magnification is unlikely in terrestrial organisms. Species of birds and mammals studied show little bioaccumulation, probably because chlordane is rapidly broken down in homoiotherms. There are very few data on birds. One report (Foster et al., 1972) refers to a study on the accumulation of chlordane in laying hens fed 0.1 mg/kg diet. CF values were maximal after 7 - 9 weeks, diet to fat was between 0.01 and 3.3, and diet to eggs was between 0.01 and 2. After 3 weeks on an untreated diet, chlordane was not detectable. McCaskey et al. (1968) dosed hens with the equivalent of a diet containing 10 - 15 mg 60% technical chlordane/kg for 5 days and obtained a maximum CF value in eggs of 0.38 on day 6.

8.5 Population and Community Effects

The fate of ^{14}C-chlordane was investigated in a terrestrial-aquatic model ecosystem composed of an alga (Oedogonium), snails (Physa), mosquito larvae (Culex), and fish Gambusia) (Sanborn et al., 1976). Accumulation of chlordane residues was evident in all organisms in the ecosystem, but no toxic effects were reported.

Exposure of a natural phytoplankton population to 5 and 10 µg chlordane/litre for 5 days had virtually no effect on its species composition (Biggs et al., 1978).

8.6 Effects on the Abiotic Environment

No data are available on abiotic effects.

8.7 Appraisal

Data on aquatic toxicity require interpretation. Although the solubility of chlordane in water has been measured at between 6 and 9 µg/litre, in many studies on its aquatic toxicity, chlordane has been applied at much higher nominal concentrations. Either the chlordane has not been in solution or was added with a solvent. Actual levels of chlordane in natural waters rarely exceed 250 ng/litre with most levels below 20 ng/litre. Test levels are therefore unrealistically high. The data should thus be critically examined unless the actual concentrations experienced by the test organisms were measured.

Few long-term studies of the chronic effects of chlordane are available. Data do not define threshold levels, although they suggest levels at which effects might be expected. Data seldom provide quantitative dose-response relationships.

Effects of chlordane on primary producers in the aquatic food chain are largely unknown because studies have used unrealistically high concentrations. Some data on lethal doses for aquatic organisms are available, but data on sub-lethal effects on reproduction or behaviour are not. There are data on the acute toxicity of chlordane for fish at concentrations approaching the water solubility, but few on long-term exposure at lower doses.

Most terrestrial studies have been on soil organisms. Effects here might be due to the heptachlor in technical chlordane or to a combination of heptachlor and chlordane. Only very high application rates of chlordane affected arthropods. Field studies do not indicate direct toxicity but a combination of toxicity and avoidance of the compound.

Of major importance is the clear toxicity of chlordane for earthworms with implications for soil fertility. Molluscs also appear to be particularly sensitive to chlordane.

9. PREVIOUS EVALUATIONS OF CHLORDANE BY INTERNATIONAL BODIES

An IARC Working Group (IARC, 1982) concluded that the available epidemiological studies on chlordane were inadequate for the evaluation of the cancer risk for man and that there was limited evidence of the carcinogenicity of chlordane for experimental animals.

WHO has recommended a guideline value of 0.3 µg/litre for chlordane (total isomers) in drinking-water (WHO, 1982).

The Joint Meeting on Pesticide Residues (JMPR) reviewed residues and toxicity data on chlordane on several occasions in the past (1965, 1967, 1970). In November 1972, it re-established residue tolerences ranging from 0.02 - 0.5 mg/kg for the sum of α- and γ-isomers of chlordane and oxychlordane (FAO/WHO, 1973). The acceptable daily intake (ADI) for human beings of 0 - 0.001 mg/kg body weight was confirmed in December 1977 (FAO/WHO, 1978). This was based on no-observed-adverse-effect-levels of:

- 5 mg/kg in the diet, equivalent to 0.25 mg/kg body weight in the rat; and
- 3 mg/kg in the diet, equivalent to 0.075 mg/kg body weight in the dog.

Both "no-observed-adverse-effect-levels" and the ADI were reviewed by the 1982 JMPR (FAO/WHO, 1983). The ADI was given "temporary" status pending the results of toxicology studies still in progress.

WHO (1984), in its "Guidelines to the Use of the WHO Recommended Classification of Pesticides by Hazard", classified technical chlordane as moderately hazardous.

The WHO/FAO (1978) has issued practical advice in its "Data Sheet on Pesticides" including one on Chlordane (No. 36) dealing with labelling, safe-handling, transport, storage, disposal, decontamination, training and medical supervision of workers, first aid and medical treatment.

Regulatory standards established by national bodies in 12 different countries (Argentina, Brazil, Czechoslovakia, the Federal Republic of Germany, India, Japan, Kenya, Mexico, Sweden, the United Kingdom, the USA, and the USSR) and the EEC is available from the IRPTC (International Register of Potentially Toxic Chemicals) Legal file (IRPTC, 1983).

The CEC reviewed the data available on chlordane in 1981.

10. EVALUATION OF HEALTH RISKS FOR MAN AND EFFECTS ON THE ENVIRONMENT

10.1 Chlordane Toxicity

Chlordane is readily absorbed in both animals and man via the skin, via ingestion, and probably also by inhalation. Some accumulation occurs in the body on repeated exposure - mainly in adipose tissue. Elimination from the body is fairly slow. The half-life in various species, including man, is of the order of a few weeks.

The oral LD_{50} values of chlordane in the rat range from 200 - 590 mg/kg body weight. Thus, chlordane is moderately toxic in acute exposures.

Acute poisoning in man and animals is characterized by manifestations of central nervous system stimulation such as disorientation, tremors, and convulsions. Death may follow respiratory failure.

In experimental animals (rats and dogs), prolonged exposure to levels in the diet exceeding 3 - 5 mg/kg resulted in the induction of hepatic microsomal enzymes and, at a later stage, liver hypertrophy with histological changes. At higher levels (i.e., > 15 mg/kg body weight per day), chlordane is hepatotoxic. For no-observed-adverse-effect levels see section 6.1.1.

At dosages above 30 mg/kg diet, chlordane interferes with reproduction in rats and mice, but this was reversible after exposure ceased. There are no indications for teratogenicity in the rabbit at 15 mg/kg body weight per day.

Chlordane produces hepatocellular carcinomas in mice. It is not generally active in short-term tests designed to measure genetic activity. Chlordane can interfere with cell to cell communication in vitro, a characteristic of many promoting agents.

10.2 Exposure to Chlordane

Food is the major source of exposure of the general population to chlordane, but the use of chlordane on food crops has decreased and residues in food from animal origin are low. Some chlordane exposure can occur in buildings where chlordane has been used for termite or other insect control.

No adverse health effects have been reported in workers engaged in the manufacture of chlordane or in pest-control operations, where exposure could be quite high. However, several cases of accidental and suicidal poisoning in man have been reported resulting in the symptoms described in section 7.1.

10.3 Evaluation of Overall Environmental Effects

Chlordane is used primarily to control soil pests. Technical chlordane is a mixture of chlorinated hydrocarbons and contains heptachlor, which might contribute significantly to the insecticidal properties of the technical formulation.

About half of the chlordane applied to soil disappears in the first season, presumably by volatalisation or by "run-off" into surface waters. Remaining residues persist for several seasons. If chlordane is applied annually for several successive seasons, residues accumulate in the soil. Most chlordane persists in the cultivated levels, since there is little leaching into subsoil.

The high rate of metabolism of chlordane in warm-blooded animals means that there is little possibility of accumulation in these animals or magnification in food chains at this level. Concentration factors are generally modest in aquatic organisms; this combined with its low solubility in water means that chlordane presents a limited hazard for aquatic vertebrates. Long-term effects are not sufficiently well-documented to say that there is not a potential hazard for fish, but this seems unlikely from the information available, as far as temperate areas are concerned. The compound shows a higher toxicity at higher temperatures. Significant mortality in tropical species of fish at concentrations well within the solubility of the compound, suggest that chlordane may be a greater aquatic hazard at lower latitudes.

The high toxicity of chlordane for earthworms may constitute its greatest potential hazard. The long-term effects of reduced numbers of earthworms in the soil cannot be readily assessed because the ecology of the animal is still poorly understood.

10.4 Evaluation of Risks for Human Health and the Environment

Although there is no evidence that incriminates chlordane as a human carcinogen, the suspicion principally arising from the mouse carcinogenicity studies cannot be entirely put aside. Further research is required to elucidate this problem. Nevertheless, in the present state of knowledge, it is concluded that:

1. As long as occupational hygiene procedures are maintained to keep exposure levels to a minimum, whether or not by the imposition of maximum allowable concentrations, there is little reason to believe that workers will be at risk from their handling, or contacts, with chlordane.

2. For the general population, consumers should suffer no adverse effects from chlordane as food residues, provided that the intake is kept within the temporary ADI set by the Joint FAO/WHO Meeting.

In certain regions of the world, the exposure of the general population to chlordane may be augmented by its use as a termiticide in buildings.

3. Apart from the possible long-term adverse effects on aquatic organisms in tropical areas and the depleted soil fertility that may arise, in time, from the suppression of the earthworm population, chlordane seems to cause little environmental concern in its normal use as a termiticide and in other non-agricultural applications.

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