ıvironmental Health Criteria 38

HEPTACHLOR

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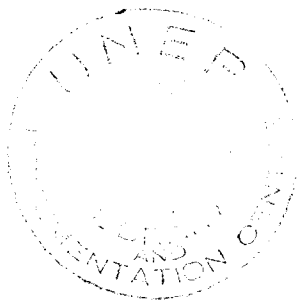

World Health Organization
Geneva, 1984

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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CONTENTS

TASK GROUP MEETING ON ENVIRONMENTAL HEALTH CRITERIA FOR ORGANOCHLORINE PESTICIDES OTHER THAN DDT (CHLORDANE, HEPTACHLOR, MIREX, CHLORDECONE, KELEVAN, CAMPHECHLOR)

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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 HEPTACHLOR

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 to 2 December, 1983. Dr K.W. Jager opened the meeting on behalf of the Director-General. The Task Group reviewed and revised the draft criteria document on heptachlor and made an evaluation of the health risks of exposure to heptachlor.

The drafts of this 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.

* * *

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1. SUMMARY AND RECOMMENDATIONS

1.1 Summary

1.1.1 Identity and analytical methods

Heptachlor is a white crystalline solid with a mild camphor odour. It is used as an insecticide.

Gas chromatography with electron capture detection is the method most commonly used for heptachlor determination.

1.1.2 Uses and sources of exposure

Heptachlor has been used for more than 30 years as a stomach and contact insecticide, mainly in the control of termites and soil insects. 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.

Exposure of the general population is mainly through residues in food, but in most countries these residues have decreased considerably over the years and exposures are generally far below the advised acceptable daily intake. In areas where heptachlor is used, there may be some additional intake from volatilisation of sprayed heptachlor and from well-water.

A significant source of heptachlor for infants is breast milk, in which the levels of heptachlor can be considerably higher than those in dairy milk.

In certain occupational exposures, heptachlor is known to have exceeded the TLV or MAC.

1.1.3 Environmental concentrations and exposures

Heptachlor is fairly stable to light and moisture and it is not readily dehydrochlorinated. Volatilization is the major mechanism of transport of topically-applied heptachlor. Its half-life in the soil in temperate regions ranges between 3/4 - 2 years, depending on the type of soil, and may be less in tropical regions. It is not likely to penetrate into groundwater but contamination of surface water and sludge can occur. Several metabolites, formed by microbial action, have been found in soil, sludge, and water. Epoxidation is an important metabolic route leading to heptachlorepoxide, which is of comparable toxicity to heptachlor but more stable in biological systems.

Bioaccumulation and biomagnification occur and bioconcentration factors of 200 - 37000X have been reported from water into hydrobiota.

Heptachlor has been shown to be toxic for aquatic life, but its toxicity is highly species variable. Marine crustacea and younger life stages of both fish and invertebrates are most sensitive. Insufficient information is available on its toxicity for terrestrial species.

1.1.4 Kinetics and metabolism

Heptachlor is readily absorbed following ingestion and skin contact and is transported throughout the body. Heptachlor epoxide, the most persistent metabolite, is rapidly formed and can be found in the body, mainly in adipose tissue. The toxicity of heptachlor epoxide is similar to that of heptachlor. Figures for its half-life in the rat are contradictory; in chickens it is of the order of 4 weeks. Excretion takes place via both urine and faeces, but detailed information is lacking. Human milk can be a major excretion route for heptachlor residues.

1.1.5 Studies on experimental animals

According to the classification of Hodge & Sterner (1956), the acute toxicity of heptachlor is moderate (acute oral LD_{50} for the rat 40 - 162 mg/kg). WHO (1984) classified the technical product as moderately hazardous. Toxic symptoms are related to hyperexcitability of the central nervous system and include tremors and convulsions. Death may follow respiratory failure. At non-lethal acute exposures, heptachlor is hepatotoxic.

Proliferation of the smooth endoplasmatic reticulum and induction of the mixed-function oxidases in liver cells is one of the earliest indications of prolonged exposure to heptachlor.

At high exposure levels, heptachlor can interfere with reproduction and the viability of offspring. Cataracts were observed in both parents and progeny in the rat.

There were no indications of teratogenicity in rats, rabbits, chickens, and beagle dogs.

Heptachlor is not generally active in short-term tests designed to detect genetic activity. There is evidence that it may have effects on cell to cell communication, which is a property of promoting agents.

There is limited evidence that both heptachlor and heptachlor epoxide are carcinogenic for mice.

1.1.6 Effects on man

There are no reports of cases of poisoning in man. Although no adverse effects have been reported in workers

manufacturing or using heptachlor, epidemiological studies are insufficient to judge the carcinogenic hazard of heptachlor for man.

1.2 Recommendations

1. Figures relating to current production and use of heptachlor should be made available.

2. More information on human exposure to heptachlor from sources such as breastmilk and applications for termite control are required.

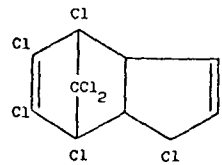
3. Further research is required in order to better assess the significance for man of the carcinogenic findings in mice.

4. Continuing epidemiological studies should be made on workers who, in the past, have been exposed to heptachlor.

2. IDENTITY, PROPERTIES AND ANALYTICAL METHODS

2.1 Identity

Chemical structure:



Molecular formula: $C_{10}H_5Cl_7$

CAS chemical name: 1,4,5,6,7,8,8-heptachloro-3_a,4,7,7_a-tetrahydro-4,7-methano-1H-indene

Common trade names: Aahepta, Agroceres, Basaklor, Drinox, E 3314, GPKh, Heptachlorane, Heptagran, Heptagranox, Heptamak, Heptamul, Heptasol, Heptox, Rhodiachlor, Soleptax, Velsicol 104

CAS registry number: 76-44-8

Relative molecular mass: 373.3

2.2 Properties and Analytical methods

2.2.1 Physical and chemical properties

Heptachlor is a white crystalline solid with a mild odour of camphor, a melting point of 93 °C (46 - 74 °C for the technical product) and a density of 1.65 - 1.67 g/ml at 25 °C. It has a boiling point of 135 - 145 °C and vapour pressure of $4 \cdot 10^{-4}$ mm Hg at 25 °C.

It is virtually insoluble in water (0.056 mg/litre) but fairly soluble in organic solvents, e.g., ethanol (45 g/litre), xylene (1020 g/litre), acetone (750 g/litre), benzene (1060 g/litre).

It is stable in daylight, air, moisture, and moderate heat (160 °C) but is oxidized biologically to heptachlor epoxide (Whetstone, 1964).

Technical heptachlor contains about 72 - 74% 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4, 7-methano-indene, 20 - 22% γ-chlordane, and 4 - 8% γ-nonachlor (Suzuki et al., 1978).

2.2.2 Analytical methods

Various methods used in the determination of heptachlor and heptachlor epoxide are summarized in Table 1.

Table 1. Methods for the determination of heptachlor and its epoxide

Sample type	Extraction/clean-up detection	Method of detection	Limit of detection	Reference
Formulations:				
liquids	extract (carbon disulphide)	GC/FID	---	Horwitz (1970)
solids	extract (pentane) in Soxhlet	GC/FID	---	Horwitz (1970)
ambient air	trap in ethylene glycol, partition and extract (methylene chloride), fractionation and clean-up through silica gel, CC	GC/ECD	0.1 ng/m³	Arthur et al. (1976); Sherma & Shafik (1975)
sediments and sewage sludge	centrifuge, extract solid (acetone), liquid/liquid partition, transfer into trimethyl pentane, treat to remove sulfur isolate in trimethylpentane	GC/ECD	1 - 10 µg/kg	Jensen et al. (1977)
soil	extract (acetone-hexane) add benzene to extract, evaporate to dryness, dissolve in hexane, CC	GC/ECD	-	Townsend & Specht (1975)
food	extract (ethyl ether in petroleum ether), Florisil CC followed by UV irradiation of sample and standards	GLC of photo-derivatives	-	Ward (1977)
crops	blend with water-acetonitrile, decant, separate liquid, concentrate, extract (hexane) transfer to hexane, CC	GC/ECD	10 µg/kg	Carey et al. (1973)

Table 1 (contd).

Sample type	Extraction/clean-up detection	Method of detection	Limit of detection	Reference
fish, crabs, shellfish	extract (hexane-acetone), dry, filter, wash, filtrate (water), distill, CC	GC/ECD	4 µg/kg	Albright et al. (1975)
fruits, vegetables, dairy products	extract (acetonitrile), dilute (water), extract (petroleum ether), CC	GC/ECD, thermionic	-	Horwitz (1975)
milk	extract (diethyl ether and hexane), partition into acetonitrile, extract (hexane)	GC	-	Gabica et al. (1974)
rice	extract (water, acetonitrile and ethanol), extract (n-hexane), clean-up $AgNO_3$-coated florisil CC	GC	-	Suzuki et al. (1979)
water, rural potable	extract (hexane), CC	GC/ECD	10 ng/litre	Sandhu et al. (1978)
adipose tissue	extract (hexane), re-extract (petroleum ether, chloroform-methanol, acetonitrile or acetone-hexane), dry, dissolve (hexane), CC	GC/ECD and TLC	-	Clausen et al. (1974)
wildlife tissue	grind with sodium sulphate, extract (ethyl ether, petroleum ether) in Soxhlet, CC	GC/ECD	5 µg/kg	White (1976)

Abbreviations: CC - column chromatography; GC - gas chromatography; FID - flame-ionization detection; ECD - electron capture detection; TLC - thin-layer chromatography.

3. SOURCES OF ENVIRONMENTAL POLLUTION, TRANSPORT AND DISTRIBUTION

3.1 Sources of Pollution

3.1.1 Industrial production and uses

Heptachlor is not known to occur naturally.

It was isolated in 1946 from technical chlordane in both the USA and the Federal Republic of Germany (IARC, 1974, 1979). Heptachlor, which was first introduced as a contact insecticide under the trade names Velsicol 104 and E 3314, was registered in the USA in 1952 as a commercial insecticide for foliar, soil, and structural applications, and for the control of malaria.

Heptachlor is produced commercially by chlorination of chlordene in the presence of a catalyst (IARC, 1974) such as Fuller's earth (Whetstone, 1964). This reaction is usually carried out at 0 - 5 °C in carbon tetrachloride. The solvent is then distilled off, and the residue recrystallized from methanol before grinding (Melnikov, 1971). Formulations include: emulsifiable concentrates, wettable powders, dusts, and granules containing various concentrations of active material.

It is a non-systemic stomach and contact insecticide.

The use of heptachlor is confined almost exclusively to the control of soil insects and termites. Production of heptachlor in the USA in 1971 was estimated at 2.7 million kg. In the period July 1975 - December 1976, an estimated 4.5 million kg were produced in the USA where it was used as an insecticide (registered from June 1971 for use on 22 crops) and applied both as a topical foliar application and as a seed treatment: 58% on corn, 26.8% by pest control operators, 13.2% as seed treatment, and 2% for miscellaneous uses including fire ant control, use on pineapples, and possibly on citrus fruits (IARC, 1979).

In 1970, the world use of heptachlor was as follows: Africa 5%, Asia 15%, Canada and the USA 5%, Europe 60%, and South America 15% (FAO/WHO, 1971). However, it would appear that world usage is diminishing.

A USA Environmental Protection Agency cancellation proceeding led to a settlement on contested uses. This settlement allowed for the limited use of heptachlor according to crop, location, amount allowed, and maximum time interval between applications. Its main use is now in termite control (Peirano, 1980).

The use of heptachlor has been restricted in Italy and Switzerland (IARC, 1974). In Japan (Environmental Protection

Agency, Japan, 1978), the only accepted use of heptachlor is for termite control. Its use is restricted in the USSR (IRPTC, 1982).

3.2 Transport and Distribution

3.2.1 Air

Volatilization is the major mechanism of transport of topically applied heptachlor. In one study, 90% of heptachlor was volatilized from bare moist soil in 2 - 3 days following application (Taylor et al., 1976). Fields treated with technical heptachlor at 2.24 kg/ha gave rise to air concentrations around the field as high as 244 ng/m^3, immediately following application. After 3 weeks, the concentrations still remained as high as 15.4 ng/m^3 (Peirano, 1980).

3.2.2 Water

Heptachlor is quickly hydrolysed in water to form 1-hydroxychlordene which in turn is degraded microbially to form 1-hydroxy-2,3-epoxychlordene. Formation of 1-hydroxychlordene seems to be one of the major degradation pathways in moist soil. It has been shown that heptachlor epoxide is also metabolized to 1-hydroxychlordene (Harris & Miles, 1975).

Heptachlor is not often found in surface waters but it has been detected at levels of 5 - 30 ng/litre while heptachlor epoxide has been detected at levels of 5 - 40 ng/litre (IARC, 1974).

3.2.3 Soil

The half-life of heptachlor in soil was 9 - 10 months when used at recommended agricultural rates (Anonymous, 1976). Vrochinshy et al. (1980) described a half-life of 2 years; it could still be detected in soil 14 years after use. Small field plots, treated with up to 224 kg heptachlor/ha, had residue levels of 95 g/kg, 16 years after the initial application (Nash & Harris, 1973). Data from tropical regions suggest that soil dissipation of heptachlor may be more rapid in tropical than in temperate regions (Stickley, 1972; Kathpal et al., 1983).

Soil surveys in the USA have showed 1-hydroxychlordene to be a major residue in soils from 5 areas, while only small amounts of heptachlor epoxide and the hydroxy epoxide were present (the half-life of 1-hydroxychlordene in soil is 3 weeks) (Brooks, 1974). It has been reported that heptachlor

can be altered in the soil environment to either heptachlor epoxide and/or 1-hydroxychlordene (Harris & Miles, 1975).

When heptachlor was applied to a grass pasture at 5.6 kg/ha, 4% of the heptachlor remained after 30 days. After 15 weeks, 2% remained (Taylor et al., 1977). In another study, heptachlor was applied to the soil at a rate of 2.24 kg/ha; the soil was rotatilled to 15 cm and tobacco plants were planted 6 days later. After 3 months, soil samples at 0 - 15 cm and 15 - 23 cm showed heptachlor levels of 0.37 mg/kg and 0.04 mg/kg, respectively (Townsend & Specht, 1975).

Tzapko et al. (1967) concluded from their studies that heptachlor penetration into ground water was likely to be insignificant.

3.2.3.1 Bacterial degradation

Some bacteria and fungi are able to metabolize heptachlor to its epoxide. Some soil bacteria have the ability to metabolize heptachlor to chlordene, while other bacteria and fungi are able to metabolize chlordene to chlordene epoxide (Harris & Miles, 1975). Microorganisms isolated from soil were examined for their ability to metabolize heptachlor. Twenty-six out of 45 bacteria and 35 out of 47 fungi isolated from soil were able to metabolize heptachlor to its epoxide. According to the author there are two other pathways of degradation, i.e., chemical hydrolysis to 1-hydroxychlordene, followed by microbial epoxidation to 1-hydroxy-2,3-epoxychlordene and conversion to an unknown product; and bacterial dechlorination of heptachlor to chlordene and then oxidation to chlordene epoxide. The author states that the former seems to be a major degradation route and that preliminary laboratory studies indicate that the production of 1-hydroxychlordene in soil is comparable to that of heptachlor epoxide.

3.2.3.2 Abiotic degradation

Heptachlor is stable to light (Worthing, 1979).

Under conditions of sunlight or ultraviolet (UV) light, heptachlor 1-exo-hydroxychlordene or 1-4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-4,7-methanionden-1-ol was photodegraded forming a cyclic ketone 1,1a,2,2,3, exo-6-hexachloro-1a,2,3,3a,5a,5b-hexahydro-1,3-methano-1H-cyclobuta (c,d) pentalen-4-one. The structure of this photodegraded product was elucidated by spectral data from mass spectrometry, infrared spectrometry and ^{1}H and ^{13}C nuclear magnetic resonance (Parlar et al., 1978).

4. ENVIRONMENTAL LEVELS AND EXPOSURES

4.1 Environmental Levels

4.1.1 Air

The typical mean concentration of heptachlor in ambient air in the USA was approximately 0.5 ng/m³ (Peirano, 1980). Air samples were taken from both rural and urban areas of 9 cities in the USA for 2 weeks per month, over a 6-month period, in 1971. Heptachlor was found in samples taken from 2 of the 9 cities at a maximum level in each city of 19.2 ng/m³ (Stanley et al., 1971). Air samples, taken from 1972-74 in a cotton-growing area of the USA, had a maximum heptachlor level of 0.8 ng/m³ (Arthur et al., 1976).

4.1.2 Water

Heptachlor and heptachlor epoxide were observed in chemical sewage sludges in Ontario at levels (combined) of up to 21.73 µg/litre (Liu et al., 1975). In the water and sediment in the upper Great Lakes, in 1974, values for heptachlor levels in water, heptachlor epoxide in water, heptachlor in sediment, and heptachlor epoxide in sediment were 0.005 µg/litre, 0.005 µg/litre, and 0.001 mg/litre and 0.001 mg/litre, respectively (Glooschenko et al., 1976).

In the major river basins of the USA, heptachlor was found at levels ranging from 0.001 to 0.035 µg/litre in a study conducted in 1967 (Peirano, 1980).

Heptachlor was found in 18 different locations in Europe and the USA in sediments, plant effluents, lakes, and rivers (Eurocop-Cost, 1976; Shackelford & Keith, 1976). The results of a survey conducted in the USA in the period 1958-65 showed that heptachlor was present in 17% of the samples of drinking-water studied. The average concentration was 3 ng/litre (Safe Drinking-Water Committee, 1977). Heptachlor and heptachlor epoxide were found in potable water supplies in rural areas of South Carolina in 45.5 and 63.6% of samples tested, with the range of residues varying from undetected to 44 ng/litre for heptachlor and from undetected to 87 ng/litre for heptachlor epoxide (Sandhu et al., 1978).

A study was conducted in the USA in 1977 to compare pesticide residue levels in the rural drinking-water of 2 states (1 sample taken per 100 houses). Heptachlor was found in 45.5% of samples from one state and in 62.5% of samples from the other at mean levels of 9 and 15 µg/litre, respectively (Sandhu et al., 1978).

In another study, the average heptachlor residues in tap water from Ottawa and The Hague were shown to be less than 0.013 µg/litre, and 0.01 µg/litre, respectively (Kraybill, 1977a). Mean concentrations of heptachlor and heptachlor epoxide of 0.6 and 3.0 ng/litre were found in Ottawa drinking-water in 1976 (Williams et al., 1978). Heptachlor levels as high as 0.46 µg/litre have been detected in ambient water in Nova Scotia (Burns et al., 1975).

A study of the effects of heptachlor on the organoleptic properties of water has revealed that a heptachlor concentration in water of 0.07 mg/litre (and higher) gives it a strange odour but does not change the taste of water. Heptachlor at concentrations of 0.1 mg/litre or less does not affect the odour or taste of raw and boiled fish products. Concentrations of 0.01 and 0.05 mg/litre do not inhibit the biochemical oxygen demand. The dynamics of the development and decay of aquatic saprophytic microflora has shown that a heptachlor concentration of 0.1 mg/litre does not inhibit the processes of "ammoniation" and nitrification of organic substances in model reservoirs (Chekal, 1965).

WHO has recommended a guideline value of 0.1 µg/litre for heptachlor and heptachlor epoxide in drinking-water (WHO, 1982).

4.1.3 Soil

A survey conducted on crop soils in 37 states of the USA in 1971 revealed heptachlor residues in 4.9% of samples, while heptachlor epoxide was detected in 6.9% of samples with maximum values of 1.37 and 0.43 mg/kg, respectively (Carey et al., 1978).

In a study conducted in the USA in 1969, crop soils from 43 states and non-crop soils from 11 states were examined. Heptachlor was found in 68 of the 1729 samples analysed, with residue levels ranging from 0.01 to 0.97 mg/kg, all the samples being from cropland areas (Wiersma et al., 1972a,c). In another study, heptachlor was found in soil samples from 7 out of 16 farms examined in 1971 at levels of up to 0.24 mg/kg (Harris & Sans, 1971), while levels in the range of 0.01 - 0.84 mg/kg were found in soil samples from 6 out of 12 states (5.7% of sites examined) in the Corn Belt region of the USA (Carey et al., 1973).

Heptachlor residue levels found in soil samples taken from 7 out of 8 cities in the USA in 1969 ranged from 0.01 to 0.53 mg/kg (Wiersma et al., 1972b). Average heptachlor and heptachlor epoxide concentrations found in soil samples from 8 cities in the USA ranged from 0.01 to 0.02 mg/kg and 0.01 - 0.05 mg/kg, respectively (IARC, 1974).

In streambed sediment and sediment from natural drainage ditches, heptachlor has been found at levels as high as 174 and 4.7 µg/kg, respectively (Burns et al., 1975).

4.1.4 Food

The Joint meeting on Pesticide residues (JMPR) estimated the acceptable daily intake of heptachlor plus heptachlor epoxide at 0 - 0.0005 mg/kg body weight (FAO/WHO, 1971). The same meeting arrived at the following recommendations for practical residue limits (FAO/WHO, 1971):

0.01 mg/kg for citrus fruit;
0.5 mg/kg for crude soya bean oil;
0.05 mg/kg for vegetables; and
0.15 mg/kg for milk and milk products.

It was calculated that the daily human intake of heptachlor epoxide in the USA ranged from 0.29 to 0.64 µg/day during the period 1971-74 (Peirano, 1980). The daily intake of heptachlor epoxide from food in 1965 in the USA was 2 µg/day. In 1970, this figure was 1 µg/day (Duggan & Corneliussen, 1972).

Market basket surveys carried out from 1972-73 in the USA showed maximum values for heptachlor epoxide ranging from trace to 2 µg/kg (Johnson & Manske, 1976), while from a study published in 1969 in the United Kingdom, the heptachlor epoxide content in the total diet was, in general, less than 0.0005 mg/kg; heptachlor was not detected (Abbott et al., 1969). In a series of studies conducted in the United Kingdom and the USA, analyses of total diets were carried out. Heptachlor epoxide was present in small amounts in fish, poultry, meat, and dairy products, and in trace amounts in fruits, vegetables, oils, and cereals. The maximum values in poultry, meat, and fish ranged from trace to 2 µg/kg (Johnson & Manske, 1976). The US EPA has established tolerances for total residue levels of both heptachlor and heptachlor epoxide at 0.1 mg/kg in or on cabbage, lettuce, rutabagas, and snap beans, and 0.0 mg/kg (zero) in or on a variety of 30 vegetable, field, and fruit crops, meat, or milk (US EPA, 1976)

Heptachlor was not found in any foods examined from August 1972 to July 1973 in the frame of the total diet study conducted by the US Food and Drug Administration (IARC, 1979). In a study conducted in 20 cities in the USA in 1974-75, only 3 out of 12 food classes contained detectable residues of heptachlor epoxide. Levels ranged from 0.0006 to 0.003 mg/kg (Peirano, 1980). A study that started in 1974 in

the USA disclosed the following mean heptachlor and heptachlor epoxide residues as µg/kg wet weight (Table 2) (Madarena et al., 1980).

Table 2. Heptachlor and heptachlor epoxide levels in food

	Level (µg/kg wet weight) in:				
	pork	horse meat	chicken	beef	turkey
Heptachlor	1.25	1.06	3.27	0.10	0.65
Heptachlor epoxide	1.95	5.28	9.58	0.50	6.66

Within the framework of the Joint FAO/WHO Food Contamination Monitoring Programme, the levels of heptachlor and heptachlor epoxide residues in various food items sampled in 1980-82 have been reported from: Austria, Canada, Denmark, Guatemala, Japan, the Netherlands, and the USA. On the fat basis, the median levels ranged from 0 (not detected) in butter and cattle fat in Denmark to 13 µg/litre in cow's milk in Japan. On the "as is" basis, median levels ranged from 0 (not detected) in hen's eggs in Denmark to 4 µg/kg in fresh onions in Guatemala. For heptachlor epoxide only, the median levels ranged from 0 (not detected) in butter and pasteurized cow's milk to 0.30 µg/litre in raw cow's milk in the Federal Republic of Germany (fat basis) (WHO, 1983).

A study of US game fish conducted in 1967-68 showed heptachlor and/or heptachlor epoxide present in 32% of 590 fish samples in a range from 0.01 to 8.33 mg/kg (Henderson et al., 1969). Fish have been shown to accumulate heptachlor and heptachlor epoxide at 0.008 mg/kg from concentrations of 0.06 µg/litre water (Hannon et al., 1970). In whole fish, residues of heptachlor plus heptachlor epoxide in the range of 0.01 - 0.26 mg/kg have been found (IARC, 1974). Average values for heptachlor and heptachlor epoxide in oysters in the USA were less than 0.01 mg/kg (Bugg et al., 1967).

Potatoes grown in soils treated with heptachlor dust at 1.5 kg/ha were found to contain residues of heptachlor and heptachlor epoxide up to 151 days following application. Processing of the potatoes failed to reduce the heptachlor and heptachlor epoxide content below the tolerance level (0.1 mg/kg) (Misra et al., 1977).

Sandy loam plots of soil were treated in 1951 with heptachlor at 0, 56, 112, or 224 kg/ha. Residue levels were examined 15 - 16 years later. In soils, after 16 years, 9.5% of the heptachlor applied at the highest dose level remained.

No heptachlor residues were found in soybeans grown on this soil 15 years after application of heptachlor, but heptachlor epoxide residue levels of 0.067 - 0.237 mg/kg were found (Nash & Harris, 1973). In Canada, an average level of heptachlor of 0.001 mg/kg was found in milk fat (Frank et al., 1979a,b). The level of heptachlor in milk-extracted lipids in the USA was 0.002 mg/kg and that of heptachlor epoxide 0.036 mg/kg (Duggan, 1967). In the Federal Republic of Germany, heptachlor epoxide residues were found at a level of 0.024 mg/kg milk extracted lipids (Heeschen et al., 1976).

Where cows (both early and late in lactation) were administered daily a mixture of aldrin, heptachlor, and beta-HCH at 1, 2, or 4 mg/day for 4 weeks, aldrin and heptachlor could not be detected in the milk-extracted lipids or in adipose tissue (Vreman et al., 1976). In cows fed heptachlor epoxide daily at 5 or 20 µg/kg for 27 days, maximum levels of 2.9, and 4.4 µg/kg, respectively, were detected in the milk (Hardee et al., 1964). Maximum levels of heptachlor and heptachlor epoxide found in milk and milk products in Ireland in 1971-72 were 62 and 21 µg/kg fat, respectively (Downey et al., 1975).

In a German study published in 1972, heptachlor and heptachlor epoxide residues were determined for cheese, butter, pasteurized milk, and human milk (Heeschen, 1972). The findings showed that for the milk and milk products, the average total residue was less than 0.05 mg/kg. Human milk residues were about 10 times higher, being 0.1 and 0.34 mg/kg in milk fat for heptachlor and heptachlor epoxide, respectively.

4.2 General Population Exposure

4.2.1 Exposure of infants

In a study conducted in Canada, heptachlor epoxide was detected in human milk, evaporated milk, and prepared baby food formulae. The ranges found are given in Table 3 (Ritcey et al., 1972).

The most significant source of exposure to heptachlor for infants appears to be human milk where heptachlor levels can be much higher than in dairy milk. Jensen (1983) recently reviewed the levels of heptachlor and heptachlor epoxide in human milk and his data are given in Table 4.

The WHO Collaborating Centre in Japan participating in the Joint FAO/WHO Food Contamination Monitoring Programme reported that the median and 90 percentile values of heptachlor and heptachlor epoxide residues in human milk ("as is" basis) were below 0.50 µg/litre and 2.10 µg/litre, respectively, in 1980 and below 0.50 µg/litre and 1.90 µg/litre,

Table 3. Heptachlor epoxide in human milk, evaporated milk, and prepared baby food formulae

	Residue level (mg/litre) in:		
	Human milk	Evaporated milk	Prepared baby formula
On whole milk basis	0.001 - 0.023	0.001 - 0.001	0.001 - 0.007
On fat basis	0.01 - 1.19	0.01 - 0.02	0.01 - 0.05

respectively, in 1981. The Collaborating Centre in Guatemala reported that the median and 90 percentile values of heptachlor epoxide only ("as is" basis) were 0 and 2 µg/litre, respectively, in 1979 (WHO, 1983).

Heptachlor epoxide and other organochlorine insecticide levels in breast milk samples from vegetarians were lower. The mean heptachlor epoxide levels were only 1 - 2% of the average level in breast milk of the US general population (Hergenrather et al., 1981).

4.2.2 Occupational exposure

During spraying, heptachlor concentrations in air of 0.6 - 1 mg/m^3 have been measured. These levels decreased to 0.007 mg/m^3, 1 - 1 1/2 h later (Osetrov, 1960). During mechanical disinfection of seeds, the same author reported workplace concentrations of 5 mg/m^3.

Permissible levels of exposure to heptachlor 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, the Netherlands, and the USA (both OSHA and ACGIH); 0.1 mg/m^3 maximum permissible concentration in Bulgaria; and 0.01 mg/m^3 maximum allowable concentration in the USSR (ILO, 1980; IRPTC, 1982; INRS, 1983).

Table 4. Heptachlor and heptachlor epoxide in human milk[a]

Area/year	Number of samples (% positive)	Fat (%) (mean)	Heptachlor and heptachlor epoxide content in[b] Whole milk (µg/litre)	Milk fat (mg/kg)	Reference
AFRICA:					
Kenya (1979)	33	-	0.5 (median)	-	FAO/WHO (1981)
AMERICAS:					
Canada					
Alberta (1966-70)	59 (5%)	-	-	0.002 (0 - 0.06)	Currie et al. (1979)
Alberta (1977-78)	33 (94%)	2.0	-	0.03 (0 - 0.11)	Currie et al. (1979)
Canada (1967-68)	147	2.7	3 ± 3 (< 1 - 23)	0.13 ± 0.14 (< 0.01 - 1.19)	Ritcey et al. (1972)
Canada (1975)	100	2.2	1/1 (0 - 3)	-	Mes & Davies (1979); FAO/WHO (1981)
El Salvador (1973-74)	40 (50%)	-	3	-	De Campos & Olszyna-Marzys (1979)
Guatemala					
Rural area (1971)	46 (50%)	-	7	-	De Campos & Olszyna-Marzys (1979)
Mexico (1976)	620	-	-	0.01[c] (median) 0.01 (median)	FAO/WHO (1981)
Uruguay (Montevideo)	10	-	2	-	Bauza (1975)
USA					
Arkansas/Mississippi (1973-74)	57 (35%)	-	12/10 (0 - 30)	-	Strassman & Kutz (1977); FAO/WHO (1981)
Colorado (1972)	40 (25%)	-	3 ± 1/1 (tr - 5)	-	Savage et al. (1973); FAO/WHO (1981)

Table 4 (contd).

Area/year	Number of samples (% positive)	Fat (%) (mean)	Heptachlor and heptachlor epoxide content in[b] Whole milk (µg/litre)	Milk fat (mg/kg)	Reference
Georgia (Atlanta) (1968)	15	-	1.7	-	Curley & Kimbrough (1969)
Hawaii (1979-80)	50 (100%)	3.2	-	0.035 (0.001 - 0.16)	Takahashi et al. (1981)
Mississippi (pesticide area) (1973-75)	34 (100%)	-	3 (< 1 - 20)	0.08 (0.02 - 0.37)	Barnett et al. (1979)
Mississippi (non-pesticide area) (1973-75)	6 (100%)	-	2 (< 1 - 3)	0.05 (0.01 - 0.08)	Barnett et al. (1979)
Missouri (St. Louis) (1973)	51 (24%)	-	2.7	-	Jonsson et al. (1977)
Pennsylvania (Philadelphia) (1970)	53	-	-	0.16 (0.06 - 0.46)	Kroger (1972)
USA-NE (1975)	233	-	-	0.07 ± 0.04 (0.018 - 0.030)	Savage (1976); Savage et al. (1981)
USA-SE (1975)	288	-	-	0.13 ± 0.21 (0.019 - 2.05)	Savage (1976); Savage et al. (1981)
USA-MW (1975)	378	-	-	0.09 ± 0.07 (0.016 - 0.73)	Savage (1976); Savage et al. (1981)
USA-SW (1975)	388	-	-	0.08 ± 0.10 (0.015 - 1.09)	Savage (1976); Savage et al. (1981)
USA-NW (1975)	149	-	-	0.07 ± 0.10 (0.019 - 0.95)	Savage (1976); Savage et al. (1981)
USA-Total (1975)	1436 (61%)	-	1 (median)	0.09 ± 0.13 (0.016 - 2.05)	Savage (1976); Savage et al. (1981)
ASIA:					
Israel (1975)	29[d]	1.5	9 ± 5	0.72 ± 0.48	Polishuk et al. (1977)

Table 4 (contd).

Japan					
Akita (1979)	29 (96.6%)	-	0.5 (0 - 1.0)	-	Sasaki et al. (1980)
Japan (1971)	108	-	1 (median)	-	FAO/WHO (1981)
Japan (1972)	283	-	1 (median)	-	FAO/WHO (1981)
Japan (1973)	112	-	1 (median)	-	FAO/WHO (1981)
Japan (1974)	131	-	1 (median)	-	FAO/WHO (1981)
Japan (1975)	49	-	1 (median)	-	FAO/WHO (1981)
Japan (1976)	31	-	0.3 (median)	-	FAO/WHO (1981)
Japan (1977)	13	-	0.2 (median)	-	FAO/WHO (1981)
Japan (1978)	26	-	2 (median)	-	FAO/WHO (1981)
Japan (1979)	33	-	0.5 (median)	-	FAO/WHO (1981)
Japan (36 prefectures) (1971)	398 (42%)	-	1.1	-	Hayashi (1972b)
EUROPE:					
Austria					
Vienna (1977-78)	20/182	2.6	-	0.010/0.013	Gyimothi (1979); FAO/WHO (1981)
Belgium					
Belgium (1968)	20 (20%)	-	2 (1 - 3)	-	Heyndrickx & Maes (1979)
Brussels (1976)	24 (100%)	-	8.2 (2 - 24)	0.35 (0.07 - 0.15)	Van Haver et al. (1977)
North Belgium (rural (area) (1976)	34 (100%)	-	12.2 (2 - 75)	0.61 (0.09 - 0.84)	Van Haver et al. (1977)
South Belgium (urban area) (1976)	20 (100%)	-	1.4 (1 - 11)	0.11 (0.02 - 3.0)	Van Haver et al. (1977)
South Belgium (rural	24 (100%)	-	1.3 (1 - 5)	0.16 (0.07 - 0.17)	Van Haver et al. (1977)
Denmark					
Copenhagen (1982)	4≤/36 (100%)	2.9	-	0.05 (0.02 - 0.07)	Orbaek (1982)
France					
France (1971-72)	≤	-	-	0.280 (0.06 - 1.30)	Luquet et al. (1975)

Table 4 (contd).

Area/year	Number of samples (% positive)	Fat (%) (mean)	Heptachlor and heptachlor epoxide content in[b] Whole milk (µg/litre)	Milk fat (mg/kg)	Reference
Lille (1970)	49[c] (27%)	-	7	-	Luquet et al. (1972)
Strassbourg (1974-75)	65 (20%)	-	-	0.08	De Bellini et al. (1977)
Germany, Federal Republic of					
Bayern (1973-74)	137 (23.4%)	2.3	3 (1 - 7)	0.14 (0.03 - 0.37)	Rappl & Waiblinger (1975)
Germany, Federal Republic of (1973-74)	320	-	-	0.11/0.94 (0.01 - 0.63)	DFG (1978); FAO/WHO (1981)
Germany, Federal Republic of (1976)	68	-	-	0.03 (median)	FAO/WHO (1981)
Germany, Federal Republic of (1976-77)	654	-	-	0.06/0.03 (0.01 -0.20)	DFG (1978); FAO/WHO (1981)
Germany, Federal Republic of (1977)	494	-	-	0.03 (median)	FAO/WHO (1981)
Germany, Federal Republic of (1977)	147	-	-	0.03 (median)	FAO/WHO (1981)
Germany, Federal Republic of (1978)	435	-	-	0.017 /median)	FAO/WHO (1981)
Germany, Federal Republic of (1979)	374	-	-	0.014/1.008 (0.001 - 0.20)	FAO/WHO (1981); Heeschen & Tolle (1981)
Kiel (1971)	99	-	-	0.34 (0.04 - 1.91)	Heeschen (1972)
Kiel (1971)	99	-	-	0.10[c] (0 - 0.49)	Heeschen (1972)
Italy					
Milano (1975)	30 (100%)	2.6	-	0.12 (0.02 - 0.31)	Cerutti et al. (1976)
Luxembourg (1973)	12	-	-	0.15 (median) (0.01 - 0.33)	Gatti et al. (1974)

Table 4 (contd).

Netherlands					
Leiden (1969)	50 (100%)	1.9	1.2 ± 0.7 (0.3 - 3.5)	0.06 ± 0.03 (median) (0.03 - 0.15)	Tuinstra (1971)
8 regions (1972)	202	3.4	3 (median)	0.08 ± 0.04/0.08	Wegman & Greve (1974); FAO/WHO (1981)
Norway					
Oslo (1975)	50 (36%)	-	1.6 (0.6 - 2.6)	-	Bakken & Seip (1976)
Spain					
Madrid (1981)	20	-	1[e]	-	Baluja et al. (1982)
Madrid (1981)	20 (77%)	-	4 ± 4 (0- 14)		Baluja et al. (1982)
Rural area (1979)	21 (100%)	-	-	2.56[e] (0.41 - 10.8)	Lora et al. (1979)
Rural area (1979)	21 (9.5%)	-	-	0.017 (0 - 0-30)	Lora et al. (1979)
Urban area (1979)	24 (100%)	-	-	2.46[e] (0.62 - 11.7)	Lora et al. (1979)
Urban area (1979)	24 (12.5%)	-	-	0.051 (0 - 1.00)	Lora et al. (1979)
Spain Total (1979)	45	-	39[e]	2.51[e]	Lora et al. (1979)
Spain Total (1979)	45	-	0.3	0.035	Lora et al. (1979)
Switzerland					
Basel (1971)	50	-	-	0.07 (0.02 - 0.45)	Schüpbach & Egli (1979)
Basel (1978)	50	-	0.8 (median)	0.03 (< 0.01 - 0.11)	Schüpbach & Egli (1979); FAO/WHO (1981)
Switzerland (1973)	15	-	1 (median)	-	FAO/WHO (1981)
Switzerland (1974)	6	-	0.5[e] (median) 3 (median)	-	FAO/WHO (1981)

[a] From: Jensen (1983).
[b] Results are expressed as means ± SD/medians, and ranges are listed in parentheses.
[c] Pooled samples.
[d] Colostrum.
[e] Heptachlor.

5. KINETICS AND METABOLISM

5.1 Animal Studies

Heptachlor is readily absorbed via all routes of exposure, and is readily metabolized to heptachlor epoxide by mammals (Hayes, 1963). Heptachlor epoxide is metabolized slowly and is the most persistent metabolite; it is mainly stored in adipose tissue, but also in liver, kidney, and muscle (FAO/WHO, 1967). Klein et al. (1968) showed that the metabolism of heptachlor in rats gave rise to heptachlor epoxide and a hydrophilic metabolite, 1-exo-hydroxychlordene epoxide. Heptachlor epoxide was found in tissues, urine, and faeces, while the hydrophilic metabolite was only detected in the urine. In rabbits, approximately 80% of the urinary radioactivity was derived from the hydrophilic metabolite and 20% from the epoxide. Mizyukova & Kurchatov (1970) found heptachlor epoxide following intragastric administration of heptachlor to female albino rats. Matsumura & Nelson (1971) isolated another metabolite from rat faeces which they identified as a dehydrogenated derivative of 1-hydroxy-2,3-epoxychlordene. Rats fed diets containing 30 mg heptachlor/kg were shown to have maximum heptachlor epoxide concentrations in adipose tissue within 2 - 4 weeks. Twelve weeks after cessation of exposure, heptachlor had completely disappeared from the adipose tissue (Radomski & Davidow, 1953). The highest concentrations of heptachlor epoxide were found in adipose tissue; markedly lower amounts were found in the liver, kidney, and muscle, and none in the brain. A similar pattern of distribution was found in the dog (Radomski & Davidow, 1953). Mizyukova & Kurchatov (1970) gave a single dose of 120 mg heptachlor/kg body weight to female albino rats. Heptachlor was found in all organs 1/2 - 1 h later. During 3 - 6 months, the heptachlor epoxide level in adipose tissue remained unchanged. During the first 5 days, excretion was mainly via the gastrointestinal tract.

The accumulation of heptachlor epoxide in the adipose tissue of laying hens was demonstrated by Kan & Tuinstra (1976). The accumulation ratio (level in adipose tissue/level in feed) was 6 for heptachlor.

Broiler chickens were fed heptachlor in concentrations of 0.01, 0.03, 0.1, and 0.3 mg/kg diet for the first 8 weeks of life. Residue concentrations in adipose tissue increased rapidly in the first 2 weeks and then tended to form a plateau at concentrations about five times higher than those in the diet. Residue concentrations decreased by about half in the first 4 weeks after cessation of exposure (Wagstaff et al., 1980). When groups of cows were fed heptachlor at doses of

0.5 - 2.0 mg/cow per day for a period of 8 weeks, the level of heptachlor epoxide in the adipose tissue was found to be below 0.1 mg/kg (Vreman et al., 1977). Phenobarbital pretreatment significantly enhanced the metabolism of heptachlor in rats. It caused a 6 to 11-fold increase in the liver heptachlor epoxidase activity (Miranda et al., 1973).

5.2 Human Studies

Although there is no direct evidence showing the conversion of heptachlor to its epoxide in human beings, there is little doubt that the epoxide that has been found in human tissues is derived from heptachlor. Some levels of heptachlor epoxide in the blood and fat of human beings from various countries are presented in Table 5. Ritcey et al. (1973) noted that the heptachlor epoxide levels in young Canadians were significantly lower than those in the older group surveyed. Kutz et al. (1977) reported that, in the USA, there was little racial difference in the levels of heptachlor epoxide and other organochlorine compounds in human adipose tissue. Studies carried out by Zavon et al. (1969) and Curley et al. (1969) suggested that, in the USA at that time, trace quantities of heptachlor were found in the adipose tissue of stillborn and newborn babies at autopsy, and that the levels were slightly lower than those found in the adult population.

Abbott et al. (1968) revealed that the levels of organochlorine pesticides including heptachlor epoxide in males from Britain were higher than those in females and that the levels compared favourably with other countries in which similar surveys had been done.

A study by Van Haver et al. (1978) on 29 samples of adipose tissue from men and 44 from women showed average residue levels of 0.19 and 0.20 mg/kg in males and females, respectively.

The mean value of heptachlor epoxide in 60 post-mortem samples of adipose tissue was 0.380 mg/kg. Comparison with results performed 6 and 9 years earlier showed an increase in heptachlor epoxide levels (Dejonckheere et al., 1978).

There is limited information available on blood levels of heptachlor epoxide, but it has been confirmed that levels in the blood are several orders of magnitude lower than those found in adipose tissue.

Because of its high lipid content, milk is one of the major excretion routes for organohalogenated compounds, including heptachlor epoxide. An extensive survey carried out in the USA indicated that women who had lactated after several births had lower pesticide levels in milk than primiparae (Savage, 1976). Heptachlor epoxide, together with DDT, dieldrin, and oxychlordane were the most common pesticides

Table 5. Concentrations of heptachlor epoxide in human blood and adipose tissue

Country	Number of samples	Blood (µg/kg)	Adipose Tissue (mg/kg)	Reference
Argentina	52		0 - 0.73	Garcia Fernandez et al. (1975)
Argentina			0.2 (m)	Astolfi et al. (1973)
Argentina			0.16 (f)	Astolfi et al. (1973)
Argentina	36	0.34	0.19	Garcia Fernandez et al. (1975)
Australia	185	0-95 (5.5)		Siyali (1972)
Australia	52	0-64 (3.1)	0 - 0.73	Siyali (1972)
Australia	81		ND - 0.5	Siyali (1972)
Canada	32		0.004 - 1.81	Larsen et al. (1971)
Canada	221		0.01 - 0.2 (0.04)	Ritcey et al. (1973)
Denmark			0.12	Jensen & Clausen (1979)
Denmark			0.08	Jensen & Clausen (1979)
England			(0 - 0.40) 0.045 (m)	Abbott et al. (1968)
England			(0 - 0.08) 0.032 (f)	Abbott et al. (1968)
USA	1092		0.08 - 0.7 (0.09)	Kutz et al. (1977)
USA	52		ND - 0.563 (0.173)	Zavon et al. (1969)

found in human milk (Savage, 1976). Whole milk had much higher levels of organochlorines than colostrum and this finding was attributed to the higher lipid content of whole milk (Miller et al., 1979).

The distribution of heptachlor epoxide, in mg/kg, in tissues obtained from autopsied stillborn infants was: adipose tissue, 0.32; spinal cord, not detected (ND); brain, 0.13; adrenals, 0.73; lungs, 0.17; heart, 0.80; liver, 0.68; kidney, 0.70; spleen, 0.35; pancreas, ND; umbilical cord blood, 0.0011 (Curley et al., 1969).

6. STUDIES ON EXPERIMENTAL ANIMALS

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

The toxicity and the residue data on heptachlor including some unpublished studies have been reviewed several times by international bodies such as FAO/WHO, IARC, IRPTC, and CEC. For their conclusions, refer to section 8.4.

The USSR literature on the toxicity of heptachlor has been reviewed by IRPTC (1982).

6.1 Short-Term Exposures

The acute toxicity of heptachlor in several animal species according to different routes of exposure, is summarized in Table 6. The symptoms associated with heptachlor poisoning include hyper-excitability, tremors, convulsions, and paralysis. Liver damage may occur as a possible late manifestation (Gleason et al., 1969).

The acute toxicity of heptachlor epoxide is greater than that of heptachlor; for instance, the intravenous lethal doses for heptachlor and heptachlor epoxide are 40 and 10 mg/kg body weight, respectively (FAO/WHO, 1967).

The acute oral LD_{50} values of 4 other heptachlor metabolites (chlordene, 3-chlordene, 1-hydroxychlordene, and chlordene epoxide) were found to be greater than 4600 mg/kg body weight (Mastri et al., 1969).

When technical grade heptachlor was fed to broiler chickens during the first 8 weeks of life at dietary levels up to 0.3 mg/kg, no adverse effects on health were observed (Wagstaff et al., 1977).

Heptachlor was fed to adult male rats at a level of 20 mg/kg diet for 12 weeks (Shain et al., 1977). Effects were noted on body weight gain and food consumption and the cytoplasmic androgen receptors of the ventral prostate were less numerous than in controls.

Rats fed heptachlor at 0, 5, or 10 mg/kg body weight for 8 months showed proliferation of the smooth endoplasmic reticulum and an increased number of mitochondria in liver cells, even at 5 mg/kg (Stemmer & Hamdi, 1964).

6.2 Long-Term Exposures

Rat

Four groups of 10 male and 20 female rats were given daily oral doses of pure heptachlor, at 0, 5, 50, or 100 mg/kg body

Table 6. Acute toxicity of heptachlor

Species	Sex	Route of administration	LD_{50}(mg/kg body weight)	Reference
rat	M	oral	40	NIOSH (1978)
rat	M	oral	100	Hayes (1963)
rat	F	oral	162	Hayes (1963)
rat	M	dermal	195	Hayes (1963)
rat	F	dermal	250	Hayes (1963)
rat	NS	dermal	119	NIOSH (1978)
rat	NS	ip	27	NIOSH (1978)
rat	NS	percutaneous	195 - 250	FAO/WHO (1963)
rat	NS	oral	80 - 90	Gleason et al. (1969)
mouse	NS	oral	68	NIOSH (1978)
mouse	NS	iv	40	FAO/WHO (1967)
rabbit	NS	oral	80 - 90	Gleason et al. (1969)
guinea-pig	NS	oral	116	NIOSH (1978)
hamster	NS	oral	100	NIOSH (1978)
chicken	M	oral	62	Sherman & Ross (1961)

weight, starting at about 4 months of age (Pelikan et al., 1968). Administration was continued for 200 days or until the animals died. By the tenth day, all the animals in the groups fed 50 or 100 mg/kg had died. On day 200, the surviving animals in the 5 mg/kg group and the control group were sacrificed for autopsy. Prior to death, the 50 and 100 mg/kg groups became irritable and had accelerated respiration by the second day. Convulsions preceded deaths. In the group given 5 mg/kg, no clinical abnormalities were seen until the 50th day, when hyper-reflexia, dyspnoea, and convulsions were observed. Two males and two females in this group died before completion of the study, compared with only one female in the controls. Weight gain was not affected by administration of 5 mg/kg. Gross pathology revealed changes in the liver, kidney, and spleen. Histological examination showed fatty

degeneration of the liver cells and moderate fatty infiltration of the epithelium of the renal tubules, as well as hyperplasia of the smooth endoplasmic reticulum of the parenchymatous cells of the liver in the group fed 5 mg/kg.

The addition of heptachlor (up to 45 mg/kg diet) or its epoxide (up to 60 mg/kg) or both to the diet of rats for 140 days produced microscopic liver changes, e.g., enlarged centrilobular cells showing big nuclei with prominent nucleoli, cytoplasmic fat droplets, and occasional cytoplasmic margination (Stemmer & Jolley, 1964). In a study involving 269 rats, it was demonstrated that these changes regressed after withdrawal of the pesticide. Electron microscopic studies demonstrated an increase in rough and smooth endoplasmic reticulum (Stemmer & Hamdi, 1964).

Groups of 10 rats (males or females) were fed diets containing heptachlor epoxide at 5, 10, 20, 40, 80, 160, or 300 mg/kg for 2 years (Velsicol Corp., unpublished data, 1959). Concentrations of 80 mg/kg or higher resulted in 100% mortality in 2 - 20 weeks. All the female animals given 40 mg/kg died within a period of 54 weeks. This concentration had no effect on the mortality of the male animals up to 104 weeks. Diets containing 20 mg/kg or less did not produce any signs of illness in male or female rats during a 2-year period, but an increase in liver weight was observed in male rats dosed with more than 10 mg/kg and in females administered 5 mg/kg.

In groups of 20 CFW strain rats fed heptachlor epoxide in the diet at 10, 20, and 40 mg/kg for 2 years, significant increases in mortality were observed only in females at the 40 mg/kg level (Velsicol Corp., unpublished data, 1959). Liver weights in the females were slightly increased. Tumour incidence was lower in the treated groups than in the controls and was independent of the content of heptachlor epoxide in the diet.

Groups each comprising 25 male and 25 female rats were fed 0, 100, 250, 500, 1000, or 2000 mg of the heptachlor metabolite 1-hydroxychlordene per kg diet for up to 224 days (Ingle, 1965). A rat of each sex was sacrificed at intervals for autopsy. After receiving the test diet for 110 days, 3 females from each dose level were selected and mated with males from the same dose level. Growth and food consumption were normal at all levels, and mortality appeared to be unaffected by the test compound. At 2000 mg/kg, the compound may have produced intestinal irritation. Within the one generation, no adverse effects were observed on fertility, litter size, litter weight, or survival and growth of the young at any dose level. Gross pathological findings were limited to one hepatoma in a female fed 2000 mg/kg and one in a male fed 500 mg/kg; one female at 100 mg/kg had a parotid

gland tumour. A breast tumour was seen in a control animal. Histopathology revealed changes in the liver only, which, at 1000 and 2000 mg/kg, showed slight to moderate cytoplasmic margination; this was also evident, to some extent, in the controls and lower-level groups. It was doubtful whether the hepatic cell enlargement that occurred was related to 1-hydroxychlordene.

The Joint Meeting on Pesticide Residues (JMPR) reviewed the toxicity data on heptachlor in its 1970 meeting (FAO/WHO, 1971) and concluded on the following "no-effect-levels":

- rat: 5 mg/kg diet (equivalent to 0.25 mg/kg body weight per day); and

- dog: 2.5 mg/kg diet (equivalent to 0.06 mg/kg body weight per day).

Dogs

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

Three dogs given heptachlor epoxide orally, at 2, 4, or 8 mg/kg body weight per day for 5 days a week, died after 22, 10, and 3 weeks, respectively. Daily oral doses of 0.25 and 0.5 mg/kg body weight did not produce any signs of illness during 52 weeks, but 0.25 mg/kg, estimated to be equivalent to 6 mg/kg diet, was reported to be the minimal dose producing a pathological effect (Velsicol Corp., unpublished data, 1959).

Diets containing 0.5, 2.5, 5.0, or 7.5 mg heptachlor epoxide per kg diet were given to groups of 5 dogs (2 males and 3 females, 23 - 27 weeks of age) for 60 weeks (Velsicol Corp., unpublished data, 1959). No deaths attributed to heptachlor epoxide occurred. The weights of the male dogs increased in inverse proportion to the concentration of the compound in the diet. The weights of the females were normal. Liver weights were increased at 5 mg/kg and above. Degenerative liver changes were seen in only 1 dog at 7.5 mg/kg diet.

Pigs

Pigs were dosed orally with heptachlor at levels of 2 or 5 mg/kg per day for up to 78 days (Dvorak & Halacka, 1975). Ultrastructural changes were observed in the liver of the low-dose group, after 78 days. These changes consisted of glycogen depletion and proliferation of agranular endoplasmic reticulum. At the higher dose level, similar changes were seen as early as 27 days after the start of exposure.

6.3 Reproduction Studies and Teratogenicity

The continuous exposure of rats to doses of either heptachlor or its epoxide exceeding 7 mg/kg increased the mortality rate of the pups during the suckling period, though 10 mg/kg fed to 3 generations of rats did not produce any adverse effects on reproductive capacity, growth, or survival (Witherup et al., unpublished data, 1955).

Male and female rats fed exclusively on diets containing a mixture of heptachlor and heptachlor epoxide (3:1) at 0, 0.3, 3, or 7 mg/kg were mated throughout three succeeding generations (Witherup et al., 1976a). The number of pregnancies in the F_1 and F_2 generations was slightly reduced in the 0.3 mg/kg group, but not in the higher dose level groups. There was a slight increase in the mortality rate of the pups in the second and third week after birth in the 3 mg/kg group. The compound did not exert any statistically significant effect on the fertility of the progenitors or the ability of the progeny to survive.

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

The feeding of rats at 1 - 10 mg/kg body weight per day during a 3-generation reproduction study resulted in an increased number of resorptions and in lower viability and lactation indices (Cerey & Ruttkay-Nedecka, 1971; Ruttkay-Nedecka et al., 1972). Cataracts were observed in test animals. Heptachlor has also been shown to block or shorten the estrous cycle in rats (Cerey et al., 1977).

In a 3-generation reproduction study, a group of 80 rats was given heptachlor at 6.9 mg/kg body weight, daily, for 3 months before mating (FAO/WHO, 1967a). Cataracts were found in 6.8% of the young and became obvious between the 19th and 26th day after birth. Among the parents, 15.2% of the animals were affected, and the lesions appeared after 4 - 9 months. Another effect was a decrease in litter size.

Twenty-four male and 24 female adult beagle dogs were used for a 2-generation reproduction and teratology study with heptachlor epoxide. The treated dogs were fed the compound at 1, 3, 5, 7, or 10 mg/kg diet. No differences in body weight or food consumption were seen between control and treated dogs. All but one of the F_1 pups at the 10 mg/kg dietary level died between birth and 10 weeks of age. Abnormal haematological values were reported in some pups at the 1, 3,

and 7 mg/kg levels. Elevated liver enzyme values were also noted in some animals at the 3, 5, and 7 mg/kg levels. No compound-related abnormalities were observed in pups from the F_1 and F_2 generations. An increase in liver weight among $P_2(F_1)$ dogs from the 7 mg/kg level was the only organ weight variation considered compound related. Finely granular "ground glass" cytoplasm in liver parenchymal cells of some $P_2(F_1)$ dogs at the 5, 7, and 10 mg/kg dietary levels was also reported (IRDC, 1973).

Pregnant female rabbits were treated orally with heptachlor epoxide at 0 (22 animals) or 5 mg/kg body weight/day (20 animals) from day 6 to 11 of gestation (Wazeter et al., 1969) and fetuses recovered by Caesarean section on day 28. There were no behavioural abnormalities apparent in the offspring, and body weight gain was not affected by heptachlor epoxide. There were no deaths. No compound-related effects were observed with respect to numbers of viable and non-viable term fetuses, resorptions, implantation sites, corpora lutea, and non-gravid females. A significant increase in fetal weight was evident in the treated group; this increase was considered to be compound-related. Survival time was not considered to be affected by heptachlor epoxide. There were no teratogenic effects attributable to the compound.

Groups comprising 4 male and 20 female chickens were fed heptachlor epoxide dietary levels of 0, 0.02, 0.1, or 0.2 mg/kg for 25 weeks (Wolvin et al., 1969). Body weight increase was not affected by heptachlor epoxide. Mortality rates were low in all groups, but a slightly higher incidence occurred in the 0.2 mg/kg group. No abnormal behaviour was observed. The total weekly egg production and mean weekly egg weights were not significantly different in the test and control groups. Hatchability was slightly decreased in the groups fed 0.1 and 0.2 mg/kg; viability of the offspring was not affected. A 12% reduction in hatchability resulted when 1.5 mg heptachlor was injected into fertile eggs (Smith et al., 1970); however, no abnormal chicks resulted. Japanese quail were given heptachlor in the diet at 10 and 50 mg/kg (Shellenberger et al., 1966). There were no obvious adverse effects on reproduction when the birds were 10 weeks of age.

6.4 Mutagenicity

Heptachlor was shown to be non-mutagenic in *Salmonella typhimurium* and *Escherichia coli* in the presence or absence of rat liver microsomal preparations (Marshall et al., 1976; Moriya et al., 1983). Heptachlor was not active in the *rec* assay with *Bacillus subtilis* (Shirasu et al., 1976).

Heptachlor did not induce X-linked recessive lethals in post-meiotic germ-cells from Drosophila melanogaster (Benesh & Shram, 1969).

The ip administration of heptachlor at 5.2 mg/kg body weight to male mice caused an increase in the frequency of chromosomal aberrations in bone-marrow cells (Markaryan, 1966).

Rats fed 1 or 5 mg/kg heptachlor diet for 3 generations showed an increased incidence of abnormal mitosis in bone-marrow cells in the second and third generations (Cerey et al., 1973).

After a single intraperitoneal administration of heptachlor to albino male mice at a dose of 5.2 mg/kg body weight in oil solution, the cytogenic analysis of bone-marrow cells, performed 21 h after administration of heptachlor revealed an increase of up to 13.75% in the incidence of nuclear lesions, and up to 9.17%, in the incidence of chromosome aberrations (Markaryan, 1966).

After a 7-month intragastric administration of heptachlor to albino rats at doses of 1/30, 1/50, and 1/100 of LD_{50} (LD_{50} = 82 mg/kg body weight), it was established that heptachlor doses of 1/30 and 1/50 of LD_{50} elicited changes in the mitotic activity of bone-marrow cells, inhibition of prophase, and chromosome adhesion. Chromosome fragments were found in a few cells. A heptachlor dose of 1/100 of the LD_{50} exerted a slight effect on rat bone-marrow cells (Kulakov & Efimenko, 1974).

Male mice dosed either orally or intraperitoneally with a mixture of heptachlor and heptachlor epoxide (1:3) at levels of 7.5 or 15 mg/kg body weight failed to show any dominant lethal response (Arnold et al., 1977).

Heptachlor was also negative in tests designed to monitor testicular DNA synthesis in mice (Seiler, 1977) and in in vitro breakage of plasmid DNA in E. coli (Griffin and Hill, 1978).

More recent studies on animal and human cells in culture have shown that heptachlor is not mutagenic or only weakly mutagenic (Maslansky & Williams, 1981; Tong et al., 1981). Further work by Telang et al. (1982) showed that heptachlor 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. (1982) proposed that heptachlor was exhibiting properties exerted by many promoting agents.

6.5 Carcinogenicity

CFN rats were fed heptachlor epoxide in the diet at concentrations of 0.5, 2.5, 5, 7.5, or 10 mg/kg (FAO/WHO, 1967). No differences were observed among the 5 experimental

groups, and the results can be considered together for all the test animals. The incidence of tumour-bearing animals was 8/23 (34%) and 13/24 (54%) in the control males and females, respectively, and 65/111 (58%) and 92/114 (80%) in the test groups of males and females, respectively. Again, many tumours were located in endocrine organs. Liver tumours were observed in 7 males and 12 females in the test groups only (overall incidence 19/225, i.e., 8.4%). Only 2 of the liver tumours were malignant.

Heptachlor dissolved in ethanol was added to the diet of CF rats at 1.5, 3, 5, 7, and 10 mg/kg for 110 weeks. Each group included 40 animals (20 of each sex). Mortality rates were comparable in all groups. The number of tumour-bearing animals was 16/40 at 0 mg/kg, 9/40 at 1.5 mg/kg, 13/40 at 3 mg/kg, 12/40 at 5 mg/kg, 15/40 at 7 mg/kg, and 12/40 at 10 mg/kg. Most tumours were found in the pituitary and other endocrine organs. No liver tumours were recorded. No preferential tumour site was observed in any particular group except for 4 thyroid tumours that were observed in the 7 and 10 mg/kg groups (Witherup et al., unpublished data, 1955).

In a study carried out on a total of 154 female rats, a mixture of heptachlor and heptachlor epoxide (3:1) was added to the diet at 0, 5, 7.5, 10, and 12.5 mg/kg, for 2 years (Velsicol Corp., unpublished data, 1959). Pituitary and mammary tumours were seen at all dose levels and in the controls; the incidence of the tumours varied from group to group but was not dose-related. At the end of the 2 years, all groups including the controls showed histological changes in the liver, i.e., hypertrophy, cytoplasmic margination, and the appearance of lipid vacuoles in the centrilobular cells. The severity of the changes was related to the dose. At 12.5 mg/kg, regenerative liver changes were present. The no-observed-adverse-effect level was 5 mg/kg.

Wistar rats were given 5 doses of heptachlor in corn oil by stomach tube, at 10 mg/kg body weight, every second day, starting at 10 days of age, until they were sacrificed (Cabral et al., 1972). A sub-group of animals was sacrificed at 60 weeks of age, the other sub-group between 106 and 110 weeks. Growth and survival rates were similar in both test and control groups; the incidence of tumours at different sites in males and females was comparable in both groups.

Heptachlor was tested for carcinogenicity in Osborne-Mendel rats by the National Cancer Institute (1977). Technical grade heptachlor containing 72% heptachlor, 18% γ-chlordane, 2% α-chlordane, 2% nonachlor, 1% chlordene, 0.2% hexachlorobutadiene, and other minor impurities, was fed in the diet at time-weighted average doses of 38.9 and 77.9 mg/kg for male rats, and 25.7 and 51.3 mg/kg for female rats. All surviving rats were killed at 110 - 111 weeks.

Rats treated with high levels of heptachlor showed decreased body weight gain. Mortality rates were dose-related in female rats. No hepatic tumours were observed in rats administered heptachlor. A statistically significant dose-related trend in proliferative follicular-cell lesions of the thyroid was found. The trend towards follicular-cell carcinomas combined with adenomas was significant for the females. The trend towards follicular-cell lesions remained significant when pooled controls were used instead of matched controls and when the data were subjected to life-table adjustment. It was concluded from this study that heptachlor possibly caused thyroid tumours in rats (NCI, 1977), notwithstanding the fact that in the judgement of the (NCI) pathologist, the nature, incidence, and severity of the proliferative thyroid lesions were not sufficient to indicate clearly a carcinogenic effect of heptachlor on rats.

Epstein (1976) reported a study carried out by the FDA in 1965 in which male or female C3H mice were fed heptachlor or heptachlor epoxide for 24 months. The incidences of hepatic nodular hyperplasia and benign hepatomas were doubled in mice treated with heptachlor and heptachlor epoxide. The incidence of hepatic carcinomas was the same in heptachlor-treated and control groups, but double in the group administered heptachlor epoxide. Following histological re-evaluation, a significant excess of liver carcinomas was found in males and females treated with heptachlor or heptachlor epoxide. When all the malignant tumours were considered, the incidence in the controls was approximately twice that of the two test groups.

Epstein (1976) also reviewed an unpublished study carried out in 1973 by the International Research and Development Corporation (IRDC) under contract to the Velsicol Chemical Corporation, where male and female Charles River CD-1 mice were fed a mixture of 75% heptachlor epoxide and 25% heptachlor at levels of 1, 5, or 10 mg/kg diet for 18 months. A dose-related incidence of liver tumours was observed in the test groups. Histological re-evaluation showed an excess of liver carcinomas in females fed 10 mg/kg and in males fed 5 or 10 mg/kg.

In the 1977 study reported earlier, groups of B6C3F1 mice were fed a technical mixture of heptachlor in the diet for 80 weeks at time-weighted concentrations of 6 and 14 mg/kg. Liver carcinomas were found in 34/47 males and 30/42 females receiving the higher dose and in 11/46 males and 3/47 females in the lower dose groups. It was concluded that heptachlor is carcinogenic for the liver of mice.

A committee of the National Academy of Sciences (NAS) in the USA was asked to review all available carcinogenicity data on heptachlor as part of the cancellation hearings.

Heptachlor was found not to be carcinogenic in rats and the target organ site for carcinogenic response in certain strains of mice was confined to 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 or 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" (NAS, 1977).

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

6.6 Other Studies

Heptachlor, when administered to rats at 1 or 5 mg/kg diet for 3 generations, caused changes in their EEG spectra (Formanek et al., 1976). Heptachlor has been shown to inhibit oxidative phosphorylation in rat liver mitochondria (Nelson, 1975), to increase serum esterase (EC 3.1) activity (Crevier et al., 1954), and to induce hepatic mixed-function oxidases in rats (Krampl et al., 1973; Den Tonkelaar & Van Esch, 1974; Krampl & Hladka, 1977; Madhukar & Matsumura, 1979). With respect to the latter, heptachlor was able to induce both aniline hydroxylase (EC 1.14.14) and aminopyrine demethylase (EC 1.5.3) activity at levels as low as 2 mg/kg diet fed for a 2-week period (Den Tonkelaar & Van Esch, 1974). Work carried out in the USSR on the influence of heptachlor on hepatic enzyme systems is reported in Onikienko & Petrun (1962) and Petrun (1962).

Age was a modifying factor for the acute toxic effects of heptachlor. Heptachlor was less toxic in newborn rats than in adult rats (LD_{50} newborn rat, 531 mg/kg; LD_{50} adult, 71 mg/kg) (Harbison, 1973, 1975). Phenobarbital enhanced the acute toxicity of heptachlor in newborn rats (Harbison, 1973).

Heptachlor was less toxic in rats fed a dietary protein level of 10% with unsupplemented gluten, than in animals fed diets containing gluten plus amino acids or casein plus 0.2%

DL-methionine (Webb & Miranda, 1973). When the dietary protein level was raised to 18%, heptachlor was twice as toxic for treated animals compared with animals fed unsupplemented gluten.

7. EFFECTS ON MAN

7.1 General Population Exposure

There is no information on cases of accidental or suicidal poisoning, and no adverse effects due to heptachlor have been reported in the general population.

7.2 Occupational Exposure and Epidemiological Studies

After reviewing 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 chlordane or heptachlor exposure, Infante et al. (1978) reported an anecdotal relationship. However, in a case-control study, no association between blood dyscrasias and occupational exposure to heptachlor was found (Wang & Grufferman, 1981).

Wang & MacMahon (1979a,b) studied one cohort of workers engaged in the manufacture of chlordane, heptachlor, and endrin and another cohort of approximately 16 000 pesticide-spraying personnel, including termite control workers. Both studies showed a deficit of deaths from all cancers but small non-statistically significant excesses of lung, skin, or bladder cancer.

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

Shindell (1981) studied the mortality experience of 783 workers engaged in the manufacture of chlordane and heptachlor. Workers must have had a minimum of 3 months work experience during 1946-76. No increase in mortality rate due to cancer was observed among 124 deaths. Taking into account length of employment (5, 10, 15, 20 years), SMRs for cancer were not increased.

In a retrospective cohort study on workers involved in the production of chlorinated hydrocarbon pesticides, Ditraglia et al. (1981) studied the workers in a plant manufacturing heptachlor; these workers were also studied by Wang & MacMahon (1979a). SMRs for all cancer deaths were lower than expected. 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 pesticide-spraying personnel, including termite control workers. Among 540 deaths for which the cause was ascertainable, small excesses of bladder cancer in termite operators and of skin and lung

cancer in other operators were observed, but these were not statistically significant.

In a follow-up mortality study of workers engaged in the production of heptachlor from 1952-79, the vital status of 207 production workers was ascertained and records were obtained for 90.8% of the population. Three deaths had occurred, none from cancer. No unusual morbidity was observed in persons still living (Shindell & Associates, 1981).

7.3 Treatment of Poisoning

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

(a) Treatment before person is seen by a physician

The person should stop work immediately. Contaminated clothing should be removed, and the affected skin washed with soap and water, if available, and flushed with large quantities of water. If swallowed, vomiting should be induced, if the person is conscious (WHO/FAO, 1975).

(b) Medical treatment

If the pesticide has been ingested, gastric lavage should be performed with 2 - 4 litres of tap water followed by saline purgatives (30 g sodium sulfate in 250 ml of water). Barbiturates (preferably phenobarbitone or pentobarbitone) or diazepam should be given im or iv in sufficient dosage to control restlessness or convulsions. Mechanical respiratory assistance with oxygen may be required. Calcium gluconate, 10% in 10 ml, should be injected iv four hourly. Contraindicated are oily purgatives, epinephrine, and other adrenergic drugs and central stimulants of all kinds (WHO/FAO, 1975).

8. EFFECTS ON THE ENVIRONMENT

8.1 Toxicity for Aquatic Organisms

Data on the toxicity of heptachlor for aquatic organisms are summarized in Table 7. Maximum levels of heptachlor to which aquatic ecosystems could be exposed were calculated to be 0.0038 µg/litre as a 24-h average for salt water species, with 0.52 µg/litre maximum exposure at any time, and 0.0036 µg/litre as a 24-h average for fresh water species, with 0.053 µg/litre maximum exposure at any time (US EPA, 1980).

Generally, the acute toxicity of heptachlor is affected by temperature and salinity. Eisler (1969), using 48-h tests on the grass shrimp Palaemonetes vulgaris, showed a reduction in mortality by increasing the salinity from 12 to 18 °/oo, but no further reduction at salinities up to 36 °/oo. Mortality rates increased with increasing temperature in the range 15 - 30 °C. Bridges (1965) showed a relationship between temperature and 24-h LC_{50} in the redear sunfish. At 7.2 °C, the heptachlor concentration required to kill 50% of the fish in 24 h was 92 µg/litre; this concentration fell consistently over a range of temperatures to 22 µg/litre at 29 °C. No clear effect of salinity or temperature was found in studies on the mummichog Fundulus heteroclitus (Eisler, 1970b).

Long-term exposure of fish to heptachlor usually reduces survival at all life stages (Andrews et al., 1966; Hansen & Parrish, 1977; Goodman et al., 1978) and induces a dose-related growth decrease (Andrews et al., 1966). Adaptation or resistance to heptachlor may develop since a natural population of mosquito fish that received run-off from cotton fields treated with pesticides were 4 times more resistant to heptachlor than newly-exposed fish (Boyd & Ferguson, 1964).

Heptachlor at a concentration of 6.8 mg/litre in the incubation medium was reported to give 50% inhibition of ATPase from liver mitochondria and a concentration of 16.4 mg/litre gave 50% inhibition of Na^+-K^+ ATPase in bluegill brain homogenate (Yap et al., 1975). In studies by Cutkomp et al. (1971), heptachlor at 15.6 mg/litre induced 58.6% inhibition of bluegill brain Na^+-K^+ ATPases, 65.6% inhibition of brain Mg^{2+} ATPase, and 66.3% inhibition of muscle Mg^{2+} ATPase. Heptachlor induced 67% inhibition of Na^+-K^+ ATPases at 37.35 mg/litre in rainbow trout gill microsomes and 70% inhibition of Mg^{2+} ATPase (Davis et al., 1972). Hiltibran (1974) also reported a reduction in oxygen utilization and phosphate utilization by liver mitochondria from bluegill at heptachlor concentrations of 37 mg/litre medium.

Table 7. Toxicity of heptachlor for aquatic organisms[a]

Organism	Flow/ stat	M/U	Grade	°C	pH	Sal °/oo	Endpoint	Parameter	Concentration (µg/litre)	Reference
American oyster (Crassostrea virginica)	flow	M	technical heptachlor (65%)	30-32		24.5-27	reduction of shell deposition	96-h EC_{50}	1.5	Schimmel et al. (1976a)
Cladoceran (Daphnia pulex)	stat	U		16	7.4-7.8		immobilisation	48-h EC_{50}	42	Sanders & Cope (1966)
Scud, 2 months (Gammarus lacustris)	stat	U	technical heptachlor	21	7.1			96-h LC_{50}	29	Sanders (1969)
	stat	U		21	7.1			24-h LC_{50}	150	Sanders (1969)
Stonefly (naiads)	stat	U	technical heptachlor (72%)	15.5	7.1			96-h LC_{50}	0.9 - 1.1	Sanders & Cope (1968)
Hermit crab (Pagurus longicarpus)	stat	U	heptachlor reference	20	8	24		96-h LC_{50}	55	Eisler (1969)
	stat	U	standard	20	8	24		24-h LC_{50}	470	Eisler (1969)
Pink shrimp (Penaeus duorarum)	flow	M	technical heptachlor	27.5-30		25.5-29.5		96-h LC_{50} 44 - 72 mm	0.11	Schimmel et al. (1976a)

Table 7 (contd).

Organism	Flow/ stat	M/U	Grade	°C	pH	Sal °/oo Endpoint	Parameter	Concentration (µg/litre)	Reference
Fathead minnow (Pimephales promelas)	stat	U	technical heptachlor (72%)	25	7.1	20[b]	96-h LC_{50}	130	Henderson et al. (1959)
	stat	U	technical heptachlor	25	8.2	400[b]	96-h LC_{50}	78	Henderson et al. (1959)
Bluegill (Lepomis macrochirus)	stat	U	technical heptachlor (72%)	25	7.1	20[b]	96-h LC_{50}	26	Henderson et al. (1959)
American eel (Anguilla rostrata)	stat	U	heptachlor	20	8	24	96-h LC_{50}	10	Eisler (1970a)
Spot (Leiostomus xanthurus)	flow	M	technical heptachlor (65%)	23-26		20-21	96-h LC_{50}	0.85	Schimmel et al. (1976a)
Rainbow trout (Salmo gairdneri)	stat	U	technical heptachlor (72%)	7.2			96-h LC_{50}	7.0	Macek et al. (1969)

[a] A more comprehensive table listing different conditions and exposure times is available on request from IRPTC, Geneva.

[b] Hardness (mg/litre).

U = Nominal concentration.

M = Measured concentration.

Data on the toxicity of heptachlor epoxide are given in Table 8. Heptachlor epoxide at a concentration of 16.2 mg/litre incubation medium caused 44.9% inhibition of bluegill brain Na^+-K^+ ATPase, 16.7% inhibition of brain Mg^{2+} ATPase, and 46.7% inhibition of muscle Mg^{2+} ATPase (Cutkomp et al., 1971).

8.2 Toxicity for Terrestrial Organisms

The LD_{50}s for heptachlor in birds are presented in Table 9. These data emphasise the variability of toxicity among species. When Japanese quail were fed heptachlor at 10 or 50 mg/kg diet from hatch, there were no obvious adverse effects on growth after 16 weeks or on the reproductive success of these birds at 10 weeks of age (Shellenberger & Newell, 1965). Injection of 1.5 mg heptachlor/egg resulted in a 12% reduction in hatchability but no abnormal chicks (Smith et al., 1970). There are no available data on the toxicity of heptachlor for non-avian species.

Heptachlor epoxide was fed to groups of 4 male and 20 female chickens at dietary levels of 0, 0.02, 0.1, or 0.2 mg/kg for 25 weeks (Wolvin et al., 1969). Body weight increase was not affected by heptachlor epoxide. Mortality rates were low in all groups, and a slightly higher mortality rate recorded for the group fed 0.2 mg/kg was of doubtful significance. No abnormal behaviour was observed. Total weekly egg production and mean egg weights were not affected by treatment. Hatchability was slightly decreased in eggs from the group fed 0.1 and 0.2 mg/kg, but the viability of hatched chicks was not affected.

8.3 Toxicity for Microorganisms

When various microorganisms, isolated from estuarine and surface slicks, were exposed to heptachlor at concentrations up to 100 g/litre and provided with glucose as the main carbon source, growth of two species was affected (Ahearn et al., 1977).

Heptachlor was found to be "highly toxic" to plate cultures of the fungus Rhizoctonia solani, even at low concentrations (Richardson & Miller, 1960). Application of 10 µmol of heptachlor to a liquid culture of a yeast Saccharomyces cerevisiae (haploid strain, D273-10B) caused 100% inhibition of cell growth, when nonfermentable energy sources were provided, and 13% inhibition when fermentable energy sources were provided (Nelson & Williams, 1971). This suggested cell division was inhibited by specific inhibition of oxidative metabolism. Technical heptachlor (74% heptachlor) at 50 µg/litre caused a reduction in cell

Table 8. Toxicity of heptachlor epoxide for aquatic organisms

Organism	Size/ age	Flow/ stat	Grade	Temp (°C)	pH	Sal °/oo	Parameter	Concentration (µg/litre)	Reference
Pink shrimp (Penaeus duroarum)	62-81 mm	flow	99%	24.2-26.5		20	96-h LC_{50}	0.04	Schimmel et al. (1976a)
Cladoceran (Daphnia magna)	24 h	stat	unspecified	18-20	7.9		24-h LC_{50}	120	Frear & Boyd (1967)

Table 9. Toxicity of heptachlor for birds

Species	Sex	Parameter	Concentration[a] (mg/kg)	Reference
Mallard, 3 months	male	acute oral LD_{50}	$\geq$ 2000	Tucker & Crabtree (1970)
Bobwhite quail		oral LD_{50+}	125	DeWitt & George (1960)
Bobwhite quail		dietary LC_{50}	450 - 700	Heath et al., unpublished data (1970)
Ring-necked pheasant		oral LD_{50+}	150 - 400	DeWitt & George (1960)
Pheasant		dietary LC_{50}	250 - 275	Heath et al., unpublished data (1970)
Japanese quail		dietary LC_{50}	80 - 95	Heath et al., unpublished data (1970)
Chicken, 7 - 14 days (New Hampshire)	female	acute oral LD_{50}	62.4	Sherman & Ross (1961)

[a] Concentration in mg/kg body weight for oral dosing; concentration in mg/kg diet for dietary dosing.

density in a culture of the marine dinoflagellate Exuviella baltica resulting in a reduction in chlorophyll a concentration (Magnani et al., 1978). As levels of chlorophyll a per cell were not significantly different in treated and untreated cultures, the observed inhibition of C^{14} uptake per treated cell was probably due to interference with chlorophyll function rather than its synthesis.

A haploid strain (D273-10B) of Saccharomyces cerevisiae in the early log phase of growth was exposed to 10 µmol of heptachlor epoxide (dissolved in dimethyl sulphoxide and added to the growth medium) for 20 h (Nelson & Williams, 1971). Heptachlor epoxide caused a 16% inhibition in growth when glucose (a fermentable substrate) was the energy source provided, and a 79% inhibition when lactate (a non-fermentable substrate) was the energy source. This suggested that inhibition of yeast growth by heptachlor epoxide was due to interference with oxidative metabolism.

8.4 Bioaccumulation and Biomagnification

Data on bioconcentration are summarized in Table 10. A weighted average bioconcentration factor for the edible portion of freshwater and estuarine aquatic organisms consumed by Americans was calculated to be 11 200 (US EPA, 1980). Fish fed continuous levels of heptachlor developed the highest residues at 56 days (Andrews et al., 1966). Lethality through biomagnification was demonstrated when crayfish died after feeding on tubificid worms that had been exposed to heptachlor at 1.5 µg/litre (Naqvi, 1973). However, worms placed in clean water after exposure to heptachlor (even after exposure to the higher dose of 3.75 µg/litre) were not lethal for crayfish. Although marine molluscs show a very high concentration of heptachlor, residues are rarely found in wild populations (Modin, 1969).

Data on the bioaccumulation of heptachlor epoxide are given in Table 11.

Po-Yung Lu et al. (1975) examined the fate and distribution of ^{14}C-heptachlor and metabolites in food chain organisms in two laboratory model ecosystems and in vitro by sheep liver microsomes. They found that chlordene and heptachlor undergo rapid epoxidation and are also hydroxylated at C_1 to form the corresponding hydroxy analogues. Heptachlor epoxide, however, is highly stable in biological systems. The rates of conversion and degradation of these compounds are influenced by microsomal oxidases, photolysis, and chemical hydrolysis. The relative balance of the epoxidation and hydroxylation determines the magnitude of persisting residues in the environment.

Table 10. Bioaccumulation of heptachlor[a]

Organism	Flow/ stat	Grade	Temp (°C)	Sal °/oo	pH	Duration	Concentration factor[b]	Organ	Reference
American oyster (Crassostrea virginica)	flow	technical				10 days	17 600	tissues	Wilson (1965)
Fathead minnow, adult (Pimephales promelas)	flow	heptachlor	20		7.5	32 days	9500	whole body	Veith et al. (1979)
Sheepshead minnow, juvenile (Cyprinodon variegatus)	flow	technical[c] heptachlor	28 - 32			28 days	3600	whole body	Goodman et al. (1978)
Spot, 20 - 40 mm, juvenile (Leiostxanthurus)	flow	technical heptachlor	23.5-26.5	18.5-21.5		24 days	1038 - 2816	edible tissue	Schimmel et al. (1976b)
Spot, 20 - 40 mm, juvenile (Leiostxanthurus)	flow	technical hetpachlor	23.5-26.5	18.5-21.5		24 days	2154 - 5126	whole body	Schimmel et al. (1976b)

[a] A more comprehensive table is available on request from IRPTC, Geneva.
[b] Concentration of heptachlor in tissue: concentration of heptachlor in water.
[c] Technical material: 65% heptachlor, 22% γ-chlordane, 2% α-chlordane, 2% nonaclor, 9% others.

Table 11. Bioaccumulation of heptachlor epoxide

Organism	Flow/ stat	Grade	Temp (°C)	Sal °/oo	pH	Medium	Duration	Concentration factor	Organ	Reference
Pink shrimp, 62-81 mm (*Penaeus duorarum*)	flow	99%	24.2-26.5	20		marine	96 h	200 - 1700[a]	whole body	Schimmel et al. (1976b)
Fathead minnow, adult (*Pimephales promelas*)	flow		20		7.5	fresh	32 days	14 400	whole body	Veith et al. (1979)

[a] Concentration in tissue: concentration in water.

8.5 Population and Community Effects

In 4 farms surveyed after treatment with heptachlor at 2.24 kg ai/ha, the following wildlife deaths were recorded: 53 mammals from 12 species, 222 birds from 28 species, 22 reptiles from at least 8 species, many fish from more than 8 different species, many miscellaneous frogs and many crayfish (Smith & Glasgow, 1963). There was considerable variation in the amounts of heptachlor and its epoxide found in the tissues of these dead animals. During a 2-year study on the effects on wild birds of a programme of fire ant control (in which heptachlor was applied at 0.28, 0.56, and 2.24 kg ai/ha), disappearance of arthropods and changes in bird behaviour and mortality rates were recorded soon after application of heptachlor (Ferguson, 1964). Nesting and ground dwelling insectivorous birds were most severely affected. Fairly complete recovery of bird and insect populations has frequently been reported. In a study area that was part of approximately 10 million ha treated with heptachlor at 2.24 kg ai/ha, nesting success of ten species of bird was 45.4% in the year following application compared with a success rate of 65% in an untreated area (Smith & Glasgow, 1963). Quail populations were still depressed 3 years after application of 2.24 kg ai/ha (Rosene, 1965). Application of 0.56 kg/ha caused a temporary decline in numbers. Bobwhite quail were introduced to areas immediately after application of heptachlor at 2.24 kg, 1.40, 0.28, and 0.14 kg/ha. Heptachlor at 1.40 and 2.24 kg/ha caused severe mortality among pairs of adult birds introduced successively during the first 15 days of application (61% died when exposed to 2.24 kg ai/ha, 53% at 1.40 kg/ha, 15% at 0.28 kg/ha and there were no deaths at 0.14 kg/ha). After the first 15 days, the mortality rate declined rapidly and was undetectable after 45 days (Kreitzer & Spann, 1968). In 2 months following an aerial application of heptachlor granules in a forest preserve, more than 300 birds of various species were found dead; 39 of these were banded birds, compared with a normal yearly recovery of 3 - 4 banded birds (Bartel, 1960). Considerable bird mortality was recorded following application of granules containing 10% heptachlor at 33.6 kg/ha to control sugarcane root weevil (Oberhau, 1971). The level of residues of heptachlor in bird carcasses indicated death from heptachlor poisoning.

In an aquatic ecosystem, application of heptachlor at 1 mg/litre caused a 94.4% decrease in productivity in natural phytoplankton communities within 4 h of initial exposure (Butler, 1963).

8.6 Effects on the Abiotic Environment

No data are available on the effects of heptachlor on the abiotic environment.

8.7 Appraisal

In some studies on the aquatic toxicity of heptachlor, concentrations exceeding its solubility in water (56 µg/litre at 25 - 29 °C) have been used. Therefore, the dose to which organisms were exposed is unknown. In studies where technical material has been used, the toxic effects attributed to heptachlor may be due to the other cyclodiene insecticides present in the formulation or be influenced by synergistic or antagonistic interactions between them.

Data on the toxicity of heptachlor epoxide are very sparse. The few data that do exist indicate that it is equally toxic and more persistent than the parent compound.

9. PREVIOUS EVALUATIONS OF HEPTACHLOR BY INTERNATIONAL BODIES

IARC (1979) concluded that there is sufficient evidence that technical grade heptachlor is carcinogenic in mice and that there is limited evidence that heptachlor epoxide is carcinogenic in experimental animals. IARC (1982) later concluded that there is limited evidence for the carcinogenicity of heptachlor in experimental animals and that human data available "do not allow an evaluation of the carcinogenicity of heptachlor or heptachlor epoxide to humans to be made".

The Joint Meeting on Pesticide Residues (JMPR) reviewed residues and toxicity data on heptachlor on several occasions in 1965, 1966, 1967, 1968, 1969, and 1970 (FAO/WHO, 1965, 1967b, 1968, 1969, 1970, 1971). In 1970, it estimated the acceptable daily intake (ADI) for man at 0 - 0.0005 mg/kg body weight. This was based on no-observed-adverse-effect levels of:

5 mg/kg diet, equivalent to 0.25 mg/kg body weight/day in the rat, and

2.5 mg/kg diet, equivalent to 0.06 mg/kg body weight/day in the dog.

WHO has recommended a guideline value of 0.1 µg/litre for heptachlor and heptachlor epoxide in drinking-water (WHO, 1982).

WHO (1984) classified heptachlor as moderately hazardous.

The WHO/FAO (1975), in its series of data sheets on pesticides, issued one on heptachlor. Based on a brief review of the use, exposure, and toxicity of the compound, practical advice is given on labelling, safe-handling, transport, storage, disposal, decontamination, selection, 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 can be obtained from the IRPTC (International Register of Potentially Toxic Chemicals) Legal File (IRPTC, 1983).

IPRTC (1982), in its series "Scientific reviews of Soviet literature on toxicity and hazards of chemical", issued a review on heptachlor.

The CEC (1981) reviewed the data available on heptachlor in 1981.

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

10.1 Heptachlor Toxicity

The acute toxicity of heptachlor is moderate (the oral LD_{50} in the rat ranges from 40 to 162 mg/kg body weight). It is readily absorbed via all routes of exposure and rapidly metabolized. On repeated exposure, heptachlor epoxide may accumulate in the body, mainly in adipose tissue. Toxic symptoms are related to CNS-hyperactivity and include tremors and convulsions. In experimental animals, prolonged low-level exposure resulted in the induction of hepatic microsomal enzymes and at a later stage in liver hypertrophy with histological changes. At higher levels, heptachlor is hepatotoxic (section 6.3).

Heptachlor was not a teratogen in the tests conducted but at higher exposure levels it may interfere with reproduction and the viability of the offspring.

Heptachlor is not generally active in short-term tests for genetic activity. There is evidence that it may have an effect on cell to cell communication which is a property of promoting agents.

There is limited evidence for the carcinogencity of heptachlor and heptachlor epoxide in experimental animals. No cases of adverse effects or occupational poisoning have been reported.

10.2 Exposure to Heptachlor

For the general population, food is the major source of exposure to heptachlor, but residue intake in most countries is below the advised acceptable daily intake. In areas where heptachlor is used, inhalation and drinking of well-water may account for some additional exposure.

Relatively high concentrations of heptachlor epoxide can be found in human milk, especially in areas with high heptachlor exposure in the general population.

Occupational exposure, especially via the skin and via inhalation, can be considerable when the material is handled in installations or in situations where safety precautions are insufficient.

10.3 Evaluation of Overall Environmental Effects

In soil, heptachlor is persistent and relatively immobile. Heptachlor itself may be lost from the soil by slow vapourisation, by oxidation to heptachlor epoxide (a more

persistent degradation product of comparable toxicity), by photoconversion to photo-heptachlor, or by conversion to less toxic metabolites by soil bacteria. The rate at which heptachlor is lost by these various mechanisms is influenced by climate, soil type, and management practices (retention being longest in undisturbed soil). Heptachlor shows little movement within the soil, the majority of heptachlor residues being found in the top few centimetres. These residues are most likely to be spread by dust particles in air currents.

Although there is no indication of widespread contamination of water by heptachlor, its residues have been found in fish from various bodies of water. Heptachlor is not very soluble in water and persists in aquatic ecosystems by being absorbed onto sediments. It has been shown to be toxic to aquatic life, but its toxicity is highly species variable. This is particularly so for marine vertebrates where acute LC_{50} values span three orders of magnitude. Marine crustacea are particularly sensitive to heptachlor; concentrations of 0.03 µg/litre may be lethal. Younger life stages of both fish and invertebrates are the most sensitive to heptachlor, "safe" concentrations being 0.1 and 0.01 µg/litre, respectively. Evaluation of the toxicity of heptachlor for wildlife depends solely on extrapolation from studies on game birds and domestic species. In these animals, toxicity is variable, with LD_{50} values ranging from 6 to 531 mg/kg body weight. Heptachlor is generally classified as a neurotoxin.

Uptake of heptachlor is fairly rapid. Superficially, clearance of heptachlor in animals is rapid and complete, but the major storage product, heptachlor epoxide, persists much longer. The relative amount of heptachlor epoxide in tissues increases with length of exposure. Few data are available on the toxicity of this metabolite, but indications are that it is of comparable toxicity to heptachlor. Its marked persistence in the environment and its tendency to accumulate in body fat make it a serious environmental hazard.

10.4 Evaluation of Risks for Human Health and the Environment

Although there is no evidence that incriminates heptachlor 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:

(a) 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 heptachlor.

(b) For the general population, consumers should not suffer any adverse effects from heptachlor residues in food, provided that the intake is kept within the ADI set by the Joint FAO/WHO Meeting.

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

The intake of heptachlor residues transferred to breast-fed infants through human milk, in areas of high heptachlor use, remains a concern.

(c) Environmentally, heptachlor causes concern because of the high sensitivity of several marine species to it and because of the persistence of the metabolite heptachlor epoxide in adipose tissue and in the environment.

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