Canadian Environmental Protection Act

Priority Substances List
Supporting Document

Chlorinated Paraffins

Government of Canada
Environment Canada
Health and Welfare Canada

Gouvernement du Canada
Environnement Canada
Santé et Bien-être social Canada

1993

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1.0 Summary

For the summary of this report, please refer to the Assessment Report.

2.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the Minister of the Environment and the Minister of National Health and Welfare to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess those substances to determine whether they are "toxic" as defined under Section 11 of the Act which states:

> "... a substance is toxic if it is entering or may enter the environment in a quantity or concentration, or under conditions:
>
> (a) having or that may have an immediate or long-term harmful effect on the environment;
>
> (b) constituting or that may constitute a danger to the environment on which human life depends; or
>
> (c) constituting or that may constitute a danger in Canada to human life or health."

Substances that are assessed as "toxic" as defined under Section 11 may be placed on Schedule I of the Act. Consideration can then be given to developing regulations, guidelines, or codes of practice to control any aspect of these substances' life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

The substance "chlorinated paraffin waxes" was included in Group 3 of the Priority Substances List. This term is generally restricted to chlorinated paraffins having long carbon chains. However, the scope of the assessment was broadened to include the short chain and medium chain chlorinated paraffins since they are also of concern due to their potential effects on the environment and human health. In this report, chlorinated paraffins having carbon chain lengths of 13 or less ($\leq$13) are termed "short", those having 14 to 17 carbon atoms (C_{14-17}) are considered to be "medium", and those having 18 or more ($\geq C_{18}$) are considered to be "long". To the extent possible, in each section of this report, these compounds are addressed in this order.

The assessment of whether chlorinated paraffins are "toxic", as defined under CEPA, was based on the determination of whether they **enter** or are likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** or humans or other biota at levels that could cause adverse **effects.**

To identify data relevant to the assessment of effects on human health, literature searches on the following computerized databases were conducted: Medline (1966 to 1989), Hazardous Substances Databank (HSDB), Registry of Toxic Effects of Chemical Substances (RTECS), Integrated Risk Information System (IRIS), Chemical Carcinogenesis Research Information System (CCRIS) (all to January, 1992), Toxlit (1981 to 1992) and EMBASE (1985 to 1992). Data included in an unpublished background document prepared under contract (Mitchell, 1991) were also considered in the preparation of this report.

To identify data relevant to the estimation of exposure of the general

population to chlorinated paraffins, literature searches were conducted in the following computerized databases: Environment Canada Departmental Library Catalogue (ELIAS) (1992), AQUAREF (1970 to 1992), Canadian Research Index (MICROLOG) (1979 to 1992) and Co-operative Documents Project (CODOC) (1992). Dr. G. Jenkins of the Ontario Ministry of Environment, Mr. D. Spink of the Alberta Ministry of Environment and Mr. H. St.-Martin of the Quebec Ministry of the Environment were also consulted in an attempt to identify relevant information on concentrations of chlorinated paraffins in environmental media to which humans are exposed (i.e., drinking water).

With respect to the approach adopted for identification of the data relevant to assessment of risks to the environment, literature searches of the following computerized databases were conducted: Chemistry Abstracts, BIOSIS Previews (1969 to 1992), National Technical Information Service (NTIS) (1980 to 1992), and Pollution and Toxicology Database (POLTOX) (1982 to 1992). Other sources of information were identified through FATERATE and the Chemical Evaluation Search and Retrieval System (CESARS) (1988).

Information on both the environmental and health aspects was also sought from the following agencies:

- Umweltbundesamt, Berlin, Federal Republic of Germany;
- Norwegian State Pollution Control Authority, Oslo, Norway;
- Office fédéral de l'environnement, des forêts et du paysage, Berne, Switzerland;
- National Chemicals Inspectorate, Solna, Sweden;
- National Environmental Protection Board, Solna, Sweden;
- National Board of Waters and Environment, Helsinki, Finland;
- British Industrial Biological Research Association, Surrey, England;
- World Health Organization, Geneva, Switzerland;
- Environmental Protection Agency, Copenhagen, Denmark;
- Environmental Agency, Japan; and
- International Agency for Research on Cancer, Lyon, France.

Every effort was also made to obtain all the detailed reports of an extensive series of studies conducted by the Working Party of the Chlorinated Paraffin Manufacturers Toxicology Testing Consortium which are briefly described in Serrone *et al.* (1987). Assistance in this regard was requested from Dr. D.M. Serrone of Ricerca Inc., Painesville, Ohio, Mr. R.J. Fensterheim of the Chlorinated Paraffins Industry Association, Dr. M.T. Richardson of Imperial Chemical Industries (ICI), U.K. and Mr. R. Zampini of ICI Canada who were unable to provide the requested reports. However, full reports of the studies in this series, which were considered critical to this assessment, were obtained from the United States Environmental Protection Agency (U.S. EPA).

Data relevant to an assessment of whether chlorinated paraffin waxes are "toxic" to human health obtained after completion of the period of peer review of human health-related sections of this report in August 1992 were not considered for inclusion. Similarly, data relevant to an assessment of whether chlorinated paraffins are "toxic" to the environment obtained after completion of the period of peer review of those sections of the report in June 1992 were not considered.

The results of recent investigations and all original studies relevant to the assessment of whether or not chlorinated paraffins are "toxic" under Section 11 of CEPA have been critically evaluated by the following Health and Welfare Canada staff (exposure of the general population and effects on human health), Environment Canada (entry, environmental exposure and effects) and Fisheries and Oceans (environmental exposure and effects):

Environment Canada	Health and Welfare Canada	Fisheries and Oceans
L. Brownlee	P.K.L. Chan	V. Zitko
K.M. Lloyd	M.E. Meek	
	D. Riedel	

Following circulation and external peer review of the health-related sections by staff of British Industrial Biological Research Association (BIBRA) Toxicology International, U.K. and Dr. D.M. Serrone of Ricerca Inc., Painesville, Ohio, they were reviewed and approved by the Guidelines and Standards Rulings Committee of the Bureau of Chemical Hazards of the Department of National Health and Welfare. As part of the review and approval process established by Environment Canada, the environmental sections were peer reviewed by Drs. J.A. Cotruvo, P. Miller, M. Zeeman, and W.S. Rabert of the United States Environmental Protection Agency and Dr. D.C.G. Muir of Fisheries and Oceans. In addition, R. Zampini (ICI Canada) and Dr. M.T. Richardson (ICI U.K.) provided comments on production, uses, sources and releases in Canada (Subsection 5.2).

In this report, the technical information is presented in greater detail than in the published Assessment Report, which contains an extended summary of technical information critical to the assessment, as well as the assessment of whether chlorinated paraffins are "toxic" under CEPA.

Copies of this unpublished Supporting document and the published Assessment Report are available upon request from:

Commercial Chemicals Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Boulevard
Hull, Quebec, K1A 0H3

Environmental Health Centre
National Health and Welfare Canada
Room 104, Tunney's Pasture
Ottawa, Ontario K1A 0L2

3.0 Identity of Substances

3.1 Terminology

Chlorinated paraffins are a class of chlorinated hydrocarbons with the general formula $C_xH_{(2x-y+2)}Cl_y$, with x ranging from 10 to 38, and y from 2 to 33. The latter corresponds to a chlorine content from 30 to 70% on a weight basis. While a chlorinated paraffin may be classified as C_{12}, the actual composition is a range of chain lengths that average C_{12}. Commercial products, of which there are over 200, are complex mixtures of homologues and isomers. The products vary in the distribution, type, and range of chain lengths, and in the degree of chlorination (Serrone *et al.*, 1987).

In the United States chlorinated paraffins are classified as short chain (x = 10-13); intermediate chain (x = 14-17), and long chain (x = 20-30). All of these are further divided according to Cl content into 3 classes: 40-50, 50-60, and 60-70% Cl.

In western Europe, paraffins with n >17 are considered "long chain", and are subdivided into liquid and solid ones. The Cl classes are <30, 31-40, 41-50, 51-60, and 61-70% Cl.

The parent hydrocarbon backbone may range from kerosine-gas oil fractions of petroleum to very pure straight chain paraffins and this adds to the complexity of chlorinated paraffin mixtures in commerce. This complexity is only partly reflected in the various CAS numbers assigned to chlorinated paraffins, some of which are listed below:

CAS Number	Name
51990-12-6	Chlorowax
61788-76-9	Alkanes, chloro; chloroparaffins
63449-39-8	Par waxes and h/c waxes, chlorinated
68920-70-7	Alkanes, C_{6-18}, chloro
85422-92-0	Paraoils, chlorinated
85535-84-8	Alkanes (C_{10-13}), chloro (50-70%)
85535-85-9	Alkanes (C_{14-17}), chloro (40-52%)
85535-86-0	Alkanes (C_{18-28}), chloro (20-50%)
97553-43-0	Normal paraffins x >10, chloro
108171-27-3	C_{23}, 43% chlorine
108171-26-2	C_{12}, 60% chlorine

Chlorinated paraffins are marketed under numerous tradenames (e.g. Cereclor, Chlorez, Chlorowax, Chlorparaffin, Witaclor, Chlorflo, Paraoil, Unichlor). A detailed list of the name, chain length and degree of chlorination of several chlorinated paraffin waxes is presented in Mukherjee (1990).

3.2. Analytical Methodology

High molecular weight, very high number of isomers and congeners, low volatility, non-polar character and loss of hydrochloric acid or chlorine at elevated temperature make the measurement of low concentrations of chlorinated paraffins very difficult. The response of electron capture and of flame ionization detectors to chlorinated paraffins is very low, the former perhaps due to decomposition in the injection port and co-elution of many individual congeners, and the latter because it responds only to the carbon chain and not

to the chlorine atoms.

The non-polar character of chlorinated paraffins as well as their high molecular weight cause problems in the separation, mainly from biological matrices. Jansson *et al.*, (1991) have exploited this to develop a method of separation of chlorinated paraffins from other organochlorines using gel permeation chromatography.

Hollies *et al.* (1979) used a thin layer chromatography method with argentation of the chlorine atoms for quantitation in environmental samples. This method is chlorine dependent and has a limit of detection of 0.5 ng/L for water and 50 ug/kg for sediments and biota. It can distinguish long chain and shorter chain length with chlorine contents of 42-45%. It has been used by some investigators (e.g., Campbell and McConnell, 1980) to study chlorinated paraffins in environmental media.

The current method of choice is gas chromatography with negative ions chemical ionization mass spectrometry, used successfully in only a few laboratories. It can differentiate between various chain lengths and chlorine content and is less affected by uncontrollable interferences. This method is described in Schmid and Müller (1985) and by Jansson *et al.* (1991) for detection of trace levels of chlorinated paraffins in human and environmental samples.

4.0 Physical and Chemical Properties

The melting point of chlorinated paraffins increases with increasing carbon chain length and with increasing content of chlorine. Consequently, at room temperature, chlorinated paraffins range from being colourless to yellowish liquids at about 40% chlorine, to white solids (softening point at about 90°C) at 70% chlorine. Log K_{ow} values, measured by reverse phase high performance thin layer chromatography, are very high ranging from about 5 to 12 (Renberg *et al.*, 1980). Their density ranges from about 1.16 to 1.63 g/mL. Chlorinated paraffins have very low vapour pressures (<10 Pa) (Campbell and McConnell, 1980).

Solubility appears to decrease with increased chlorine content and chain length. Solubility ranges from 3.6 - 6.6 μg/L for the long chain mixtures (C_{20-30}) to 95 - 470 μg/L for the short chain mixtures (C_{10-13}). The solubility of four specific chlorinated paraffin substances (i.e. not a commercial mixture) at 19°C was determined by Madeley and Gillings (1983). The substances tested were 59% chlorinated n-undecane-6-^{14}C, 51% chlorinated n-pentadecane-8-^{14}C, and two long chain paraffins: 43% chlorinated n-pentacosane-13-^{14}C, and 70% chlorinated n-pentacosane-13-^{14}C. Based on parent compound analyses, the solubilites were 150, 5, <5 and <5 μg/L, respectively. These values were slightly lower than those estimated using radioactivity measurements. The discrepancy was thought to be caused by some breakdown of the parent compound during the course of the test. Chlorinated paraffins are generally well soluble in non-polar organic solvents.

Chemically, chlorinated paraffins are fairly stable compounds, but not as stable as polychlorinated biphenyls (PCBs) and can be dechlorinated or dehydrochlorinated with relative ease at elevated temperature (>200°C) or by the action of bases. At 300-400°C extensive decomposition of chlorinated paraffins occurs, whereupon chlorine radicals and HCl are formed (KEMI, 1991). The distribution of chlorine atoms along the hydrocarbon backbone is more or less statistical. Tertiary and secondary carbons are chlorinated more readily than primary carbons, but chlorines on these atoms are also less stable.

5.0 Production, Use and Releases to the Environment

5.1 Natural Sources

Chlorinated paraffins are not known to occur naturally.

5.2 Man-made Sources

5.2.1 Production

ICI Canada is the only domestic producer, operating a 5-kt/year plant in Cornwall, Ontario, although this facility has been running well below capacity for a number of years. For example, production in 1990 was estimated at 2.9 kt, and in 1992, 4 kt. The company's products are sold under the trade name Cereclor. The products manufactured are Cereclor S-52, S-52HV, S-45, C-42, C-42SS and 51-L. Refined paraffin wax is used in the manufacture of Cereclor C-42 and C-42SS. n-paraffin oil is used in the manufacture of S-45, 51-L,, S-52 and S-52HV. Examples of chemical formulas of these substances are: Cereclor S-52: $C_{15}H_{26}Cl_6$, 50-52% chlorination (Cl); Cereclor 42: $C_{24}H_{44}Cl_6$, 40-42 % Cl.

5.2.2 Canadian Imports and Exports

The estimated total imports from all countries (United States, United Kingdom and Germany) were 2.5 kilotonnes for 1989 and 2.3 kilotonnes for 1990 (Camford Information Services, 1991). ICI suggests that these estimates may be high, and that the total imports for 1992 will be between 1.0 and 1.5 kilotonnes (ICI, 1992b).

ICI imports about 400-500 tonne/year of material from other ICI plants. Imported grades are generally those with a chlorine content of 50-60% and are used chiefly as additives in lubricating oils. Van Waters and Rodgers, a distributor of Dover Chemicals, imports from the United States about 500 tonne/year.

Total exports from Canada are about 200 tonne/year (Camford Information Services, 1991), although ICI Canada estimates that sales are approximately 60% exports (to the United States) and 40% domestic (Titcomb, 1993).

5.2.3 Manufacturing Processes

Chlorinated paraffins are obtained by direct chlorination of paraffins (n-alkanes) of high purity in the liquid phase, in the presence of hydrogen chloride. Chlorinated paraffins are manufactured commercially by reacting gaseous chlorine with paraffin wax (C_{22-28}) or n-paraffin oil (C_{14-17}) in a chlorinator. The temperature is kept between 80 and 100°C depending on the chain length of the feedstock. Some producers catalyze the process using UV-light. Further details are presented in Houghton (1989) and Murray *et al.* (1988).

While relatively inert, chlorinated paraffins can be dehydrochlorinated by prolonged exposure to heat or light and stabilizers are normally added to prevent degradation during storage and use. Commercial chlorinated paraffins contain very small levels of aromatic hydrocarbon impurities. Current feedstocks generally contain less than 50 ppm aromatics (ICI, 1992b). The bulk of

commercial chlorinated paraffins contain 40-70% chlorine.

5.2.4 Uses

In Canada, chlorinated paraffins are used mainly (65% of use) as plasticizers for plastics (Table 5.1). The products offer reasonable plasticizing ability, good inherent flame retardancy and are cheaper than the general purpose primary plasticizers. The other major market (20%) for chlorinated paraffins is as an extreme-pressure lubricant additive used in metalworking, to lower heat and allow fast metal work. Smaller applications for chlorinated paraffins include flame retardant additives in heavy duty rubber (8%), paints and coatings (3%), and adhesives and sealants (2%) (ICI, 1992a).

Although the reports by Zitko and Arsenault (1974) and by Howard *et al.* (1975) cite a number of patents related to applications of chlorinated paraffins, they do not contain a clear description of the relationship of carbon chain length and application. It appears now that chlorinated paraffins of short and intermediate chain length are used mainly as lubricants. As for the relationship between chlorine content and applications, it seems that the classes with the highest chlorine content are used primarily as flame retardants, whereas those with the intermediate chlorine level are used as plasticizers. It is not uncommon to encounter formulations containing more than one class of chlorinated paraffins (Table 5.2).

5.2.5 Canadian Demand

Total Canadian demand is about 4-5 kt/year as estimated by Camford Information Services (1991) (Table 5.3), although ICI suggests the number is lower at 3.5 to 4.0 kt/year (ICI 1992b). The market is extremely mature and will likely grow at about 1% per year (Camford Information Services 1991).

Canadian demand is considerably smaller than that in the United States which is about 44-45 kt/year (ICI, 1992b). The estimated production in 1989 by four industries in the United States was 29 kt. The major use for chlorinated paraffins in the United States is in high-pressure lubricants (50%), while the plastics industry is the second largest market (20%). The situation in Sweden resembles that in Canada in that the main market (68%) is for plasticizers and only 10% is for lubricants (KEMI, 1991).

Table 5.1. Uses of chlorinated paraffins in Canada (ICI, 1992a)

Use	%
Plastics	65
Lubricating additives	20
Rubber	8
Paints	3
Adhesives and sealants	2
Miscellaneous	2

Table 5.2. Chain length and chlorine content of various applications of chlorinated paraffins (Annema, 1989).

Paraffin	% Cl	Applications
C_{10-13}	50-70	high pressure additives, flame retardants
C_{14-17}	45-60	secondary PVC plasticizers
C_{20-30}	40-70	paint plasticizers, high pressure additives, flame retardants

Table 5.3. Demand pattern in Canada for chlorinated paraffins (Camford Information Services, 1991).

	Demand (kilotonnes)		
Use	1989	1990	1995[2]
Plasticizers	2.7	2.6	2.7
High-pressure lubricant additive	1.7	1.6	1.8
Miscellaneous[1]	0.5	0.4	0.4

[1] Primarily coatings and rubber applications
[2] Forecast

5.2.6 Releases

Estimates for chlorinated paraffin releases into the Canadian environment were not identified. Due to lack of data from Canada, data from other countries are presented here. Although release could occur during manufacture, use, transport and disposal, the two major sources of release to the environment are likely manufacturing and use in metalworking. The estimates of releases from these sources were prepared by the Chlorinated Paraffins Industry Association (CPIA, 1992) for the United States EPA, and were provided by ICI for this assessment.

Among the possible sources of releases to water from manufacturing are spills, facility wash-down and stormwater runoff. CPIA (1992) estimates these releases to be negligible as chlorinated paraffins are insoluble in water, and releases from these sources are routinely collected and treated in the facilities' wastewater treatment system.

Metalworking/cutting fluids, composed of short-chained, 50-60% chlorination, are a potential source of chlorinated paraffin release into aquatic environments. Releases can result from drum disposal, carry-off and spent bath use. Drum recycling is common, and users often return the drums for refill. Drums can also be sent to drum reconditioning companies where they are washed and refurbished (CPIA, 1992). Estimates of releases as a result of wash-down are not available, however industry proposes that as they are carefully controlled, release is negligible. The United States EPA estimates that fluid releases due to carry-off from work pieces may range from 0.01 kg/site-day for a small user to 10 kg/site-day for a large user (or 2.5 and 2500 kg/site-year, respectively). CPIA (1992) estimates water releases due to disposal of spent chlorinated paraffin baths may vary from 12 kg/site-year (small shops, which have 25-gallon recirculating systems) to 1500 kg/site-year (large shops which have 25000-gallon recirculating systems). Daily release is 0.0329 and 4.1 kg/site, respectively. Assuming that there are 900 small shops and 100 large shops, the total annual release of chlorinated paraffins from spent bath discharge is 161000 kg/year in the United States. The number of metalworking shops in Canada which use chlorinated paraffins is not known, but is estimated to be considerably smaller than that in the United States.

Estimates by the CPIA (1992) are considerably lower than those in Sweden where about 50% of the material used as high pressure lubricant is estimated to be directly discharged as waste (KEMI, 1991).

Another source of chlorinated paraffin releases to the aquatic environment occurs during painting operations. Most chlorinated paraffins in paint are used in industrial and marine paints which tend to be brush applied. Paint losses would be of a chlorinated paraffin bound up in a complex mixture of paint resin, from which the chlorinated paraffins would leach slowly, due to their insolubility in water.

Minimal release is expected due to paint formulating or in situations where they are used as flame retardants. According to Swedish estimates, less than 0.001% is released during use as a flame retardant (KEMI, 1991).

Emissions measured at a manufacturing plant in the Federal Republic of Germany in 1988 were in the order of 30 mg/normal cubic metre (temperature not stated). The process loss of chlorinated paraffins was about 0.1 g/kg of chlorinated paraffin production (Gesellschaft Deutscher Chemiker 1989, cited in Mukherjee, 1990). This would be considerably higher than the estimates provided by CPIA (1992).

Incineration of solid waste containing chlorinated paraffins may contribute to the formation of chlorinated dibenzodioxins, dibenzofurans and other

chlorinated organic compounds (Tysklind *et al.*, 1989), although ICI (1992b) proposed that this is not the case. Chlorinated paraffins are not likely to survive the incineration and are not expected to form de novo.

6.0 Environmental Transport, Transformation and Levels

6.1 Transport

Little environmental fate data are available on chlorinated paraffins because of the complex nature of the mixtures and the difficulties in measuring low levels. From general patterns of behaviour of hydrophobic organics in the environment, it is likely that chlorinated paraffins are fairly immobile, remain adsorbed on soil or sediment particles, are transported through the environment with the particles, and may be only slowly degraded.

Little data exist which demonstrate mobility and transport of chlorinated paraffin residues from sites of manufacturing, use or disposal. Very low solubility in water and low vapour pressure would predict low mobility, but monitoring data in the United Kingdom (Campbell and McConnell, 1980) and Sweden (Jansson *et al.*, 1993) indicate widespread levels of low contamination in water, sediments, aquatic and terrestrial organisms and even commercial foods. Some airborne dispersion does therefore occur. The range of chloroparaffin vapour pressures are not too dissimilar from polychlorinated biphenyl (PCB) values, which indicates some potential for atmospheric transport to distant environments.

6.2 Transformation

6.2.1 Abiotic

Chlorinated paraffins are generally considered persistent. In the aqueous phase, rates of hydrolysis, photolysis with visible or near UV radiation, oxidation and volatilization are insignificant under ambient temperatures. Friedman and Lombardo (1975) showed that chlorinated paraffins do not absorb high energy light, and noted no degradation.

No experimental data are available on the fate of any chlorinated paraffin which volatilizes into the atmosphere. However, it may be assumed that any volatilized chlorinated paraffin would be subject to attack by hydroxyl radicals in the troposphere. Using of the method of Atkinson (1986) for estimating the rate constant for reaction of CPs with hydroxyl radicals, the likely tropospheric half-life is of the order of a few days under summer conditions (Bunce, 1993).

No information was found on the identity and persistence of metabolites.

6.2.2 Biotic

In the natural environment, chlorinated paraffins are generally stable, but studies have shown that degradation is possible by microorganisms. The ability of aerobic microorganisms to oxidize a range of chlorinated paraffins depends upon their previous acclimatization, the chain length and degree of chlorination. Chlorinated paraffins, C_{10-20}, are degraded most rapidly.

Zitko and Arsenault (1974, 1977) studied the aerobic and anaerobic biodegradation of Cereclor 42 and Chlorez 700 in flasks containing sediment and

decomposing organic matter in sea water. One set of flasks contained 463 μg Cereclor 42 per g sediment and another set 277 μg Chlorez 700 per g sediment. The rate of biodegradation was higher under anaerobic than aerobic conditions, but rates could not easily be calculated due to poor recovery of sorbed residues and erratic data.

Assessment of the readily biodegradability of 58% chlorinated, short chain paraffins by activated sludge showed the substances not to be readily biodegradable over a 28 day period (as determined by biological oxygen demand) under either aerobic or anaerobic conditions (Street *et al.*, 1983; Street and Madeley, 1983b). Concentrations of the CP studied were 100 and 20 mg/L, respectively. In a study to determine the fate during aerobic sewage treatment, at a concentration of 10 mg/L the CPs were found to adsorb onto the solids of the activated sludge (Street and Madeley, 1983a).

Madeley and Birtley (1980) reported that the ability of aerobic microorganisms to oxidize a range of chlorinated paraffins depended upon their previous acclimatization, the chain length and degree of chlorination. The CPs with chain length C_{10-20}, were degraded most rapidly. Longer chain paraffins chlorinated up to 45% degraded more slowly by acclimatized organisms. Microorganisms not acclimatized and added to a mixture of Cereclor 42 (C_{20-30}, 42% Cl) and a ^{14}C-labelled C_{26} CP, caused 11% of the ^{14}C to be evolved as CO_2 after 8 weeks of incubation.

In another study, seventy enrichment cultures were established in an attempt to obtain bacteria capable of using CPs as the sole carbon source, but no microorganisms able to grow well were found (Omori *et al.*, 1987). The chlorinated paraffins were dechlorinated by n-hexadecane-using bacteria isolated from soil. The bacteria dechlorinated the terminal chlorine to produce 2-, or 3-chlorinated fatty acids via ß-oxidation. Sludge acclimatized to n-hexadecane dechlorinated 2% of CP-150 (C_{15}). A mixed culture dechlorinated 15 to 57% of the chlorinated paraffin after 36 hours. The longer the carbon chain and the higher the chlorine content, the less the amount of chlorine was removed.

6.3 Bioconcentration and Biomagnification

While data indicate a potential for bioaccumulation, few bioconcentration factors (BCF) or biomagnification factors (BAF) have been determined. The uptake and accumulation of chlorinated paraffins in fish from water (bioconcentration) and food (biomagnification) appear to be inversely proportional to molecular weight, however general conclusions are difficult to make as uptake rates are slow and long exposure periods are required to achieve steady-state equilibrium. In several tests, it is unclear whether steady-state had been reached. It is noteworthy that the highest BCF, recorded for mussels (Renberg *et al*,. 1986), was achieved at a much lower concentration of the substance in the water (i.e., 0.13 μg/L) than most other studies, and that BCFs generally declined with water concentration for all organisms. This has also been found for BCF studies of dioxins and furans where pg/L rather than ng/L exposure concentrations resulted in higher BCFs (Cook *et al.*, 1991).

Reported BCFs vary dramatically between different chlorinated paraffins and between species, and range from 0.007 to 139,000 (Sundstrom and Renberg, 1985) (Table 6.1). Biomagnification factors from food are less than 40, on a whole body basis, but would be higher if calculated on a lipid basis (Table 6.2). Given the very high log K_{ow}s for chlorinated paraffins, accumulation of chlorinated paraffins through the food chain could be signficant (Thomann, 1989).

Studies on the bioavailability of chlorinated paraffins sorbed to sediments or soils to benthic organisms, filter feeders or soil organisms were not identified.

6.3.1 Bioconcentration

One of the few data sets on the bioconcentration of chlorinated paraffins used 58% chlorinated, short-chain CP. Organisms studied included the common mussel (*Mytilus edulis*), rainbow trout (*Oncorhynchus mykiss*), the diatom *Skeletonema costatum* and the green alga *Selenastrum capricornutum* (Table 6.1). Mussels exposed to 2.35 µg/L for 147 days had a BCF value of 40,900 (Madeley *et al.*, 1983). Whole organism depuration half-lives were 9.2 to 19.8 days. Equilibrium between water levels and whole organism residue levels were reached after about 45 to 80 days.

Trout were exposed for 168 days to test concentrations of 3.1 and 14.3 µg/L (Madeley and Maddock, 1983f). They were then removed to freshwater for a depuration period of 105 days. Due to the low solubility of the chlorinated paraffin, acetone (250 ppm v/v) was used for dissolution. Residues varied amongst tissues, with viscera having the greatest amount. On a whole body basis, plateau concentrations were attained after approximately 75 to 80 days, and the bioconcentration factors were 3550 for fish exposed to 3.1 µg/L and 5260 for those exposed to 14.3 µg/L. The elimination half-lives were 19.8 and 18.7 days, respectively. During the 168 day period of exposure, two fish died at the high concentration and one at the low concentration. However, starting at day 63 of depuration, fish which had been exposed to chlorinated paraffins began behaving abnormally, deaths started occurring on day 64 and by day 69 all fish in the higher exposure concentration had died. Some fish from the lower exposure also died, but remaining fish recovered by day 70. The cause of death was undefined, however symptoms resembled those experienced by fish exposed to acutely toxic levels of CPs (i.e., >33 µg/L, Madeley and Maddock, 1983d).

After 10 days of exposure to 58% chlorinated, short-chain CP, algae showed considerably lower bioconcentration factors of 3.5 for the diatom *Skeletonema costatum* when exposed to 17.8 µg/L, and 1.5 for the green alga *Selenastrum capricornutum* when exposed to 35 µg/L (Thompson and Madeley, 1983a). These estimates likely indicate absorption of the chlorinated paraffins to the algal cells rather than active uptake.

Renberg *et al.* (1986) studied bioconcentration of two ^{14}C-labelled CPs (C_{18}, 34% Cl; C_{12}, 69% Cl) in the common mussel in a flow-through, 4-week accumulation test. They reported a BCF of almost 140,000 for the short chain CP and about 7,000 for the medium chain CP (on a fresh weight basis). On a lipid weight basis, BCFs were 50 times higher.

Bengtsson *et al.* (1979) reported that uptake of CPs by bleaks (*Alburnus alburnus*) from water (125 µg/mL) was inversely proportional to chain length. For example, whole body levels of Witaclor 149 in these fish (C_{10-13}, 49% Cl) reached about 100 µg/g after exposure to 125 µg/L for 14 days. Retention was apparently proportional to the degree of chlorination. A 37-day depuration period did not significantly reduce levels of Clorparaffin 70C.

Svanberg *et al.* (1978) reported BCFs ranging from 28.6 to 328 for bleaks for Chlorparaffin 70C (C_{10-13}, 70% Cl). Whole body levels ranged from 20 - 33 µg/g (wet weight) following exposure to 100 - 1000 µg/L for 29 days. The published report did not include sufficient detail to assess the validity of these data.

Darnerud *et al.* (1989) administered three ^{14}C-labelled C_{12-18} CPs (23%, 51% or 68% Cl) to rainbow trout via water. Uptake and retention in fat rich tissues were proportional to the degree of chlorination. There was a selective uptake of radioactivity in the olfactory organs and gills for all three paraffins. After a 21-day depuration period, retention of radioactivity in the olfactory organs and gills was relatively higher for the 23% Cl CP than for the more highly chlorinated paraffins. The authors speculated that this could be due to metabolic incorporation of CO_2 into endogenous substances.

Table 6.1. Bioconcentration factors for some chlorinated paraffins.

Species	Chain Length, %Cl	Exposure Conc. (μg/L)	Exposure Duration (d)	BCF (whole animal)	Reference
marine diatom (*Skeletonema costatum*)	C_{10-12}, 58%	1.4	10	<1	
		2.5	10	<1	
		6.6	10	2.4	
		12.1	10	4.0	
		17.8	10	3.5	Thompson and Madeley 1983a
freshwater green alga (*Selenastrum capricornutum*)	C_{10-12}, 58%	35	10	1.5	
		62	10	1.9	
		79	10	3.2	
		100	10	4.1	
		140	10	7.6	
		150	10	4.1	Thompson and Madeley 1983a
mussel (*Mytilus edulis*)	C_{10-12}, 58%	2	147	40,900	
		10	91	24,800	Madeley *et al.*, 1983
	C_{10-12}, 58%	13	60	25,292	
		44	60	16,427	
		71	60	5,785	
		130	60	12,177	Madeley and Thompson, 1983c
	C_{16}, 34%	0.13	28	6,920	
	C_{12}, 69%	0.13	28	138,000	Renberg *et al.*, 1986
	C_{14-17}, 52%	220	60	2,856	
		3,800	60	429	Madeley and Thompson, 1983b
	C_{22-26}, 43%	20	60	1,158	
		2,180	60	261	Madeley and Thompson, 1983a
	C_{22-26}, 70%	460	60	341	
		1,330	60	223	Madeley and Thompson, 1983d

(continued)

Table 6.1. Bioconcentration factors for some chlorinated paraffins (Con't).

Species	Chain Length, %Cl	Exposure Conc. (μg/L)	Exposure Duration (d)	BCF (whole animal)	Reference
rainbow trout *(Oncorhynchus mykiss)*	C_{10-12}, 58%	3	168	3,550	
		14	168	5,260	Madeley and Maddock, 1983f
	C_{10-12}, 58%	33	60	7,155	
		100	60	7,816	
		350	60	3,723	
		1,070	60	2,642	
		3,050	60	1,173	Madeley and Maddock, 1983d
	$C_{14\ 17}$, 52%	1,050	60	45	
		4,500	60	67	Madeley and Maddock, 1983c
	$C_{22\ 26}$, 43%	970	60	18	
		4,000	60	38	Madeley and Maddock, 1983b
	C_{20-30}, 70%	840	60	54	
		1,900	60	6	
		3,800	60	33	Madeley and Maddock, 1983e
bleaks *(Alburnus alburnus)*	C_{10-13}, 70%	0.1	15	203	
		0.1	28	328	
		0.1	29	262	
		1.0	27	48	
		1.0	29	29	Svanberg *et al.*, 1978
	C_{10-13}, 59%	125	14	760	
		125	14	720	
		125	14	160	
		125	14	20	Bengtsson *et al.*, 1979

Darnerud *et al.*, (1983) reported that after ^{14}C-labelled polychlorohexadecane (34% Cl) was administered intra-arterially to carp or via contaminated water to bleaks, radioactivity was concentrated mainly in the bile and intestinal contents, and also in the kidney, liver, gills, nasal cavity and skin. In carp, 6% of the administered dose was excreted as CO_2 in 96 hours.

6.3.2 Biomagnification

Few data exist on the degree of biomagnification of chlorinated paraffins. Madeley and Birtley (1980) reported on accumulation and degradation of a ^{14}C-labelled long chain chlorinated paraffin (Cereclor 42; C_{20-30}, 42% Cl) in mussels, after exposure of 524 μg/g-diet, and in rainbow trout after exposure to 47 or 385 μg/g-diet. Mussel uptake was relatively low, and tissue concentrations were always below 10 μg/g. Uptake in trout was higher and related to dietary concentration, both before and after a 49-day depuration period. Total tissue concentrations were 10 and 100 μg/g, respectively, with levels in the gut and liver approaching the food concentrations. Mussels expelled radioactivity as the parent compound, but trout appeared to metabolize the chlorinated paraffin.

Zitko (1974) reported that juvenile Atlantic salmon did not accumulate Cereclor 42 (C_{20-30}, 42% Cl) or Cereclor 70 (C_{10-13}, 70% Cl) from suspended solids (silica contaminated at 1 mg/g at levels of 1 g/L) or food (at levels of 10 and 100 μg/g).

Lombardo *et al.*, (1975) reported that rainbow trout fed a diet containing 10 μg/g Chlorowax 500C (C_{12}, 59% Cl) accumulated up to 1.1 μg/g (whole body, wet weight), equivalent to 18 μg/g on a fat weight basis. It was unclear whether the duration of exposure was long enough to reach steady state. Gas chromatography patterns suggested differential uptake and/or elimination of isomers.

Bengtsson and Ofstad (1982) exposed bleaks to three CP formulations in their diet (590 - 3400 μg/g) for 91 days, and studied them for a further 316 days. They reported that uptake of CPs was inversely proportional to chain length, while retention was apparently proportional to the degree of chlorination and possibly to chain length. This may reflect a lack of achievement of steady state conditions for the higher molecular weight substances. A 45-week depuration period did not significantly reduce levels of Witaclor 171P (C_{10-13}, 71% Cl). Uptake efficiency of Witaclor 149 (C_{10-13}, 49% Cl) ranged from 5 to 49% and was inversely proportional to dose (590 - 5800 μg/g), which may also be a reflection of a lack of achievement of steady state conditions.

6.4 Levels in the Environment

Because of their physical and chemical properties, chlorinated paraffins are difficult to measure in low concentrations in environmental matrices. As a result, data on levels of chlorinated paraffins in the environment are scarce and their reliability is often not known. No data were identified on levels in the Canadian environment, therefore only levels found in other countries are discussed below.

6.4.1 Air

No reports on levels in air in Canada or elsewhere were found. Although chlorinated paraffins have low vapour pressures, the Henry's Law constants are similar to those for pesticides like toxaphene, chlordane and aldrin (Sunito *et al.*, 1988), which are known to be transported in the atmosphere. Campbell and

Table 6.2. Biomagnification factors for some chlorinated paraffins.

Species	Chain Length, %Cl	Exposure Conc. (μg/g-diet)	Exposure Duration (d)	BCF (whole animal)	Reference
rainbow trout (*Oncorhynchus mykiss*)	C_{10-13}, 60%	10	82	2.8	Lombardo *et al.*, 1975
bleaks (*Alburnus alburnus*)	C_{10-13}, 49%	590	91	41	Bengtsson and Ofstad, 1982
		2,500	91	9	
		5,800	91	4.6	
	C_{10-13}, 71%	3,180	91	5.5	
	C_{18-26}, 49%	3,400	91	2	
Atlantic salmon (*Salmo salar*)	C_{20-30}, 42%	10	33	0.11 μg Cl/g[1]	Zitko, 1974
		10	109	n.d.	
		10	181	n.d.	
		100	33	0.51 μg Cl/g	
		100	109	n.d.	
		100	181	n.d.	
	C_{20-30}, 70%	10	33	0.29 μg Cl/g	
		10	109	n.d.	
		10	181	n.d.	
		100	33	0.49 μg Cl/g	
		100	109	n.d.	
		100	181	n.d.	

[1] μg Cl/g wet weight; detection limits not given

McConnell (1980) in the United Kingdon and Jansson *et al.* (1993) in Sweden have found levels of chlorinated paraffins in water, sediment and biota at sites distant from manufacturing facilities, suggesting potential atmospheric transport of chlorinated paraffins to distant environments.

6.4.2 Surface Water

Levels in marine water in various locations remote from industry in the United Kingdom ranged from 0.5 μg/L (limits of detection) to 2 μg/L for C_{20-30} and 4 μg/L for C_{10-20} (Campbell and McConnell, 1980). Similarly in freshwaters remote from industry, levels were mostly undetectable, with a maximum of 2 μg/L of C_{20-30} and 1 μg/L of C_{10-20}. In contrast, freshwaters receiving industrial effluent had detectable levels of CPs more frequently, with levels ranging from 1 to 6 μg/L, C_{10-20} predominating. In this study, results did not differentiate between short chain and medium chain CPs. Studies in 1985 and 1986, using some of the same sampling locations but an improved analytical technique able to differentiate between the short and medium chain CPs, found the short chain CPs were less than half (and often less) the levels of the medium chain CPs (ICI, 1992c). Levels of C_{10-13} ranged from ND (undefined) to 1.45 μg/L in 1986 (n=16), while levels of C_{14-17} ranged from 0.62 to 3.75 μg/L. Levels were slightly higher in 1985, ranging from 0.93 to 4.08 μg/L for C_{10-13} and from 3.75 to 13.81 μg/L for C_{14-17} (n=4).

The only other data available for levels in water were also collected close to industry. Levels in water measured in a creek downstream from a drainage ditch carrying effluent from a manufacturing plant in Ohio were non-detectable (0.15 μg/L), with levels in the particulates filtered from the water being 0.21, 0.18 and 0.62 μg/L for short, medium and long CPs, respectively. Levels in particulates from the water in a sewage lagoon were an order of magnitude higher at 3.3, 3.8 and 7.7 μg/L, for short, medium and long chains, respectively (Murray *et al.*, 1988).

6.4.3 Ground Water

No reports on levels in ground water were identified. Due to the lipophilicity of chlorinated paraffins, any release from a landfill would likely become tightly bound to particulate and dissolved organic carbon and thus if in ground water, they would be transported in this form (McCarthy and Black, 1988).

6.4.4 Sediment

Murray *et al.*, (1988) found high levels (i.e., 5.5 to 7.3 μg/kg-dw for short chain, 8.2 μg/kg-dw for medium chain, and 21 μg/kg-dw for long chain) of chlorinated paraffins in sediments in a creek receiving effluents from a plant producing chlorinated paraffins in Ohio. Levels were about 10^6-fold higher (i.e., maximum values of 40,000, 50,000 and 170,000 μg/kg-dw, for short, medium and long chain, respectively) in sediment from an impoundment lagoon. Measurements of sediments in a ditch which carries the lagoon drainage to the creek showed levels of 1200, 760 and 3600 μg/kg-dw for short, medium and long chain, respectively.

Campbell and McConnell (1980) found that sediments contained 1000- to 2000-fold higher residue levels than measured in the overlying water column. In industrialized areas, detectable residues were more frequently found than in areas remote from industry, with detectable residue levels in sediments ranging from 100 to 15,000 μg/kg (wet weight) for C_{10-20} and as high as 3200 μg/kg for C_{20-30}. The areas remote from industry in which detectable amounts were found in the

sediments were the Irish Sea and the North Sea, where residues ranged from 50 to 300 μg/kg, with the higher levels being C_{20-30}.

Schmid and Müller (1985) found 5 μg/kg of Witaclor 352 (C_{14-18}, 52% Cl) in surface sediment from Lake Zürich collected near Zürich. They found higher levels (i.e 200 μg/kg) in sewage sludge containing 5% solid matter taken from a sewage treatment plant in an urban industrialized region known for high contamination of heavy metals and organochlorine compounds.

6.4.5 Soil

No reports on levels in soil were identified. Chlorinated paraffins released to soil are likely to remain tightly bound and be persistent.

6.4.6 Biota

Chlorinated paraffins were not detectable in shellfish from 30 locations in Atlantic Canada (Zenon Environmental Inc., 1989). Detection limits were 0.4 μg/g.

In the study in the United Kingdom by Campbell and McConnell (1980), C_{20-30} was rarely present at detectable levels in biota, but C_{10-20} was more common with highest levels in mussels (*Mytilus edulis*) ranging up to 1 mg/kg (wet weight) in waters receiving effluent and up to 12 mg/kg near the effluent. Levels in marine fish were considerably lower with levels in plaice (*Pleuronectes platessa*), and pouting (*Trisopterus luscus*) ranging from non detectable (i.e. <0.05) to 0.2 mg/kg. Levels in the freshwater predatory pike (*Esox lucius*) ranged from non detectable (i.e., <0.05 mg/kg-ww) to just detectable. Their study also investigated levels in eggs of the following seabirds: the cormorant (*Phalocrocoracidae carbo*), gannet (*Morus bassanus*), Great skua (*Catharacta skua*), guillemot (*Uria aalge*), kittiwake (*Rissa tridactyla*), puffin (*Frateruela arctica*), Manx shearwater (*Puffinus puffinus*), razorbill (*Alca torda*) and shag (*Phalacrocorax aristotelis*). For C_{10-20}, the maximum level was 0.6 mg/kg measured in 1 egg (species unspecified), and seven of the 23 eggs analyzed had undetectable levels (i.e., <0.05 mg/kg). For C_{20-30}, the maximum level was 0.1 mg/kg, measured in 3 eggs (species unspecified). Seventeen of the 23 eggs analyzed had undetectable levels (i.e. <0.05 mg/kg). Levels in livers of the heron (*Ardea cinerea*), guillemot (*Uria aalge*), and herring gull (*Larus argentatus*) ranged from 0.1 to 1.2 mg/kg for C_{10-20}, and from <0.1 to 1.5 mg/kg for C_{20-30}. Levels in the liver and blubber of the grey seal (*Halichoerus grypus*) ranged from 0.04 to 0.1 mg/kg for C_{10-20} and from non detectable to around detection limits (i.e., 0.05 mg/kg) for C_{20-30}. Campbell and McConnell (1980) also detected 0.35 mg/kg C_{10-20} in wool of sheep near manufacturing plants.

Murray *et al.*, (1988) found high levels (i.e. 0.28 mg/kg of short chain, 0.17 mg/kg of medium chain and 0.18 mg/kg of long chain) of chlorinated paraffins in mussels (species not given) downstream of a drainage ditch receiving effluents from a plant producing chlorinated paraffins in Ohio.

Levels of CPs (chain length not specified) have also been measured in several species from various ecosystems in Sweden. The rabbit (*Oryctolagus cuiculus*), a herbivorous mammal from southern agricultural Sweden contained 2.9 μg/g-lipid. Other herbivorous mammals, such as the moose (*Alces alces*) from the central forest district, and the reindeer (*Rangifer tarandus*) from the northern mountain district contained 4.4 and 0.14 μg/g-lipid, respectively. Freshwater whitefish (*Coregonus* sp.) from northern Sweden and Arctic char (*Salvelinus alpinus*) from industrialized south-central Sweden contained 1.0 and 0.57 μg/g-lipid, respectively. A pooled sample from specimens from across Sweden of osprey

(*Pandion haliaetus*), a migratory bird which eats freshwater fish, contained 0.53 μg/g-lipid. From the Baltic Sea, herring (*Clupea harengus*), ringed seal (*Pusa hispida*) and grey seal (*Halichoerus grypus*) contained 1.5, 0.13 and 0.28 μg/g-lipid, respectively (Jansson *et al.*, 1993). The lower levels in seal compared to herring suggests that little or no biomagnification may be occurring. These levels indicate, as did the study by Campbell and McConnell (1980) that transport from the site of use or manufacture is occurring.

6.4.7 Food

In a limited study reported by Campbell and McConnell (1980), a C_{10-20} CP was detected at low levels (< 0.05 to 1.5 ppm w/w), in at least one human tissue (liver, adipose, kidney, brain) from every subject analyzed (n = 24). In the same study, the mean levels of a C_{10-20} CP in dairy products and vegetable oil and derivatives were reported to be higher (0.15 to 0.3 ppm) than in fruit and vegetables and beverages (<0.05 ppm to 0.025 ppm). Data available in the published account of this early study were insufficient, however, to permit evaluation of the validity of these results.

6.4.8 Summary

Two studies measured chlorinated paraffins in several environmental matrices. Murray *et al.* (1988) found that chlorinated paraffins were generally present at quantifiable concentrations in the ppb to ppm range in both the discharge from a Ohio manufacturing plant and in the creek downstream from the discharge. Chlorinated paraffins were most prevalent in the sediment, suspended solids and biological samples. Where detected in water, chlorinated paraffins were generally present in trace (low ppb) amounts. The long-chains C_{20-30} were found at the highest levels. Levels in sediment in an impoundment lagoon which sequesters the plant effluent before allowing it to discharge were as high as 170 mg/kg. Concentrations in sediment downstream from the drainage ditch ranged from trace levels to 0.021 mg/kg. Concentrations in particulates were generally less than those in sediments, and even less in filtered water. Concentrations in mussels downstream were as high as 0.280 mg/kg.

Campbell and McConnell (1980) measured levels of chlorinated paraffins in marine and freshwater environments, close to and distant from, industry in the United Kingdom. Levels in half of the marine waters sampled showed C_{10-20} at 0.5 to 4 μg/L, and less than half showed C_{20-30} at 0.5 to 2.0 μg/L. Chlorinated paraffins were present in only a few marine sediments at up to 0.5 mg/kg. In freshwater systems, levels remote from industry were similar to those in marine environments. Biota from areas remote from industry contained up to 0.4 mg/kg C_{10-20} and a maximum of 0.2 mg/kg C_{20-30}. Where chlorinated paraffins were measured near industry, levels in water were 1 to 6 μg/L, and in sediments they were 1 to 10 mg/kg, C_{10-20} predominating. In mussels collected in a river receiving CP plant effluent, levels were up to 1 mg/kg C_{10-20}, and 6 to 12 mg/kg close to the effluent discharge. Levels in aquatic biota were thus close to the sediment levels where they live. Low levels were found in coastline seabirds' eggs, with C_{20-30} rarely detected (0.05 mg/kg) and C_{10-20} showing a maximum of 2 mg/kg.

Levels in biota in Sweden suggest that terrestrial herbivores as well as aquatic organisms accumulate detectable residues of CPs, and that little or no biomagnification is occurring, based on levels in the herring and seal (Jansson *et al.*, 1993).

7.0 Population Exposures

7.1 Wildlife Population Exposure

Chlorinated paraffins are likely to be released in several cases into the water compartment. Due to their high octanol:water partition coefficient, and low water solubility, they are bioaccumulated by aquatic organisms. Therefore, the main route of exposure is likely to be ingestion of contaminanted food sources. The wildlife likely to be most exposed are piscivorous animals and birds, although data in Sweden also show higher levels in terrestrial herbivores. Inhalation and dermal routes of exposure are likely insignficant routes of exposure. Exposure is likely to be highest adjacent to manufacturing sites.

Due to the lack of data on levels in the Canadian environment, quantitative estimates of exposure could not be made. Estimation on the basis of fugacity modelling is also inappropriate owing to the questionable measurements of physical-chemical properties and the lack of sorption and biodegradation information.

7.2 General Human Population Exposure

Owing to their high octanol:water partition coefficients, it is likely that the principal source of exposure of the general population to chlorinated paraffins would be food. However, due to the lack of available information on concentrations in environmental media to which humans are exposed, it is not possible to quantitatively estimate the total daily intake of chlorinated paraffins by the general population. Estimation on the basis of fugacity modelling is also inappropriate, for the reasons stated above (see 7.1).

8.0 Toxicokinetics and Metabolism

8.1 Absorption

8.1.1 Short and Medium Chain CPs

During 56 hours continuous contact with human skin *in vitro*, no absorption of ^{14}C-labelled neat Cereclor S52 (C_{14-17}, 52% Cl) was detected. Absorption of ^{14}C-labelled Cereclor 56L (C_{10-13}, 56% Cl) as a 18.5% w/w solution in cutting oil was very slow (0.04 $\mu g/cm^2/h$) with detection of absorbed radioactivity only after 23 hours of continuous contact (Scott, 1989). The author concluded that these chlorinated paraffins were very poorly absorbed through human skin. No data were available on absorption of CPs following exposure by other routes.

8.1.2 Long Chain CPs

In Sprague-Dawley rats (n = 5 to 7 per sex) exposed to 1-^{14}C-labelled CPs (C_{18}, 50-53% Cl and C_{28}, 47% Cl) both compounds were poorly absorbed following dermal application of 2 g/kg-b.w. (Yang *et al.*, 1987). Less than 1% of the shorter chain CP and less than 0.1 % of the longer chain CP, respectively, were recovered in the excreta, expired air and tissues after 96 hours.

Yang *et al.* (1987) reported that 86.2% of a single oral dose of 0.5 g/kg b.w. of neat 1-$^{14}C_{18}$ (50-53% Cl) CP administered by gavage was recovered in the excreta, expired air and tissues of Sprague-Dawley rats (n = 5 to 7 per sex) at 96 hours. A significantly higher proportion of total radioactivity was present in the feces (76.4% of the dose) than in the expired air (3.3%) and urine (1.9%). Approximately 20% of the ^{14}C found in the feces (approximately 16% of the dose) was the parent compound.

8.2 Distribution

Twenty four hours following administration intravenously or by gastric intubation of 50 µL (200 mg/mL lipid emulsion) of three ^{14}C-labelled polychlorodecanes (17.4, 55.9 or 68.5% Cl, respectively) and a polychlorohexadecane (34.1% Cl) to C57Bl mice (n = 4), radioactivity was concentrated in the liver, fat and other tissues with a high metabolic activity/cell turnover (e.g. intestinal mucosa, bone marrow, salivary glands and thymus). The retention of heptane-soluble radioactivity (indicating unmetabolised substance) in fat 24 hours and 30 days after oral dosing increased with the degree of chlorination, but the less chlorinated compounds appeared to be selectively retained in the central nervous system 30 to 60 days after injection (Darnerud *et al.*, 1982; Darnerud and Brandt, 1982).

When 1.6 µmol/kg-b.w. and 0.48 µmol/kg-b.w. of a lipid emulsion (200 mg/mL) of a uniformly ^{14}C-labelled polychlorohexadecane (69% Cl) was administered orally by gavage to C57Bl mice (n = 3 to 6) and to Japanese Quail (*Coturnix coturnix*) (n = 4 to 5), respectively, the general distribution pattern was similar in both species, with radioactivity being concentrated in the bile, liver, kidney and intestinal contents at periods up to 30 days following exposure. In mice, extensive accumulation and retention was also reported in the corpora lutea up to 30 days post-dosing, and in quail, radioactivity was high in the hypophysis, retina, blood and egg yolk (Biessmann *et al.*, 1983).

Radioactivity was concentrated in the liver and kidney and in adipose and ovarian tissue following administration of unreported doses of ^{14}C-labelled CPs of various chain lengths and degrees of chlorination (C_{10-13}, 58% Cl; C_{14-17}, 52% Cl; C_{20-30}, 43% Cl) by gavage to F344/N rats (number unspecified) (Serrone *et al.*, 1987), as well as a uniformly ^{14}C-labelled polychlorinated hexadecane (65% Cl) (1.0 to 1.6 mg) administered intravenously to bile-duct-cannulated Sprague-Dawley rats (n = 6) (Ahlman *et al.*, 1986). A small part of the ^{14}C-labelled dose was absorbed following oral administration of a C_{22-26} (70% Cl) CP. The highest concentration of radioactivity occurred in the liver; there was little accumulation in the ovary compared to that for the other chlorinated paraffins administered (Serrone *et al.*, 1987). Radioactivity was found primarily in the liver, intestines and fat of Sprague-Dawley rats (n= 5 to 7 per sex) 96 hours after a single oral administration by gavage of a single dose of 0.5 g/kg-b.w. of 1-^{14}C-labelled C_{18} (50-53% Cl) CP (Yang *et al.*, 1987).

8.3 Metabolic Transformation, Retention and Elimination

Based on the results of available studies, the rate of breakdown of CPs, based on determination of expired radiolabelled CO_2 following administration, appears to be inversely proportional to the degree of chlorination. In most studies, metabolites were not identified, primarily due to the lack of adequate analytical methods.

A study of the impact of microsomal enzyme inducers and inhibitors on the degradation of 1-^{14}C-labelled polychlorododecanes (56% or 68% Cl), administered intravenously to C57Bl mice, indicated that degradation via cytochrome P-450 was

relatively more important for the more highly chlorinated compounds (Darnerud, 1984). Other studies suggest that cytochrome P-450 catalyses a de-chlorination reaction which is followed by beta-oxidation and incorporation of the carbon chain into cellular metabolism (Darnerud and Brandt, 1982).

8.3.1 Short and Medium Chain CPs

Ahlman *et al.* (1986) reported that 5 to 6 mg/kg-b.w. of a uniformly-labelled (1.14 μCi/mg) polychlorinated hexadecane (65% Cl), administered intravenously to bile-duct-cannulated Sprague-Dawley rats (n = 6), was extensively metabolised; less than 3% of the radioactivity excreted in the bile in two to three days was parent compound. Metabolites were not definitively identified, but appeared to be conjugates of mercapturic acid and of glutathione. Approximately 10% of the administered dose was excreted in the bile after 24 hours, while excretion of ^{14}C in the urine and feces was < 0.5% after 48 hours. It was not possible to precisely determine percentage recoveries on the basis of reported data.

Elimination as $^{14}CO_2$ was inversely proportional to the degree of chlorination, with 52.2%, 31.8% and 7.7% of the radioactivity being exhaled within 12 hours after intravenous (i.v.) administration of 50 μL (200 mg/mL) of three 1-^{14}C labelled polychlorodecanes (17.4%, 55.9% and 68.5% Cl, respectively) to C57Bl mice (n = 4). Similar results were obtained after intragastric administration (p.o.) of the same doses of two 1-^{14}C labelled polychlorodecanes (55.9% and 68.5% Cl) with 33.2% and 8.1% of the radioactive doses being exhaled as CO_2, respectively. There was a marked difference in fecal radioactivity by 12 hours post-dose for the two routes of administration, (e.g. 8.6% by i.v and 21.1% by p.o. for the CP with 68.5% Cl) (Darnerud *et al.*, 1982). For a 1-^{14}C-labelled polychlorohexadecane (34.1% Cl), $^{14}CO_2$ exhalation by the mice differed somewhat between the two routes of exposure; 44% and 33% of the administered radioactive dose was eliminated as $^{14}CO_2$ within 12 hours after intravenous and peroral administration, respectively (Darnerud and Brandt, 1982).

Eriksson and Darnerud (1985) administered 1.1 mg/kg-b.w. radiolabelled polychlorohexadecane (69% Cl) by gavage to pre-weaning NMRI mice on the 3rd, 10th or 20th day after birth, and measured distribution and retention in the brain at 24 hours and 7 days after exposure. Retention was most pronounced in mice exposed on the 10th day of life. Radioactivity was concentrated in myelinated areas, and levels at 7 days were almost the same as those at 24 hours. The authors suggested that the relatively high retention following exposure on day 10 may be related to a spurt in brain growth.

Biessmann *et al.* (1982) administered 50 μL of two (1-^{14}C)-labelled medium and short chain CPs (C_{16}, 34% Cl and C_{12}, 56% Cl) in a lipid emulsion (200 mg/mL) by gavage to Japanese Quail (n = 4). Excretion as CO_2 was proportional to the chain length and/or inversely proportional to the degree of chlorination, with 40% and 20% of the administered radioactivity, respectively, excreted as CO_2 within 8 hours. In a similar study, Biessmann *et al.* (1983) administered a uniformly ^{14}C-labelled polychlorohexadecane (69% Cl) orally and intravenously to C57Bl mice (1.6 μmol/kg-b.w.) and to Japanese Quail (0.48 μmol/kg-b.w.). In both species, non-volatile metabolites were excreted in the bile and feces. The quail also excreted these metabolites via the egg yolk and uropygial gland. The mice eliminated 66% of the radioactivity in feces, and 3% in urine, within 96 hours after oral administration, with a slightly lower level in the feces after intravenous administration. In quail, combined urinary and fecal excretion after 96 hours was 58% of the administered oral dose. In both species, only about 1% of radioactivity was excreted as $^{14}CO_2$, in contrast to the studies on less chlorinated hexadecanes described above (Biessmann *et al.*, 1982; Darnerud and Brandt, 1982). It is difficult to compare directly the results of these studies

due to differences in the position of the ^{14}C-label.

Birtley *et al.* (1980) investigated tissue retention and elimination of a (^{36}Cl)-labelled Cereclor S52 (C_{14-17}, 52% Cl) in male Wistar rats, at weekly intervals, during and after administration in the diet of 0.4 or 40 ppm radiolabelled compound for eight or ten weeks (dose as mg/kg-b.w. not reported, approximately 0.02 or 2 mg/kg-b.w./day, respectively). Radioactivity in liver, abdominal fat, brain and adrenal glands was determined, and increased in the liver and abdominal fat until equilibrium was reached at 1 and 7 weeks, respectively; the highest concentrations in abdominal fat never exceeded levels in the diet. After cessation of dosing, the half-time for removal of radioactivity was about 8 weeks for abdominal fat and less than 1 week for liver. No radioactivity was detected in the brain and the adrenal glands.

8.4 Microsomal Enzyme Induction

The results of most studies indicate that CPs induce microsomal enzymes at least to a slight degree, with short chain compounds being the most potent.

Nilsen *et al.* (1980, 1981) and Nilsen and Toftgard (1981) administered 1 g/kg-b.w./day CPs of various chain lengths and degrees of chlorination (C_{10-13}, 49, 59 or 71% Cl; C_{14-17}, 50% Cl; C_{18-26}, 49% Cl) to Sprague-Dawley rats by intraperitoneal injection for 4 days. Generally, induction of cytochrome P-450, proliferation of the smooth endoplasmic reticulum, and increases in the number and size of liposomes, autophagosomes and peroxisomes, and increases in the numbers and size of mitochondria correlated inversely with carbon chain length and, for the short chain paraffins, also with the degree of chlorination. There was a significant increase in relative and absolute liver weight for the compounds with chain lengths shorter than C_{17}.

Various CPs (C_{10-23}, 70% Cl; C_{14-17}, 58% Cl; C_{23}, 70% Cl) induced epoxide hydrolase, DT-diaphorase and glutathione-S-transferase activities in the livers of C57Bl/6 mice and Sprague-Dawley rats at respective doses of 400 and 1000 mg/kg b.w./day administered intraperitoneally for 5 days (Meijer *et al.*, 1982; Meijer and DePierre, 1987). However, the activity of epoxide hydrolase was not affected and the activity of the glutathione-S-transferase was slightly decreased following similar exposure to a C_{22-26} (42%) CP (Meijer *et al.*, 1982).

Lundberg (1980) reported a slight, but significant, dose-related increase in total cytochrome P-450 in mice (strain not reported) injected with organic material from smoke of combusted Cereclor S52 (C_{14-17}, 52% Cl). The N-demethylation of ethylmorphine, a cytochrome P-450 dependent reaction, decreased at low concentrations but increased at higher concentrations.

Ahotupa *et al.* (1982) administered 100 mg/kg b.w. of two CPs to Wistar rats by intraperitoneal injection and reported only minor changes in both hepatic and renal drug-metabolizing enzyme activity when compared with polychlorinated biphenyls and naphthalenes. Paroil (C_{11}, 70% Cl) and, to a lesser degree, chlorez (C_{20}, 70% Cl) increased intestinal aryl hydrocarbon hydroxylase and ethoxycoumarin deethylase activity, and Paroil decreased intestinal UDP glucuronosyl transferase activity.

9.0 Mammalian Toxicology

9.1 Acute Toxicity

The acute toxicity of all CPs examined to date is low. The LD_{50}s following

oral administration to three strains of rats and one strain of mouse has been greater than, and in some cases much greater than, 4 g/kg-b.w. for all CPs examined (Dover Chemical Corp., 1975; Birtley *et al.*, 1980; Bucher *et al.*, 1987). Bucher *et al.* (1987) reported no toxic effects in F344/N rats or B6C3F$_1$ mice following exposure by gavage in corn oil to a C_{10-12} (60% Cl) CP at doses up to 13.6 and 27.2 g/kg-b.w., respectively. In the same study, no toxic effects were reported in F344/N rats or B6C3F$_1$ mice following exposure by gavage in corn oil to a C_{22-26} (43% Cl) CP at 11.7 and 23.4 g/kg-b.w., respectively. Signs of toxicity in rats following oral administration of various CPs included piloerection, muscular incoordination and urinary and fecal incontinence. These signs were most evident when short chain CPs were administered and when doses exceeded 4 g/kg b.w. (Birtley *et al.*, 1980).

In a review by Howard *et al.* (1975), data on acute oral and dermal toxicity in several studies conducted by the Diamond Shamrock Co. were summarized. The information presented therein is inadequate to serve as a basis for assessment of the reliability of these data. However, the reported results of these studies generally support those of the investigations summarized above, and indicate that the acute toxicity of CPs (different chain lengths) is also low by the oral route for guinea pigs (25 g/kg produced no mortality), the dermal route for rabbits (LD_{60} > 10 mL/kg) and the inhalation route for rats (no effects observed at 3.3 mg/L after 1 h).

9.2 Irritancy

Birtley *et al.* (1980) examined the dermal irritancy of a number of CPs containing between 10 to 30 carbon atoms with chlorine content between 40 and 70% (W/W), following covered applications for alternate 24-hour periods to the skin of Wistar rats (n = 3). Most of the compounds (0.1 mL neat) caused some degree of irritation, generally by the third application, but subsequently the condition often improved. A mild skin response was confined to short and medium chain compounds containing 10 to 13 and 14 to 17 carbon atoms, and was generally independent of the degree of chlorination, although occasional moderate reactions were produced by the C_{10-13} paraffins chlorinated to 70%. The authors also commented that it is possible that the irritancy response was partly due in some cases to the presence of stabilizer in the test substance. The ocular irritancy of these CPs was also examined in New Zealand White rabbits (n = 3). Mild and transient irritation was observed following contact with short chain compounds, but not with medium or long chain CPs.

9.3 Short-term Repeated Dose Toxicity

9.3.1 Short Chain CPs

In a well documented study conducted by the National Toxicology Program (NTP, 1986a; Bucher *et al.*, 1987), groups of five F344/N rats of each sex were administered 0, 469, 938, 1875, 3750 or 7500 mg/kg-b.w./day of a C_{12} (60% Cl) CP by gavage in corn oil 5 days per week for 16 days. Necropsy was performed on all animals but tissues were not examined histologically. One of five male and 2 of 5 female rats that received 7500 mg/kg b.w./day died before the end of the study. All rats in this top dose group had diarrhea, and mean body weights of males and females in this group were 22% and 14% lower than those of the vehicle controls. Enlarged livers were observed in 3 to 5 rats in each dose group except the female rats administered the lowest dose (469 mg/kg-b.w./day). The lowest-observed-effect-level (LOEL) was considered to be 469 mg/kg-b.w./day.

In a similar study, groups of five B6C3F$_1$ mice received 0, 938, 1875, 3750,

7500 or 15000 mg/kg-b.w./day of the same CP, by gavage in corn oil. All mice that received 3750, 7500 or 15000 mg/kg-b.w./day and 4 of 5 males and 2 of 5 females that received 1875 mg/kg-b.w./day died before the end of the study. Animals in all dose groups had diarrhea except the females administered the lowest dose (938 mg/kg-b.w./day). Final mean body weights of survivors were not different from those of the vehicle controls. Livers were enlarged in exposed mice that survived to the end of the study (LOEL, 938 mg/kg-b.w./day).

In studies conducted by the Working Party of the Chlorinated Paraffin Manufacturers Toxicology Testing Consortium, a C_{10-13} (58% Cl) CP was administered to male and female Fischer 344 rats (groups of 5 of each sex) in the diet at concentrations of 900, 2700, 9100 or 27300 ppm (54, 162, 546 or 1638 mg/kg b.w./day) (Serrone *et al.*, 1987) or by gavage in corn oil at doses of 30, 100, 300, 1000 or 3000 mg/kg-b.w./day, for 14 days (IRDC, 1981a). The liver weights were increased in both male and female rats administered the C_{10-13} (58% Cl) in the diet or by gavage at dose levels of 100 mg/kg-b.w./day or above. Hepatocellular hypertrophy was observed when the livers were examined microscopically at these doses. In the study by gavage administration, there were clinical signs of toxicity, reductions in growth and in thymus and ovary weights in the high dose group. The no-observed-effect-level (NOEL) determined by the Working Party was considered to be 30 mg/kg-b.w./day for the C_{10-13} (58% Cl) CP administered by gavage.

9.3.2 Medium Chain CPs

In studies conducted by the Working Party of the Chlorinated Paraffin Manufacturers Toxicology Testing Consortium and summarized by Serrone *et al.* (1987), a C_{14-17} (52% Cl) CP was administered to male and female Fischer 344 rats (groups of 5 of each sex) in the diet at concentrations of 150, 500, 1500, 5000 or 15000 ppm (9, 30, 90, 300 or 900 mg/kg-b.w./day) for 14 days. Liver weights were increased in both male and female rats at 5000 ppm (300 mg/kg-b.w./day) and 15000 ppm (900 mg/kg-b.w./day) and liver weight relative to body weight was increased in females receiving 1500 ppm (90 mg/kg-b.w./day). There was mild diffuse hepatocellular hypertrophy of the livers upon microscopic examination in all rats receiving the two highest dose levels (300 and 900 mg/kg-b.w./day). The NOEL determined by the Working Party was considered to be 500 ppm (30 mg/kg b.w./day).

9.3.3 Long Chain CPs

In another well documented study conducted by the National Toxicology Program (NTP, 1986b; Bucher *et al.*, 1987), groups of five F344/N rats and five $B6C3F_1$ mice of each sex were administered a C_{23} (43% Cl) CP by gavage in corn oil 5 days per week for 16 days. Doses were 0, 235, 469, 938, 1875 or 3750 mg/kg b.w./day in rats and 0, 469, 938, 1875, 3750 or 7500 mg/kg-b.w./day in mice. Necropsy was performed on all animals but tissues were not examined histologically. No animals died during the study and no compound-related clinical signs or gross pathologic effects were observed. Body weights of exposed animals were no different from those of the vehicle controls. As no gross effects were observed at any dose level, the NOELs were considered to be the highest doses (3750 mg/kg-b.w./day for rats and 7500 mg/kg-b.w./day for mice).

In studies conducted by the Working Party of the Chlorinated Paraffin Manufacturers Toxicology Testing Consortium (IRDC, 1981b; 1981c), the C_{20-30} (43% Cl) or C_{22-26} (70% Cl) CPs were administered to male and female Fischer 344 rats (groups of 5 of each sex) by gavage in corn oil or in the diet, respectively, for 14 days. Doses administered for the C_{20-30} (43% Cl) and the C_{22-26} (70% Cl) CPs were

30, 100, 300, 1000 or 3000 mg/kg-b.w./day and 150, 500, 1500, 5000, 15000 ppm (17.1, 55, 169, 565 or 1715 mg/kg-b.w./day), respectively. For the study in which the C_{20-30} (43% Cl) was administered, tissues from the liver, kidneys, spleen and any other organs showing gross lesions were examined microscopically; for the C_{22-26} (70% Cl), tissues from the lungs and mesenteric lymph nodes were also examined. No treatment-related effects on clinical signs, organ weights or microscopic appearance of the tissues were found in either male or female rats administered either compound. The NOELs for these compounds were considered, therefore, to be the highest doses [3000 mg/kg-b.w./day for the C_{20-30} (43% Cl) CP by gavage and 15000 ppm (1715 mg/kg-b.w./day) for the C_{22-26} (70% Cl) CP in the diet].

9.4 Long-term Repeated Dose Toxicity

The results of available long-term (subchronic) studies are summarized in Table 9.1. In long-term studies in rats and mice administered CPs by gavage or in the diet, toxicity was similar for both methods of administration and target organs were the liver, kidney and the thyroid-parathyroid gland. The severity of effects was inversely related to chain length, and possibly related to the degree of chlorination (increasing toxicity with increasing degree of chlorination).

9.4.1 Short Chain CPs

Bucher *et al.* (1987; NTP, 1986a) did not establish a NOEL in a well documented 13-week study with a C_{12} (60% Cl) CP administered by gavage in corn oil to F344/N rats and B6C3F$_1$ mice. In this study, groups of 10 male and 10 female rats ingested 0, 313, 625, 1250, 2500 or 5000 mg/kg-b.w./day. In rats, no compound-related deaths or gross lesions were observed. Animals in the 625 mg/kg-b.w./day and higher dose groups were generally inactive after dosing. A dose-related increase in relative liver weights upon necropsy and in the incidence of hypertrophy of hepatocytes was observed. Microscopic evidence of nephrosis was present in the kidneys of all 10 males and 3 of 10 females that received 5000 mg/kg-b.w./day. Nephrosis was also observed in 8/10 male vehicle controls but was subjectively judged to be more severe in exposed male rats than in vehicle controls. Rats in other dose groups were not examined microscopically (LOEL = 313 mg/kg-b.w./day).

Doses administered to mice in this study were 0, 125, 250, 500, 1000 or 2000 mg/kg-b.w./day. In mice, all deaths were considered to be due to gavage error. The final mean body weights of male mice that received the two highest doses were 8% and 13% lower than those of the vehicle controls. Relative liver weights were increased in both male and female mice in all exposure groups. The incidence of hypertrophy of hepatocytes was increased in both males and females at doses of 250 mg/kg-b.w./day and above while focal necrosis of the liver was observed at 125 mg/kg-b.w./day or at higher doses in the males, and at 2000 mg/kg b.w./day only in the females (LOEL = 125 mg/kg-b.w./day).

In a 90-day study conducted by the Working Party of the Chlorinated Paraffin Manufacturers Toxicology Testing Consortium and summarized by Serrone *et al.* (1987) in F344 rats administered a short chain CP (C_{10-13} 58% Cl) by gavage or in the diet at doses of 0, 10, 100 or 625 mg/kg-b.w./day, there were increases in the weights of the liver and the kidneys of both sexes at doses of 100 mg/kg b.w./day and above. In the groups exposed to 625 mg/kg-b.w./day, thyroid-parathyroid weights were increased. The incidence of hepatocellular hypertrophy in both males and females was increased at 100 and 625 mg/kg-b.w./day, based on histopathological examination. Hypertrophy and hyperplasia of the thyroid were also observed in males at the mid and high doses ($\geq$ 100 mg/kg-b.w./day) and in

females at the high dose (625 mg/kg-b.w./day). The incidence of trace-to-mild chronic nephritis in the kidneys of mid- and high-dose males ($\geq$ 100 mg/kg b.w./day) and of pigmentation of the renal tubules in high-dose females (625 mg/kg-b.w./day) was increased. The NOEL was considered by the authors to be 10 mg/kg-b.w./day on the basis that no treatment-related microscopic changes were found in any tissues at this dose. The number of animals per group and range of tissues examined were not reported in the summary of this study published by Serrone *et al.* (1987).

9.4.2 Medium Chain CPs

In a 90-day study in which four different concentrations of a C_{14-17} (52% Cl) CP (0, 250, 500, 2500 or 5000 ppm) were administered in the diet, Birtley *et al.* (1980) reported a dose-related proliferation of the smooth endoplasmic reticulum in the hepatic cells of Wistar rats (n = 24 of each sex per group) receiving 500 ppm or above. There were significant increases in relative liver weight in females at 500 ppm and above and in males at 2500 and 5000 ppm, and in relative kidney weight at 5000 ppm in both sexes. There were also dose-related decreases in food consumption and body weight gain in males at all doses [NOAEL = 250 ppm (13 mg/kg-b.w./day), LOAEL = 500 ppm (25 mg/kg-b.w./day)]. In beagle dogs (n = 4 of each sex per group) fed a diet containing 0, 10, 30 or 100 mg/kg-b.w./day for 90 days, observed effects were confined principally to the males which received 100 mg/kg-b.w./day, in which there were significant increases in serum alkaline phosphatase activity and in liver weight-to-body weight ratios. Electron microscopy revealed an increase in smooth endoplasmic reticulum of the hepatocytes in all exposed dogs at 30 mg/kg b.w./day and above (NOEL = 10 mg/kg b.w./day, LOEL = 30 mg/kg-b.w./day).

In another 90 day study conducted by the Working Party of the Chlorinated Paraffin Manufacturers Toxicology Testing Consortium and summarized by Serrone *et al.* (1987), three different doses (0, 10, 100 or 625 mg/kg-b.w./day) of a medium chain CP (C_{14-17} 52% Cl) were administered in the diet to F344 rats. The weights of the liver and kidneys of both sexes were increased at doses of 100 mg/kg-b.w./day and above. At 625 mg/kg-b.w./day, weights of the thyroid-parathyroid were increased in male rats and adrenal weights were increased in both males and females. Microscopic findings at this dose included increased hepatocellular hypertrophy in the livers of both males and females, hypertrophy and hyperplasia of the thyroid in males, trace-to-mild chronic nephritis in males, and renal tubular pigmentation in the females. The authors considered the NOEL (more appropriately a NOAEL) to be 10 mg/kg-b.w./day on the basis that although the relative liver weight was increased, no treatment-related microscopic changes were found in any tissues at this dose. The number of animals per group and range of tissues examined were not reported in the summary of this study provided in Serrone *et al.* (1987).

9.4.3 Long Chain CPs

In a well documented study (Bucher *et al.*, 1987; NTP, 1986b), doses of 0, 469, 938, 1875, 3750 or 7500 mg/kg-b.w./day of a C_{23} (43% Cl) CP were administered to $B6C3F_1$ mice (n = 10 of each sex per group) by gavage for 5 days per week for 13 weeks. All animals were necropsied and histological examinations were conducted on the high dose and vehicle control groups. No deaths were attributed to chemical toxicity although 17 mice died of gavage-related trauma. No clinical signs of toxicity, effects on body weight or gross lesions at necropsy were noted. The NOEL was considered to be 7500 mg/kg-b.w./day.

Under similar conditions, F344/N rats (n = 10 of each sex per group) were administered the same CP at concentrations of 0, 235, 469, 938, 1875 or 3750 mg/kg-b.w./day by gavage. A dose-related granulomatous inflammation of the liver

was observed in all exposed females but not in the males (NOEL for the males and LOEL for the females was 235 mg/kg-b.w./day).

In a study conducted by the Working Party of the Chlorinated Paraffin Manufacturers Toxicology Testing Consortium and summarized by Serrone *et al.* (1987) in which three doses (0, 100, 900, or 3750 mg/kg-b.w./day) of a C_{20-30} (43% Cl) CP were administered by gavage in corn oil for 90 days to F344/N rats (number unspecified), hepatic lesions in females were similar to those observed in the NTP study. Liver weights were increased and a multifocal granulomatous hepatitis characterized by inflammatory changes and necrosis was observed on microscopic examination of the livers of all exposed females. In addition, mild nephrosis in the kidneys of male rats and mineralization in the kidneys of female rats at the highest dose (3750 mg/kg-b.w./day) were also observed. The NOEL (more appropriately a NOAEL on the basis of observed effects in the kidneys) in males was considered by the authors to be 3750 mg/kg-b.w./day, though the basis was not specified. A NOEL for females could not be established since effects were observed at all dose levels (LOEL = 100 mg/kg-b.w./day). In similar 90-day dietary studies on a C_{22-26} (70% Cl) CP as summarized by Serrone *et al.* (1987), hepatocellular hypertrophy and cytoplasmic fat vacuolation were observed in the liver at 3750 mg/kg-b.w./day. Increases in alanine aminotransferase (ALT) activity were recorded in both males and females in the high dose group while aspartate aminotransferase (AST) was also increased in females at this high dose. The authors concluded, therefore, that the NOEL was 900 mg/kg-b.w./day for both sexes on the basis of the observed effects in the liver. The number of animals per group and range of tissues examined were not reported in the summary of this study provided in Serrone *et al.* (1987).

9.5 Chronic Toxicity/Carcinogenicity

The only studies on the chronic toxicity of CPs identified were two year bioassays in rats and mice conducted by the National Toxicology Program on a short chain CP (C_{12}, 58% Cl) and a long chain product (C_{23}, 43% Cl) (NTP, 1986a; 1986b; Bucher *et al.* 1987). Tumours occurred predominantly in the same organs in which toxic effects were observed in the subchronic studies, namely the liver, the kidneys and the thyroid.

9.5.1 Short Chain CPs

In the studies with the short chain CP (C_{12}, 60% Cl), groups of 50 male and female F344/N rats were administered 0, 312 or 625 mg/kg-b.w./day in corn oil by gavage, 5 days per week for 2 years (NTP, 1986a; Bucher *et al.*, 1987). Necropsy and histological examinations of a wide range of tissues were performed on all animals. Mean body weights of high dose male rats were 8 to 12% lower than in the control group after week 20 and there were clinical signs of chemical-related changes (e.g., decreased activity) after week 90. Survival of male rats in both the low dose group after week 92 and the high-dose group after week 89 was lower than that of vehicle controls, perhaps due to renal toxicity (final survival: vehicle control, 27/50; low dose, 6/50; high dose, 3/50). Survival of female rats in the low dose group at termination was significantly less than that in controls (34/50; 24/50; 29/50, respectively). Examinations of serum enzyme levels or other biochemical or haematological effects appear not to have been included in the study. Non-neoplastic lesions induced by the short chain CP at both dose levels in rats included necrosis, hypertrophy and angiectasis of the liver in both sexes, hyperplasia of the parathyroid in exposed males and in the high dose females, erosion, inflammation, and ulceration of the glandular stomach and forestomach in male rats and the formation of multiple cysts in the kidney. The incidence of nephropathy was also increased in all groups of exposed female rats (LOAEL = 312 mg/kg-b.w./day).

TABLE 9.1 Long-term Toxicity

Species	Protocol	Results	Effect Levels	Reference
Rats (F344/N, groups of 10 of each sex, 4-6 wks old)	0, 313, 625, 1250, 2500 or 5000 mg/kg b.w./day of C_{12} (60% Cl) CP, 5 d/wk for 13 weeks (in corn oil by gavage)	No compound related deaths or gross lesions. Animals in the 625 mg/kg b.w./day and higher dose groups were generally inactive after dosing. Males had slightly decreased body weights at 2500 mg/kg b.w./day or above. A dose related increase in relative liver weight in both sexes at all doses. Some evidence of renal nephrosis at highest dose (10/10 in males and 3/10 in females).	LOEL = 313 mg/kg b.w./day	NTP, 1986a; Bucher et al., 1987
Mice ($B6C3F_1$, groups of 10 of each sex, 4-6 wks old)	0, 125, 250, 500, 1000 or 2000 mg/kg b.w./day of C_{12} (60% Cl) CP, 5 d/wk for 13 weeks (in corn oil by gavage)	No compound related deaths or clinical signs. Males had slightly decreased body weight at 1000 mg/kg b.w./day and above. Dose related increases in relative liver weight and hepatocyte hypertrophy were observed in both sexes at all doses. Focal hepatic necrosis was increased in all exposed groups of males but only in high dose females.	LOEL = 125 mg/kg b.w./day	NTP, 1986a; Bucher et al., 1987
Rats (F344, males and females, number unspecified)	0, 10, 100 or 625 mg/kg b.w./day of $C_{10\text{-}13}$ (58% Cl) CP for 90 d administered in the diet or in corn oil by gavage	"Similar effects in the target organs whether administered in the diet or by gavage". Slight reduction in body weight gain, changes in water consumption and slight skin atonia in high dose males. Increased liver and kidey weight, hepatocellular hypertrophy in both sexes at 100 mg/kg b.w./day and above. Thyroid-parathyroid weights increased at highest dose. Thyroid hypertrophy and hyperplasia in males at 100 mg/kg b.w./day and above and in females at 625 mg/kg b.w./day. Mild chronic nephritis in kidneys of males at 100 mg/kg b.w./day and above. Increased pigmentation of renal tubules in females at 625 mg/kg b.w./day.	NOEL = 10 mg/kg b.w./day	Serrone et al., 1987
Rats (Wistar, groups of 24 of each sex, 160 - 180 g)	0, 250, 500, 2500 or 5000 ppm (0, 13, 25, 125 or 250 mg/kg b.w./day) $C_{14\text{-}17}$ (52% Cl) CP (Cereclor S52, 0.2% epoxidised vegetable oil stabilizer) for 90 d in the diet	Dose-related decreases in food consumption and body weight gain in males at all doses. In males, trend to increased food conversion ratio, statistically significant at 5000 ppm. No effect on female body weight or food consumption. Dose-related tendency towards kidney congestion in both sexes. Significant increase in relative liver weight in females at 500 ppm and above and males at 2500 ppm. Significant increase in relative kidney weight at 5000 ppm in both sexes. Some evidence of dose related proliferation of the smooth endoplastic reticulum in the hepatic cells of both sexes at 500 ppm and above.	NOAEL = 250 ppm (13 mg/kg b.w./day) LOAEL = 500 ppm (25 mg/kg b.w./day)	Birtley et al., 1980

Table 9.1 (continued)

Species	Protocol	Results	Effect Levels	Reference
Dogs (Inbred Beagle, groups of 4 of each sex, 10 - 14 kg)	Concentrations in the diet equivalent to doses of 0, 10, 30 or 100 mg/kg b.w./day C_{14-17} (52% Cl) CP (Cereclor S52, 0.2% epoxidised vegetable oil stabilizer) for 90 d	Significant increases in relative liver weight and in serum alkaline phosphatase in males at 100 mg/kg b.w./day, and increases in smooth endoplasmic reticulum of the hepatocytes in some male and female dogs at 30 mg/kg b.w./day and higher.	NOEL = 10 mg/kg b.w./day	Birtley et al., 1980
Rats (F344, males and females , number unspecified)	0, 10, 100, 625 mg/kg b.w./day of C_{14-17} (52% Cl) CP for 90 d administered in the diet	Increase in relative liver weight in males receiving 10 mg/kg b.w./day was not considered to be biologically significant (no dose-response, one sex and no accompanying histopathological changes). Increase in liver and kidney weights at doses of 100 mg/kg b.w./day and above in both sexes. At 625 mg/kg b.w./day, thyroid-parathyroid weights were increased in males and adrenal weights were increased in both sexes. At the high dose (625 mg/kg b.w./day), microscopic findings included increased hepatocellular hypertrophy in the livers of both sexes, thyroid hypertrophy and hyperplasia in the males, trace-to-mild chronic nephritis in males and renal tubular pigmentation in the females.	NOEL = 10 mg/kg b.w./day	Serrone et al., 1987
Rats (F344/N, groups of 10 of each sex, 4-6 wk old)	0, 235, 469, 938, 1875, 3750 mg/kg b.w./day of C_{23} (43% Cl) CP, 5 d/wk for 13 weeks (in corn oil by gavage)	No compound-related effects on body weight, mortality, clinical signs or gross lesions. Significantly increased incidences of granulomatous liver inflammation in all exposed females.	NOEL = 235 mg/kg b.w./day (male rats) LOEL = 235 mg/kg b.w./day (female rats)	NTP, 1986b; Bucher et al., 1987
Mice ($B6C3F_1$, groups of 10 of each sex, 4-6 wk old)	0, 469, 938, 1875, 3750, 7500 mg/kg b.w./day of C_{23} (43% Cl) CP, 5 d/wk for 13 weeks (in corn oil by gavage)	17 mice died of gavage-related trauma in control and dose groups. No compound related deaths or signs of toxicity observed on gross necropsy or by histopathologic examination. There was no adverse effect of exposure on body weights.	NOEL = 7500 mg/kg b.w./day	NTP, 1986b; Bucher et al., 1987
Rats (F344, males and females , number unspecified)	0, 100, 900, 3750 mg/kg b.w./day of C_{20-30} (43% Cl) CP for 90 d (in corn oil by gavage)	Increases in liver weight and multifocal granulomatous hepatitis characterised by inflammatory changes and necrosis, in females at all doses. Mild kidney nephrosis in males and mineralisation of kidneys in females at 3750 mg/kg b.w./day.	LOEL = 100 mg/kg b.w./day (female) NOEL = 3750 mg/kg b.w./day (male, more appropriately a NOAEL)	Serrone et al., 1987

Table 9.1 (continued)

Species	Protocol	Results	Effect Levels	Reference
Rats (F344, males and females, number unspecified)	Dose equivalent to 0, 100, 900, 3750 mg/kg b.w./day $C_{22\text{-}26}$ (70% Cl) CP for 90 d. (Actual dietary concentrations not presented in review).	Slight decreases in body weight gain of both sexes at 3750 mg/kg b.w./day. Slight increases in food consumption in males at all doses. Increases in liver weight, hepatocellular hypertrophy, cytoplasmic fat vacuolation and in hepatocellular alanine aminotransferase levels in both sexes at 3750 mg/kg b.w./day. Increases in hepatocellular aspartate aminotransferase in females and chronic nephritis in males at 3750 mg/kg b.w./day.	NOEL = 900 mg/kg b.w./day	Serrone et al., 1987

The incidences of hepatic "neoplastic nodules" (including adenomas) (vehicle control, 0/50; low dose, 10/50; high dose, 16/48 in male rats; 0/50, 4/50, 7/50 in female rats) and "neoplastic nodules or hepatocellular carcinomas" (combined) (0/50; 13/50; 16/48 in male rats; 0/50; 5/50; 7/50 in female rats) were significantly increased in both sexes. (The incidences of hepatic adenomas were not reported separately). In the kidney, the incidences of adenomas (0/50; 7/50; 3/49) or hyperplasia (1/50; 9/50; 12/49) of the renal tubular cells were significantly increased in exposed male rats; two males in the low dose group had tubular cell adenocarcinomas. The incidence of follicular cell adenomas or carcinomas (combined) of the thyroid gland was significantly increased in female rats (0/50; 6/50; 6/50). The incidence of endometrial stromal polyps in low dose female rats was greater than those in the vehicle controls (probably not treatment-related since there was no increase at higher doses). The incidence of mononuclear cell leukemia was also significantly increased in all groups of exposed male rats (7/50; 12/50; 14/50) and in female rats in the low dose group (11/50; 22/50; 16/50). Based on the observed increase in this tumour type in both sexes and the dose-related trend in males, it was concluded that these results were suggestive of an association of mononuclear cell leukemias with the administered chlorinated paraffin, though the absence of a dose-response relationship (for either incidence or severity) in females weakens the argument. Though the incidence of pancreatic acinar cell tumours was increased in male rats in the low dose group, owing to much higher incidence in the concurrent vehicle control group compared to the historical average and absence of a dose-response relationship, it is difficult to attribute this effect to the administered chlorinated paraffin.

In similarly sized groups of B6C3F_1 mice administered 0, 125 or 250 mg/kg b.w./day of the same CP, the body weights of exposed females were about 10% lower than those of the control group during the second year. Survival of female mice in the high dose group (250 mg/kg-b.w./day) was significantly less than that of controls after week 100, but survival of the other groups of exposed and control mice was similar. Results of examination of serum enzyme levels or other biochemical or haematological effects were not included. The only non-neoplastic lesion reported was an increase in the incidence of nephrosis in high dose females (LOAEL = 125 mg/kg-b.w./day). The incidences of hepatic adenomas in exposed male and female mice (11/50; 20/50; 29/50 in males; 0/50; 18/50; 22/50 in females), hepatocellular carcinomas in high dose female mice (3/50; 4/50; 9/50), and hepatocellular adenomas or carcinomas (combined) in both sexes (20/50; 34/50; 38/50 in male mice and 3/50; 22/50; 28/50 in female mice) were significantly increased. The incidence of follicular cell adenomas or carcinomas (combined) of the thyroid gland were significantly increased in the high dose group of female mice (trend significant) (8/50; 12/49; 15/49). In addition, alveolar/bronchiolar carcinomas were increased significantly in the high dose group of male mice (trend significant) (0/50; 3/50; 6/50); however, the incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in males (5/50; 6/50; 9/50) were not significantly greater than those in vehicle controls.

The NTP concluded that "under the conditions of these 2-year gavage studies, there was clear evidence of carcinogenicity of chlorinated paraffins (C_{12}, 60% Cl) for F344/N rats and B6C3F_1 mice. However, the maximum tolerated dose may have been exceeded in male and female rats". It should be noted, however, that most of the mortality in exposed male rats occurred after 80 weeks, whereas overall survival in exposed female rats was reasonable compared with that in vehicle controls. The fact that the maximum tolerated dose may have been exceeded has probably not, therefore, jeopardized the validity of the findings to any significant extent.

There have been some criticisms of the use of the NTP bioassay on short chain CPs for human risk assessment (Serrone et al., 1987) including that B6C3F_1 mice are known to be susceptible to tumours; this comment seems to be undermined, however, by the observation of excesses of tumours at several sites in both rats and mice. It has also been suggested that the use of corn oil as a vehicle may

have altered the normal nutritional status of the animals which in turn may have influenced the carcinogenic response. However, the use of a corn oil vehicle would be expected to alter the normal nutritional status of both the vehicle controls and exposed groups to the same extent. Though the possibility of an interactive effect between the vehicle and the administered chlorinated paraffin in inducing tumours cannot be ruled out, considering the high fat content of the western diet, it can be argued that a bioassay in rodents involving dietary administration of the test compound is no better an indicator of potential carcinogenicity to humans than one involving gavage administration in corn oil. Moreover, in investigations described in the same report, Serrone *et al.* (1987) concluded that results in a subchronic study in which a medium chain CP was administered were similar, "whether administered in the diet or by gavage".

9.5.2 Long Chain CPs

The carcinogenic response following exposure to the long chain CP (C_{23}, 43% Cl), administered to rats and mice under identical conditions was not as clear as that for the short chain CP; however, there were some increases in tumour incidence in both species (NTP, 1986b; Bucher *et al.*, 1987). Because the granulomatous inflammation in the 90-day study was considered to be potentially life threatening, doses selected for female rats in this study were lower than those for males (0, 100, 300 or 900 mg/kg-b.w./day for females and 0, 1875 or 3750 mg/kg-b.w./day for males by gavage in corn oil, 5 days per week for 2 years). Additional groups of 20 male and 20 female rats were exposed concurrently to the same doses for 6 or 12 months for analyses of the weights of the spleen, liver, thymus, adrenal glands, brain, kidneys and heart, serum hepatic enzymes including sorbitol dehydrogenase, AST and ALT and haematological parameters. In the two-year study, necropsy and histological examinations were performed on all animals.

In rats, relative liver weights were increased in exposed males at 12 months and in exposed males and females at 6 and 12 months. There was a dose-related increase in liver weights at 6 (females only) and 12 months. Activities of several serum enzymes were also slightly elevated at both 6 and 12 months. There were also variations in haematological parameters at 6 and 12 months observed only in females. There were no significant differences in survival, in clinical signs of toxicity or in mean body weights of exposed and control groups in either sex in the two-year study. Members of the NTP Peer Review Panel commented that although the high viscosity of the vehicle may have prevented administration of maximum tolerated doses (as indicated by the lack of observed effects on survival or body weight gain), the linear increase in liver weight and increases in serum enzyme levels indicated achievement of a biologically effective dose in rats.

The primary nonneoplastic lesion related to administration of this CP included a diffuse lymphohistiocytic inflammation in the liver and in the pancreatic and mesenteric lymph nodes in male and female rats. Splenic congestion was a secondary effect. These lesions occurred earlier and at lower doses in female rats than in male rats (LOAEL = 100 mg/kg-b.w./day). There was a significant positive trend in the incidence of pheochromocytomas of the adrenal medulla in female rats (1/50; 4/50; 6/50; 7/50) with the incidence in the high dose group being significantly greater than that in vehicle controls. Though islet cell adenomas of the pancreas occurred with a positive trend in male rats, the incidences in each of the dose groups were not significantly greater than that in the vehicle controls (0/49; 1/50; 4/50). At 100 mg/kg-b.w./day in female rats, there was also an increased incidence of endometrial stromal polyps and endometrial stromal polyps or sarcomas (combined) but this was probably not treatment-related since there was no such increase at higher doses.

Male and female B6C3F_1 mice were exposed to 0, 2500 or 5000 mg/kg-b.w./day. There were no significant differences in survival or in clinical signs of toxicity between exposed and control groups in either sex. No significant increases in nonneoplastic lesions were attributed to exposure to the C_{23} (43% Cl) CP in mice. However, for female mice, 60 to 70% of the early deaths in each group were attributed to utero-ovarian infection and this may have decreased the sensitivity of the study to detect a carcinogenic effect. Both males and females in the low dose group gained less weight than did those in the control and the high dose groups. There was a positive trend in malignant lymphomas in male mice, the incidence in the high dose group being significantly greater than that in vehicle controls (6/50; 12/50; 16/50). There were marginal increases (not statistically significant) in the incidences of hepatocellular carcinomas (1/50; 1/49; 6/50) and of adenomas or carcinomas of the liver (combined) (4/50; 3/49; 10/50) in female mice. Follicular cell carcinomas in male mice occurred with a positive trend (0/49, 0/48, 3/49) in the thyroid gland; however, the incidence of follicular cell adenomas or carcinomas (combined) was not significantly greater than that in vehicle controls (1/49; 3/48; 5/49), and was within the range for historical controls at this test laboratory.

Under the conditions of these 2-year gavage studies, the NTP concluded that there was no evidence of carcinogenicity for male F344/N rats, there was equivocal evidence of carcinogenicity for female F344/N rats and female B6C3F_1 mice and there was clear evidence of carcinogenicity for male B6C3F_1 mice. However, there was considerable disagreement among members of the Peer Review Panel as to whether the evidence in male mice should be considered as "clear" or "some".

9.6 Mutagenicity and Related End-points

Chlorinated paraffins [C_{10-13}, 50% Cl; C_{14-17}, 52% Cl; C_{20-30}, 42% Cl (Birtley *et al.*, 1980) and C_{12}, 60% Cl (NTP, 1986a; Zeiger *et al.*, 1990); C_{23}, 43% Cl (NTP, 1986b)] were not mutagenic to several strains of *S. typhimurium* in the presence or absence of an exogenous metabolic system from Aroclor 1254-induced liver of rats or Syrian hamsters. However, Meijer *et al.* (1982) reported a small but significant response to Cereclor 70L (C_{10-23}, 70% Cl) in the Ames test in one strain of *S. typhimurium* (TA 98) in the presence but not in the absence of S9 fraction from the liver of rats; this compound was not mutagenic in two other strains (TA 100 and TA 1537) under the same test conditions.

A short chain CP (C_{12}, 60%) was mutagenic in L5178Y mouse lymphoma cells at concentrations of 48 to 60 μg/mL, inducing trifluorothymidine resistance in the absence of S9 (Myhr *et al.*, 1990). A long chain CP (C_{23}, 43% Cl) induced chromosome aberrations in the absence of S9 at concentrations up to 5000 μg/mL, and induced sister chromatid exchanges with and without S9 at 5 μg/mL in Chinese hamster ovary cells *in vitro* (Anderson *et al.*, 1990).

The potential of five concentrations (0.25, 2.5, 25, 250 and 2500 μg/mL) of each of several compounds [i.e. C_{10-13}, 50% Cl CP; C_{14-17}, 52% Cl CP; C_{20-30}, 42% Cl CP] to induce cell transformation in baby hamster kidney (BHK) cells was reported by Birtley *et al.* (1980). There were no increases in the cell transformation frequency as compared with those of the background values of the CPs tested, even at the LC_{50} concentrations. However, in a later study conducted by the same authors (ICI, 1982a; 1982b), there was an increase in transformed colonies in BHK cells after exposure to the LC_{50} concentrations of 44 μg/mL and 58 μg/mL of a C_{10-13}, 58% Cl CP in the absence and presence of S9 mix, respectively. Similarly, there was an increase in cell transformation frequency in BHK cells at the LC_{50} concentrations of 10 μg/mL and 294 μg/mL of a C_{22-26}, 70% Cl CP in the presence and absence of S9 mix. No explanation was offered by the authors for the variation in results.

A CP containing 10 to 13 carbon atoms and chlorinated to 58%, was administered orally by gavage in corn oil on 5 consecutive days to groups of 15 male Charles River rats at doses of 0, 250, 750 and 2000 mg/kg-b.w./day. Two days after the end of exposure, each of the males was paired with two females for 5 days. Following two days of rest, the pairing was repeated with two new females per male and this cycle was repeated ten times. This CP did not produce a dominant lethal mutation affecting the post-meiotic stage of spermatogenesis. Data presented in the published summary of this study (Serrone *et al.*, 1987) were inadequate for evaluation.

In another *in vivo* study summarized by Serrone *et al.* (1987), chlorinated paraffins (C_{10-13}, 58% Cl; C_{14-17}, 52% Cl; C_{20-30}, 43% Cl and C_{22-26}, 70% Cl) administered orally by gavage (the first three in corn oil and the last one in 1% carboxymethylcellulose) to groups of 8 mature male F344/N rats for 5 consecutive days at doses up to 5 g/kg-b.w./day did not increase the frequency of chromosomal or chromatid aberrations in bone marrow cells. Therefore, these CPs were not considered to be clastogenic in this test system. Though data presented in the published summary of this study were inadequate for evaluation, it appears that a toxic dose was administered for at least two of the CPs tested (C_{10-13}, 58% Cl and C_{22-26}, 70% Cl), since reduced body weight gain was observed.

In a study designed to evaluate the effects on unscheduled DNA synthesis (UDS) and cell proliferation of a CP (C_{12}, 60% Cl) in rat liver (Ashby *et al.*, 1990), male Alpk:AP rats were administered 500, 1000 or 2000 mg/kg-b.w. by gavage in corn oil. No evidence of UDS was observed at any dose at either 2 or 12 hours. However, a strong positive response was observed in the cell proliferation assay; there was a dose and time-related increase in the incidence of hepatocytes in the S-phase. The authors concluded that this CP is not genotoxic but may act as a peroxisome proliferator in the induction of liver adenomas in rats.

In a study conducted by Elcombe *et al.* (1989) reported in the form of an abstract, various CPs (C_{10-12}, 60% Cl; C_{10-12}, 56% Cl; C_{14-17}, 40% Cl; C_{23-26}, 43%) were administered by gavage in corn oil to male F344/N rats at a dose of 2000 mg/kg b.w./day and to female F344/N rats and male and female B6C3F_1 mice at a dose of 1000 mg/kg-b.w./day for 14 days. The liver was removed, weighed and examined histologically, biochemically and ultrastructurally. Three CPs (C_{10-12}, 60% Cl; C_{10-12}, 56% Cl; C_{14-17}, 40% Cl) increased liver/body weight ratios and elicited the proliferation of smooth endoplasmic reticulum and peroxisomes. Enzyme activities associated with peroxisome proliferation (peroxisomal beta-oxidation and microsomal fatty acid hydroxylation) were also markedly induced. The long chain CP (C_{23-26}, 43%) had little effect upon these parameters.

9.7 Developmental and Reproductive Toxicity

9.7.1 Developmental Toxicity

In a series of studies conducted for the Chlorinated Paraffins Manufacturers Toxicology Testing Consortium, the number and location of viable and nonviable fetuses, early and late resorptions, the number of total implantations and corpora lutea and the incidence of foetal malformations was examined following administration of short, medium or long chain CPs (C_{10-13}, 58% Cl, C_{14-17}, 52% Cl, C_{20-30}, 43% Cl) by gavage in corn oil and a C_{22-26} (70% Cl) CP in 1% carboxymethyl cellulose to pregnant Charles River rats on gestation days 6 to 19 and pregnant Dutch Belted rabbits on days 6 to 27 of gestation and compared to that in vehicle controls (Table 9.2). With the exception of an increase in the incidence of adactyly and/or shortened digits in the offspring of rats exposed to a maternally toxic dose (2000 mg/kg-b.w./day by gavage in corn oil) of a C_{10-13} (58% Cl) CP, teratogenic effects were not observed. In only one of the

studies (short chain chlorinated paraffin) (IRDC, 1983a), were embryo- or foeto-toxic effects observed at doses less than those which were toxic to the mothers. Maternal toxicity appeared to be related to chain length and in several cases, pregnant rabbits were more sensitive to CPs than pregnant rats.

9.7.1.1 Short Chain CPs

Doses of 100, 500 or 2000 mg/kg-b.w./day of a C_{10-13} (58% Cl) CP were administered to groups of 25 pregnant rats (IRDC, 1982a). Eight of 25 (32%) dams in the group receiving 2000 mg/kg-b.w./day died between gestation days 15 and 20. Clinical signs of maternal toxicity were observed in both the mid- and high-dose groups. There was a statistically significant ($p<0.05$) increase in the number of post implantation losses (attributed to an increased incidence of early and late resorptions), a resultant decrease in the number of viable fetuses per dam, and increased incidence of adactyly and/or shortened digits at the high dose (NOEL in mothers = 100 mg/kg-b.w./day; NOEL in offspring = 500 mg/kg-b.w./day).

Pregnant rabbits were more sensitive to this chlorinated paraffin than the pregnant rats as determined by the doses that could be tolerated in an earlier range finding study as cited in IRDC (1983a). There was no maternal toxicity in groups of 16 pregnant rabbits at any of the test doses (10, 30 or 100 mg/kg b.w./day). Embryotoxicity (litter resorption; increase in early and late embryonic death and corresponding increase in mean postimplantation loss) was seen in both the mid- and high-dose groups but there were no effects on the occurrence of malformations or skeletal variation at any dose level (NOEL in mothers = 100 mg/kg-b.w./day; NOEL in offspring = 10 mg/kg-b.w./day).

9.7.1.2 Medium Chain CPs

In groups of 25 pregnant rats administered 500, 2000 or 5000 mg/kg-b.w./day of a C_{14-17} (52% Cl) CP, there was an increase in clinical signs compared to controls in the mid- and high-dose groups, which indicated slight maternal toxicity (IRDC, 1984). There were no dose-related differences in necropsy findings, mean maternal weight gain, or mean uterine weight between the control and the exposed groups (NOEL in mothers = 500 mg/kg-b.w./day; NOEL in offspring = 5000 mg/kg-b.w./day).

Pregnant rabbits were more sensitive to this CP than pregnant rats (as determined in an earlier range finding study) as cited in IRDC (1983b). In groups of 16 rabbits exposed to 10, 30 or 100 mg/kg-b.w./day, there was congestion of the lobes of the lung in all the exposed groups which was not dose-related and therefore, unlikely to have resulted from treatment. Five dams aborted: one in the control group, two in the mid- and two in the high-dose group, though the authors did not comment on the biological significance of these results. There were no differences in mean maternal body weight gain, in the number of litters/foetuses with malformations or in developmental and genetic variations (unspecified) when compared to the controls (NOAEL in mothers = 30 mg/kg-b.w./day; NOEL in offspring = 100 mg/kg-b.w./day).

9.7.1.3 Long Chain CPs

Groups of 25 pregnant rats were exposed to 500, 2000 or 5000 mg/kg-b.w./day of a C_{20-30} (43% Cl) CP (IRDC, 1983c). One rat died on day 18 of gestation at 5000 mg/kg-b.w./day but the cause of death could not be determined. There were no adverse effects of exposure on maternal appearance, behaviour, necropsy findings or mean body weight gain (NOEL in mothers = 2000 mg/kg-b.w./day; NOEL in offspring = 5000 mg/kg-b.w./day).

The authors reported that rabbits were not more sensitive than rats when groups of 16 pregnant rabbits received the same doses of this CP (IRDC, 1981d). There were no treatment-related effects on mean maternal body weight gain, appearance and behaviour at any dose except for a dose-related increase in the incidence of soft stools and/or anogenital staining. Three dams aborted, one in the mid-dose group (2000 mg/kg-b.w./day) and two in the high-dose group (5000 mg/kg-b.w./day) but these observations were not statistically significant. A "slight" but statistically non-significant increase in mean post-implantational loss and a corresponding "slight" but statistically non-significant decrease in mean number of viable fetuses at 5000 mg/kg-b.w./day were also reported. Based on a limited number of fetuses examined, the authors concluded that exposure to the high dose of this CP (5000 mg/kg-b.w./day) did not induce teratogenic effects; however, owing to the few offspring examined, definitive conclusions could not be drawn (NOAEL in mothers and offspring = 5000 mg/kg-b.w./day).

Groups of 25 pregnant rats were exposed to 500, 2000 or 5000 mg/kg-b.w./day C_{22-26} (70% Cl) CP (IRDC, 1983d). Survival for the control and for all exposed groups was 100%. There were no differences in observations at necropsy or in maternal body weight change in any exposed group when compared with those of the control group. There were no differences in incidences of developmental variations and fetal malformations in the exposed as compared to the control group (NOEL in mothers and offspring = 5000 mg/kg-b.w./day).

In groups of 16 rabbits exposed to 100, 300 or 1000 mg/kg-b.w./day of a C_{22-26} (70% Cl) CP, one rabbit in the mid-dose (300 mg/kg-b.w./day) group died from an undetermined cause and two rabbits in the high-dose group (1000 mg/kg b.w./day) died because of intubation error (IRDC, 1982b). At necropsy, there was a slight increase in the occurrence of congested lungs in the exposed versus control groups. This increase appeared to be treatment-related but not dose-related on the basis that neither the severity nor the incidence in a particular severity category were increased in a dose-related manner in the exposed groups. There were no differences in maternal appearance, behaviour and body weight gain between the exposed and the control groups. There were no statistically significant differences in the weight of the uterus, the number and location of viable and nonviable fetuses, early and late resorptions, the number of total implantations and corpora lutea or the incidence of fetal malformations in litters of the exposed versus control groups (LOEL in mothers = 100 mg/kg b.w./day; NOEL in offspring = 1000 mg/kg-b.w./day).

9.7.2 Reproductive Toxicity

In a reproductive study conducted for the Chlorinated Paraffins Manufacturers Toxicology Consortium (IRDC, 1985), a C_{14-17} (52% Cl) CP was fed in the diet to Charles River rats at levels of 0, 100, 1000 or 6250 ppm (0, 6, 62 or 384 mg/kg-b.w./day for the males, 0, 8, 74 or 463 mg/kg-b.w./day for the females based on food consumption data). The diet was fed to both males and females for 28 days before mating, during mating and in the case of the females, continuously up to postnatal day 21. The dams and 10 pups/sex/group were then sacrificed and examined for gross lesions. Pups were administered the same diet as their parents from weaning until the offspring were 70 days of age (i.e. 0, 5.7 or 58.7 mg/kg-b.w./day for the males and 0, 7.2 or 70.1 mg/kg-b.w./day for the females; all animals in the highest dose group died before weaning). There were no dose-related differences in appearance, fertility, body-weight gain, food consumption or reproductive performance in the parental generation. A significant decrease in the survival of pups was apparent in the high-dose group on lactation day 10 and none of the pups in this group survived to weaning. Pup survival was decreased at doses ≥ 1000 ppm in the diet by lactation day 21. Observations in pups in the mid- and high-dose groups included bruised areas, decreased activity, laboured breathing, pale discoloration and/or blood around the orifices. Effects observed at necropsy in pups that died during the study

included pale liver, kidneys and lungs, and blood in the cranial cavity, brain, stomach and intestines. Reduced erythrocytes, hemoglobin, and hematocrit were noted in the pups in the high-dose group on lactation day 6 relative to the control values obtained on lactation day 7 (there was no haematological assessment of animals in the low- and mid-dose groups at this point in time). Though these findings were suggestive of toxicity, the sample size (single litter/group) was too small to permit definitive conclusions. There were no differences in litter size and body weight at birth. However, pup weights in males and females were slightly (but not significantly) lower in the low- and mid-dose groups on lactation day 21 and continued after weaning. The authors suggested that these effects were more likely attributable to lactational rather than to *in utero* exposure [NOEL = 6250 ppm (384 mg/kg-b.w./day for the male and 463 mg/kg-b.w./day for the female parents); LOEL = 100 ppm (5.7 mg/kg-b.w./day for the male and 7.2 mg/kg-b.w./day for the female pups)]. The authors added that based on preliminary results from a cross fostering study, mortality in pups exposed via milk was greater than that in pups exposed only *in utero* (Serrone *et al.*, 1987).

9.8 Neurological Effects

Eriksson and Kihlstrom (1985) administered two short chain CPs (C_{10-13}, 49% Cl and C_{10-13}, 70% Cl) by a single intravenous injection (30 to 300 mg/kg-b.w.) to NMRI adult male mice (n = 5 per group) and assessed their performance in a rotarod test 15 and 40 minutes after treatment. There was a dose related trend of decreased motor capacity which was statistically significant at the highest dose for the 49% Cl paraffin. There was also a trend to decreased rectal temperature following exposure to both substances, which was statistically significant at the highest dose. In another study, there was no effect on the density of muscarinic cholinergic receptors in the brain, but there was a 65% decrease in V_{max} for sodium-dependent choline uptake, indicating a presynaptic effect on the cholinergic system in the immature mouse brain when a single dose (1 mg/kg b.w.) of polychlorohexadecane was administered orally to 10-day-old male and female NMRI mice (Eriksson and Nordberg, 1986).

10.0 Effects on Humans

10.1 Case Reports and Clinical Studies

Reported cases of industrial poisoning or contact dermatitis in workers involved in the production and handling of chlorinated paraffins have not been identified.

Dermal application of PAROIL 142 and CHLOREZ 700 (composition unspecified) did not produce irritation of the skin, or, on re-application, an allergic response in humans (Dover Chemical Corp., 1975). No other details were provided in this report. In a review of data from the Diamond Shamrock Co., Howard *et al.* (1975) reported that in similar studies with Chlorowax 70 (C_{24}, 70% Cl), Chlorowax 500-C (C_{12}, 59% Cl) and Chlorowax 40 (C_{24}, 43% Cl), there was no skin irritation or allergic response in tests in humans. However, the doses used in all of these studies were not reported, and may have been below a threshold level for a response. English *et al.* (1986) first reported that allergic reactions to CP have been observed but on subsequent testing of the components of the CP, it was found that the glycidyl ester of hexahydrophthalic acid (added as a chloride/chlorine scavenger) was responsible.

TABLE 9.2 Reproductive and Developmental Effects

Species	Protocol	Results	Effect Levels	Reference
Rats (Charles River, groups of 25)	0, 100, 500, 2000 mg/kg b.w./day C_{10-13} (58% Cl) CP by gavage in corn oil daily on days 6-19 of gestation	Eight of 25 (32%) dams in the 2000 mg/kg b.w./day treatment group died between gestation days 15 and 20. A moderate reduction in mean maternal body weight gain occurred in the 2000 mg/kg b.w./day group when compared with controls. Yellow or brown matting and staining of the anogenital haircoat, soft stool, red or brown matter (or staining) in the nasal region, decreased activity, oily haircoats, emaciation and excessive salivation were observed in dams exposed at 500 and 2000 mg/kg b.w./day. The frequency of these observations increased with increasing dosage level. A statistically significant ($p < 0.05$) increased number of post implantation losses and of early and late resorptions, decreased number of viable fetuses per dam, and increased incidence of adactyly and/or shortened digits at the high dose.	NOEL = 100 mg/kg b.w./day (mothers) NOEL = 500 mg/kg b.w./day (offspring)*	IRDC, 1982a
Rabbits (Dutch Belted, groups of 16)	0, 10, 30, 100 mg/kg b.w./day C_{10-13} (58% Cl) CP by gavage in corn oil daily on days 6-27 of gestation	"Pregnant rabbits were more sensitive to this chlorinated paraffin than were pregnant rats, as judged by the doses that could be tolerated". No unscheduled deaths in any of the study groups. There were no effects on the appearance or behaviour, mean body weights and body weight change in the mothers. Litter resorption was seen in both the mid-dose and high-dose groups and this correlated with an increase in early and late embryonic death with a corresponding increase in the mean postimplantation loss. No effects on the occurrence of malformations at any dose level.	NOEL = 100 mg/kg b.w./day (mothers) NOEL = 10 mg/kg b.w./day (offspring)	IRDC, 1983a
Rats (Charles River, groups of 25)	0, 500, 2000, 5000 mg/kg b.w./day C_{14-17} (52% Cl) CP by gavage in corn oil daily on days 6-19 of gestation	Signs of maternal toxicity which included an increased incidence of wet matted and yellow stained haircoat in the anogenital area (high-dose group only) and/or soft stool occurred in rats in the mid- (2000 mg/kg b.w./day) and high-dose (5000 mg/kg b.w./day) groups. No differences in the weight of the uterus, the number and location of viable and nonviable fetuses, early and late resorptions, the number of total implantations and corpora lutea and in the incidence of foetal malformations in exposed vs control animals.	NOEL = 500 mg/kg b.w./day (mothers) NOEL = 5000 mg/kg b.w./day (offspring)*	IRDC, 1984
Rabbits (Dutch Belted, groups of 16)	0, 10, 30, 100 mg/kg b.w./day C_{14-17} (52% Cl) CP by gavage in corn oil daily on days 6-27 of gestation	Pregnant rabbits were more sensitive than pregnant rats (as determined in range finding study). There was congestion of the lobes of the lung in all the exposed groups but this observation did not occur in a dose-related pattern, and was, therefore, probably unrelated to exposure. No differences in the weight of the uterus, the number and location of viable and nonviable fetuses, early and late resorptions, the number of total implantations and corpora lutea, in the number of litters/foetuses with malformations or in developmental and unspecified genetic variations when compared to those of the controls.	NOAEL = 30 mg/kg b.w./day (mothers) NOEL = 100 mg/kg b.w./day (offspring)**	IRDC, 1983b

* maternally toxic dose

** maternally toxic dose

Table 9.2 (continued)

Species	Protocol	Results	Effect Levels	Reference
Rats (Charles River, groups of 25)	0, 500, 2000, 5000 mg/kg b.w./day C_{20-30} (43 % Cl) CP by gavage in corn oil daily on days 6-19 of gestation	One rat died on day 18 of gestation at 5000 mg/kg b.w./day. No adverse treatment-related effects on maternal appearance, behaviour, necropsy findings or mean body weight gain of any exposed groups. No statistically significant differences in the weight of the uterus, the number and location of viable and nonviable fetuses, early and late resorptions, the number of total implantations and corpora lutea, or the incidence of fetal malformations in the exposed groups.	NOEL = 2000 mg/kg b.w./day (mothers) NOEL = 5000 mg/kg b.w./day (offspring)*	IRDC, 1983c
Rabbits (Dutch Belted, groups of 16)	0, 500, 2000, 5000 mg/kg b.w./day C_{20-30} (43 % Cl) CP by gavage in corn oil daily on days 6-27 of gestation	Rabbits were not more sensitive than rats - able to tolerate the same doses. There were no treatment-related effects on mean maternal body weight gain, appearance and behaviour. One female died in the high dose group due to a gavage injury. 1/13 at mid-dose (2000 mg/kg b.w./day) and 2/12 at high dose (5000 mg/kg b.w./day) aborted but not statistically significant. "Slight" but statistically insignificant increase in mean post-implantation loss and corresponding decrease in mean number of viable fetuses at 5000 mg/kg b.w./day. Based on a limited number of fetuses examined, the authors concluded that treatment with this CP at the high dose (5000 mg/kg b.w./day) did not induce teratogenic effects; however, the sample size in this group was considered small to make a definitive conclusion in regard to the teratogenic potential at this dose level.	NOAEL = 5000 mg/kg b.w./day (mothers and offspring)	IRDC, 1981d
Rats (Charles River, groups of 25)	0, 500, 2000, 5000 mg/kg b.w./day C_{22-26} (70 % Cl) CP by gavage in 1 % carboxymethyl cellulose daily on days 6-19 of gestation	No differences in the necropsy observations, maternal body weight and body weight change in exposed group. There was a slight increase in postimplantation loss in all the exposed groups not considered to be compound-related. No differences in incidences of developmental variations and fetal malformations in the exposed group.	NOAEL = 5000 mg/kg b.w./day (mothers and offspring)	IRDC, 1983d
Rabbits (Dutch Belted, groups of 16)	0, 100, 300, 1000 mg/kg b.w./day C_{22-26} (70 % Cl) CP by gavage in 1 % carboxymethyl cellulose daily on days 6-27 of gestation	Two high-dose rabbits died on days 9 and 10 of gestation because of intubation error and one mid-dose animal died on day 16 from an undetermined cause. At necropsy, there was a slight increase in the occurrence of congested lungs in all exposed groups. This increase appeared to be treatment- but not dose-related on the basis that neither the severity nor the incidence in a particular severity category were increased in a dose-related manner in the exposed groups. No differences in maternal appearance, behaviour or body-weight gain or in the occurrence of unspecified genetic and developmental variations in the exposed vs control animals. There were no statistically significant differences in the weight of the uterus, the number and location of viable and nonviable fetuses, early and late resorptions, the number of total implantations and corpora lutea or in the incidence of foetal malformations in the litters of the exposed groups.	LOEL = 100 mg/kg b.w./day (mothers) NOEL = 1000 mg/kg b.w./day (offspring)*	IRDC, 1982b

* maternally toxic dose

Table 9.2 (continued)

Species	Protocol	Results	Effect Levels	Reference
Reproduction				
Rats (Charles River, groups of 5 males and 10 females)	0, 100, 1000, 6250 ppm (equivalent to 0, 6, 62, or 384 mg/kg b.w./day for the males, 0, 8, 74, or 463 mg/kg b.w./day for the females based on food consumption data) C_{14-17} (52% Cl) CP in the diet. Both sexes exposed for 28 days pre-mating, during mating, then females continuously exposed to postnatal day 21. The dams and 10 pups/sex/grooup were sacrificed and examined for gross lesions. Pups exposed from weaning until 70 d old (equivalent to 0, 5.7 or 58.7 mg/kg b.w./day for the males and 0, 7.2 or 70.1 mg/kg b.w./day for the females).	There were no statistically significant differences in F_0 male and female appearance, behaviour, necropsy findings or fertility, F_0 male body weight and food consumption or F_0 female gestation body weight and food consumption or reproductive performance in the exposed groups when compared with the control group. No toxicity or adverse effects in pups prior to lactation day 7. A significant decrease in pup survival was apparent at 6250 ppm on lactation day 10 - none survived to weaning. Survival at 1000 ppm was reduced by lactation day 21. Additional evidence of toxicity in the F_1 pups at the mid (1000 ppm) and high (6250 ppm) concentrations included bruised areas, decreased activity, laboured breathing, pale discolouration and/or blood around orifices. Necropsy findings included pale liver, kidneys and lungs, and blood in cranial cavity, brain, stomach and intestines. Reduced erythrocytes, hemoglobin, and hematocrit were noted in the pups in the high dose group on lactation day 6 relative to the control values obtained on lactation day 7 [though these findings were suggestive of toxicity, the sample size (single litter/group) was too small to permit a definitive conclusion]. There were no differences in litter size and body weight at birth. However, pup weights at all doses were reduced by lactation day 21 and in female pups, the reduced weight continued after weaning but became less pronounced in males. There were no exposure-related differences in F_1 post-weaning appearance, behaviour, food consumption, clinical signs or histopathological examinations in the low (100 ppm) and mid (1000 ppm) exposure groups. "The haematological effects appeared to be a dysfunction in the vitamin K dependent elements of the intrinsic component of the clotting process." Based on preliminary results of a cross-fostering study, mortality in pups exposed via milk was greater than in pups exposed only in utero.	NOEL= 6250 ppm (384 mg/kg b.w./day for the male and 463 mg/kg b.w./day for the female parents) LOEL = 100 ppm (5.7 mg/kg b.w./day for the male and 7.2 mg/kg b.w./day for the female pups)	IRDC, 1985

10.2 Epidemiological Studies

No relevant data were identified.

11.0 Effects on the Environment

11.1 Aquatic Environment

The vast majority of data available to determine effects on the aquatic environment have been produced by the Chlorinated Paraffins Manufacturers Toxicology Testing Consortium (a consortium of international manufacturers). They determined the toxicity of C_{10-13}, 58% Cl; C_{14-19}, 52% Cl; C_{20-30}, 42% Cl; and C_{20-30}, 70% Cl to a number of aquatic organisms. There are few studies outside of the Consortium database to evaluate effects on the environment. Due to the low solubility of the substances, chlorinated paraffins were dissolved in acetone before dilution with water in most of the laboratory studies discussed below.

Data on aquatic toxicity are summarized in Table 11.1 (short chain CPs) and Table 11.2 (medium and long chain CPs).

11.1.1 Microorganisms

11.1.1.1 Short Chain CPs

No data were identified on the toxicity of short chain CPs to microorganisms.

11.1.1.2 Medium and Long Chain CPs

No data were identified on the toxicity of medium chain CPs to microorganisms.

A preliminary assessment of the effects of Cereclor 42 (C_{20-30}, 42% Cl) (concentrations up to 10% (w/w)), on mixed populations from anaerobic sewage sludge digesters, containing both facultative and strict anaerobes, indicated no significant effect on overall microbial activity after 30 days (Madeley and Birtley, 1980).

The EC_{50}, 15 minutes, to marine luminescent bacteria in the Microtox test was reported as 1 to 1.5 mg/L (Tarkpea, 1982 as cited in KEMI 1991). The specific chlorinated paraffin studied was not specified.

11.1.2 Aquatic Plants

No data were identified on the toxicity of chlorinated paraffins to higher aquatic plants. Studies were available only on the effects on algae.

11.1.2.1 Short Chain CPs

The short term growth (day 1-3) of the marine diatom *Skeletonema costatum* was significantly inhibited (44%) by short chain, C_{10-13}, 58% Cl at 19.6 µg/L (Thompson and Madeley, 1983b). The 96-h EC_{50} was 42.3 (27.3 - 93.1) µg/L. The effect on growth rate was transient, as by Day 10 no difference was found in growth rate when compared to controls. The highest reduction in growth rate occurred during the first two days, the 48-h EC_{50} being 31.6 µg/L. The 48-hour NOAEL was 12.1 µg/L.

When this study was repeated with the freshwater alga *Selenastrum capricornutum*, there was insufficient growth inhibition in the first four days to calculate an EC_{50} based on this effect (Thompson and Madeley, 1983a). The lowest measured concentration with significant growth inhibition was 570 µg/L. Based on reduction of cell density, the calculated 96-, 168- and 240-hour EC_{50} values were 3690, 1550 and 1310 µg/L respectively. These values exceeded the highest concentration in the study (1200 µg/L), due to limitations of water solubility. In the latter days of the study, increasing differences in growth rates compared to controls were reported indicating that longer exposures would likely have produced lower effect levels, but they remain undefined.

For both of these static studies, interpretation is difficult due to loss (50 to 80%) of residues from the water during the course of the study due to sorption to algal cells. In addition, the nutrient media for the studies were created to provide sufficient nutrients for algal log growth for the normal 96 hour test period. The test duration extended beyond the period where log growth occurred, making the comparison of treatment and control inappropriate. For example, in the study discussed in the previous paragraph, *Selenastrum* growth was reduced during the initial test period and by day 10 the differences between the controls and treatments were insignificant. The transient toxic effect may actually have been that the growth rate in controls slowed as nutrient levels decreased and by day 10 slower growth rates in the treatments were able to reach the same cell density as that of controls.

11.1.2.2 Medium and Long Chain CPs

No data were identified on the toxicity of medium and long chain CPs to algae.

11.1.3 Invertebrates

11.1.3.1 Short Chain CPs

The static 48-h EC_{50} value for immobilization of *Daphnia magna* exposed to short chain 58% chlorinated n-paraffins was 530 µg/L (Thompson and Madeley, 1983c). Mean measured concentrations tested were 12, 24, 43, 75, 145, 255 and 415 µg/L. At concentrations of test substance ≥75 µg/L, *D. magna* tended to float at or near the surface of the test vessel, an indicator of poor health. Those *Daphnia* neither immobilized nor floating displayed erratic and reduced swimming activity at all concentrations except the lowest tested. The only test concentration where no acute effect was observed was 12 µg/L. These results are considered to underestimate the acute toxicity of the substance, however, as results from the chronic flow-through and static renewal studies show very different toxicities.

In a 21-day chronic study of *Daphnia magna* with a continuous flow-through system, the 3-, 4-, 5- and 6-day LC_{50} values for short chain 58% Cl, were 24, 18, 14 and 12 μg/L respectively (Thompson and Madeley, 1983c). Mean measured concentrations tested were 2.7, 5.0, 8.9, 16.3, 25.5 and 38.7 μg/L. Interpretation of effects is difficult due to problems with the controls. For example, total offspring per parent was 50.5 for control 1, 105.4 for control 2, and 100.9 for the solvent control. A dose-response curve was not found, as the total offspring per parent was 56.6 at 2.7 μg/L, 87.8 at 5 μg/L, and 50.6 at 8.9 μg/L. Similarly for the number of dead offspring per parent, there were 4.3, 8.2 and 6.3 for control 1, control 2 and solvent control, respectively, and for treated samples were 3.2, 8.7 and 18.5 at 2.7, 5 and 8.9 μg/L. Total mortality was observed at test concentrations ≥16.3 μg/L after 6 days. There were no mortalities at 8.9 μg/L. In a 14-day static renewal study, 50% mortality of daphnids was seen after 6 days of exposure to 10 μg/L (Thompson and Madeley, 1983c).

The acute toxicity of 58% chlorinated, short-chained n-paraffins to the marine mysid shrimp (*Mysidopsis bahia*) under continuous flow conditions resulted in 72- and 96-hour LC_{50} values of 20 μg/L and 14 μg/L, respectively (measured concentrations). No mortalities were observed at 7.1 μg/L (Thompson and Madeley 1983d).

In a 28-day chronic study, mysid shrimp were exposed to mean measured concentrations of 58% chlorinated, short chain CP of 0.6 to 7.3 μg/L. Mortalities were 20% in the control and 27.5% in the solvent control, as high or higher than the 20% recommended in study guidelines. A dose-response was not found as there were significant differences in mortality from the control for 1.8 and 3.2 ug/L but not for 1.0, 5.6 and 10.0 ug/L. None of the tests were significantly different in mortality compared to the solvent control. The number of offspring per female was 9.14 for the control, 11.07 for the solvent control and 7.46 for the highest concentration tested. A significant difference was found between the control and highest concentration, but not between the solvent control and highest concentration. Male mortality accounted for 77% of all mortality occurring between day 15 and day 28 (Thompson and Madeley 1983d).

The acute and chronic toxicity of 58% chlorinated, short chained CP to second instar midge larvae (*Chironomus tentans*) was determined by EG&G Bionomics (1983). The larvae are benthic, tube dwelling aquatic organisms fed by grazing and filtering. In the acute study, second instar larvae were exposed to concentrations ranging from 18 to 162 μg/L. The static 48-hour LC_{50} was >162 μg/L. Due to the solubility of the test substance, this was the highest concentration tested. In a 49-day life cycle study, concentrations of 61 to 394 μg/L were used. The chronic exposure was initiated by incubating egg masses in each exposure concentration, and after hatching the larvae were introduced to the test solutions. Problems of insolubility of the test substance occurred in the study. Variable results were found in percentage hatch with the control being 87%, 78 ug/L 34%, 121 ug/L 89% and 394 ug/L 38%. No emergence of adult midges occurred at 121 μg/L and 394 μg/L, relative to 67% emergence in the control, and 83% in the solvent control.

The filter-feeding common mussel (*Mytilus edulis*) was exposed to mean measured concentrations of 58% short chain CP of 2.3 μg/L and 9.3 μg/L sea water for 12 weeks in a flow-through system to determine growth effects (Thompson & Shillabeer, 1983). At 9.3 μg/L reduction of growth occurred, as measured by shell length and weight of soft tissue increase with respect to controls. No significant response occurred at 2.3 μg/L and no mortalities occurred at either dose.

The 60 day LC_{50} to the common mussel (*Mytilus edulis*), a filter-feeding marine mollusc, was 74 μg/L, tested in a dynamic system for 58% chlorinated short chain CP (Madeley and Thompson, 1983c). Due to solubility problems, acetone (500 ppm v/v) was used to maintain the chlorinated paraffins in solution. Natural

seawater was used for the experiments. Mean measured concentrations tested were 13, 44, 71, 130 and 930 μg/L. In the two higher concentrations, the water solubility was exceeded and a cloudy appearance indicated that some of the chlorinated paraffins had been lost from the dispersion. Significant mortalities occurred in the three highest concentrations. Visual observations suggested that the feeding activity of the mussels was reduced at the two lowest concentrations tested, thus that sublethal effects may be occurring even at the lowest concentrations tested. Residues in the mussels after 60 days were 260, 890, 780 and 1030 μg/g wet weight, following exposure to 12, 44, 71 and 130 μg/L, respectively. Bioconcentration factors therefore were 20000, 20227, 10986 and 7923, respectively.

Ninety-six hour LC_{50}s for the harpacticoid copepod (*Nitocra spinipes*) were 60 to 100 μg/L for C_{10-13}, 49% Cl, and <300 μg/L for C_{10-13}, 70% Cl (KEMI, 1991). However, *Leander adsperus* was not affected by Witaclor 149 (C_{10-13}, 49% Cl) at concentrations up to 1 g/L (Tarkpea, 1982 - unpublished data cited in Svanberg, 1983). Given the low (i.e., < 1 mg/L) water solubility of this chlorinated paraffin, the results of the latter study are questionable.

11.1.3.2 Medium and Long Chain CPs

The toxicity over 60 days to the mussel (*Mytilus edulis*) in a dynamic system at 15°C was determined for 3 chlorinated paraffins: a 52% chlorinated medium chain and 43% and 70% chlorinated long chain (Madeley and Thompson, 1983b, 1983a and 1983d). Due to solubility problems, acetone (500 ppm v/v) was used to maintain the chlorinated paraffins in solution. Natural seawater was used for the experiments.

In the study using the 52% chlorinated medium chain CP (Madeley and Thompson, 1983b), the mean measured concentrations tested were 220 and 3800 μg/L. In the higher concentration test, the water solubility was exceeded and a cloudy appearance and a fine white deposit indicated that some of the chlorinated paraffins had been lost from the dispersion. There was no mortality of the mussels at either concentration, however at the higher concentration, reduced filtration activity was consistently observed (Madeley and Thompson, 1983b). The concentration of parent compound in the mussels at the end of the study was 480 μg/g wet weight after exposure to 220 μg/L and 1290 μg/g wet weight after exposure to 3800 μg/L. The bioconcentration factors therefore were 2182 and 339, respectively.

The mean measured concentrations tested of the 43% chlorinated long chain CP were 120 and 2200 μg/L. As in the previous study, the higher concentration exceeded the water solubility of the chloroparaffin. There was no mortality of the mussels at either concentration, however at the higher concentration, reduced filtration activity was consistently observed (Madeley and Thompson, 1983a). The concentration of parent compound in the mussels at the end of the study was 120 μg/g wet weight after exposure to 120 μg/L and 190 μg/g wet weight after exposure to 2200 μg/L. The bioconcentration factors therefore were 1000 and 86, respectively.

In a similar study, the toxicity of 70% chlorinated long chain CP (Madeley and Thompson, 1983d) was studied. The mean measured concentrations tested were 460 and 1330 μg/L. As in the previous studies, the higher concentration exceeded the water solubility of the chloroparaffin. There was no mortality of the mussels at either concentration, however at the higher concentration, reduced filtration activity was observed. The concentration of parent compound in the mussels at the end of the study was 77 μg/g wet weight after exposure to 460 μg/L and 140 μg/g wet weight after exposure to 1330 μg/L. The bioconcentration factors therefore were 160 and 105, respectively.

Mussels fed dry yeast containing 524 μg/g-dry weight of Cereclor 42 (C_{22-26}, 42% Cl) for 47 days showed no significant mortality (Madeley and Birtley, 1980).

The acute toxicity of Chlorowax 45 LV (chain length unspecified) to *Daphnia magna* was determined under static conditions using nominal concentrations of 75, 150, 300, 600, 1200, 5000 and 10000 μg/L. These concentrations were based on a water solubility of 10000 μg/L at 25°C (Analytical Bio-Chemistry Laboratories Inc., 1986a). The acute 24- and 48-hour LC_{50} values were 6800 μg/L and 120 μg/L, respectively (Analytical Bio-Chemistry Laboratories Inc., 1986b). The NOEL was estimated to be < 75 μg/L as all treated concentrations exhibited mortality and/or abnormal effects such as surfacing, dumping or lying on the bottom.

11.1.4 Fish

There are little data concerning the acute toxicity of chlorinated paraffins to fish, primarily due to limitations of water solubility. The absence of acute toxicity in some species may be the slow uptake rate of chlorinated paraffins, and chronic effects may therefore be of greater concern.

11.1.4.1 Short Chain CPs

Short-term studies indicate short chain chlorinated paraffins may be toxic to fish at relatively low doses. Neurotoxic effects (motor impairment) were noted for short chain CPs at doses as low as 0.1 mg/L or 2.5 mg/kg-diet (Svanberg *et al.*, 1978; Bengtsson *et al.*, 1979; Bengtsson & Ofstad 1982) (see Table 11.1).

Lombardo *et al.*, (1975) reported decreased weight gain when fingerling rainbow trout were fed a diet containing 10 mg/kg Chlorowax 500C (C_{12}, 60% Cl) for 82 days.

Haux *et al.*, (1982) reported that female flounder (*Platichthys flesus* L.) dosed orally (via gelatin capsules) with 1000 mg/kg-bw of Witaclor 149 (C_{12}, 49% Cl), had altered erythrocyte balance and hypoglycemia. Hülz 70C (C_{12}, 70% Cl) caused slight hyperglycemia. Both compounds showed signs of inducing mixed function oxidase (MFO) activity. Observations were recorded 13 and 27 days after dosing.

The embryos and larvae of sheepshead minnow (*Cyprinodon variegatus*) were exposed in a flow-through test system to 58% short chain CP at mean measured concentrations of 2.4 to 54.8 μg/L sea water for 28 days (Hill and Maddock, 1983a). There was no effect on hatchability of embryos or survival of larvae or larval development, relative to saline or acetone controls. A significant difference in length was found between the saline control and the acetone control, with those in the saline control being longer. In addition, all larvae in exposed vessels were significantly longer relative to those in the acetone control.

In a similar study, the embryos and larvae of sheepshead minnow (*Cyprinodon variegatus*) were exposed in a flow-through test system to 58% short chain CP at mean measured concentrations of 32.2 to 620.5 μg/L for 32 days (Hill and Maddock, 1983b). At test concentrations ≤ 71 μg/L, larvae were significantly larger than the corresponding acetone control (400 ppm v/v). At 620.5 μg/L, the larvae were significantly smaller than controls. No difference between survival of treated and controls were found. However, as in the above study, a significant difference in length was found between the saline control and the acetone control, with those in the saline control being longer. Similarly, a significant difference in weight was found between the saline control and the acetone control, with those in the saline control being heavier.

Rainbow trout (*Oncorhynchus mykiss*) were exposed to 58% chlorinated short chain CP at mean measured concentrations of 3.4 (range 1.5-13.3) and 17.2 (range 9.5-58.2) μg/L for 24 weeks (168 days) in a flow-through system (Madeley and Maddock, 1983a). No significant mortality or growth inhibition with respect to controls was observed.

Madeley and Maddock (1983d) reported that significant mortality of rainbow trout occurred over a 60 day period in a dynamic system at measured test concentrations of 33, 100, 350, 1070 and 3050 μg/L. Acetone (500 ppm v/v) was required to maintain the chlorinated paraffin in suspension. The test solution at the highest concentration was cloudy, indicating solubility problems. Median lethal times (LT_{60}) for the three highest concentrations were 44.7, 31.0 and 30.4 days respectively. Lethal effects were observed at concentrations ≥33 μg/L with the first mortalities occurring by day 9-12. The 60-day LC_{50} for this study was 340 μg/L. At all concentrations the fish exhibited abnormal movement and feeding behaviour, with the severity corresponding to test concentration. Residues in fish at the end of the study period were 240, 360, 570, 1060 and 1750 μg/g (wet weight) for test concentrations of 33, 100, 350, 1070 and 3050 μg/L, respectively. Bioconcentration factors were 7273, 3600, 1629, 990 and 574, respectively.

Another study indicating the toxicity to fish was a bioconcentration study by Madeley and Maddock (1983f) studying 58% chlorinated, short-chain CP (see Section 6.3.1). They exposed trout for 168 days to test concentrations of 3.1 and 14.3 μg/L The fish were then removed to freshwater for a depuration period of 105 days. During the 168 day period of exposure, two fish died at the high concentration and one at the low concentration. However, starting at day 63 of depuration, fish which had been exposed to chlorinated paraffins began behaving abnormally, deaths started occurring on day 64 and by day 69 all fish in the higher exposure concentration had died. Some fish from the lower exposure also died, but remaining fish recovered by day 70. The cause of death was undefined, however symptoms resembled those experienced by fish exposed to acutely toxic levels of chloroparaffins (i.e. >33 μg/L, Madeley and Maddock 1983d). This study shows that fish may require long exposure periods to demonstrate the actual toxicity of chlorinated paraffins, and that short exposure studies may be underestimating the toxicity.

Linden *et al.* (1979) reported that the 96 hour LC_{50} to bleaks (*Alburnus alburnus*), for Witaclor 49 (49% Cl), Witaclor 63 (63% Cl) and Witaclor 71 (71% Cl) was > 5 g/L and for Witaclor 55EN (56% Cl) it was > 10 g/L. Little detail was given to evaluate these data, however the concentrations are well above the water solubility of the CPs.

Chronic studies such as those on sheepshead minnow, are not appropriate measures of chronic toxicity for fish reproduction. Chemical uptake by fish eggs is a passive process, and for high log K_{ow} substances, such as chlorinated paraffins, the chemical residue concentrations in the eggs never reach the levels deposited in the eggs by exposed females.

11.1.4.2 Medium and Long Chain CPs

The acute toxicity of Chlorowax 45 LV to bluegill sunfish (*Lepomis macrochirus*) was studied under static conditions using nominal concentrations of 150, 300, 600, 1200, 2500, 5000 and 10000 μg/L (Analytical Bio-Chemistry Laboratories Inc., 1986c). Actual measured concentrations were not determined. The nominal concentrations were estimated based on a reported water solubility of 10 mg/L at 25°C (Analytical Bio-Chemistry Laboratories Inc., 1986a). A light surface film was present at concentrations ≥ 1200 μg/L. The acute 24-, 48- and 96-hour LC_{50} values were all >10000 μg/L. At 96 hours, abnormal effects of surfacing and/or loss of equilibrium were observed at 10000 μg/L. The 96-h NOEC was estimated to be 5000 μg/L based on no mortality or sub-lethal effects.

The acute 96-hour LC_{50} value for rainbow trout when exposed to Chlorowax 45 LV was >5000 µg/L at 12°C (Analytical Bio-Chemistry Laboratories Inc., 1986d). As in the previous study, the nominal concentrations were 150, 300, 600, 1200, 2500, and 5000 µg/L. The solubility of Chlorowax 45 LV in aged fish dilution water at 12°C was reported to be 2.73 ± 1.4 mg/L (Analytical Bio-Chemistry Laboratories, 1986e). A light surface film was present at concentrations ≥ 600 µg/L. The static 96-h NOEC was estimated to be 600 µg/L due to lack of mortality and abnormal effects, such as surfacing, loss of equilibrium or quiescence.

Linden *et al.* (1979) reported that the 96-hour LC_{50}s to bleaks (*Alburnus alburnus*), for the C_{14-17} chlorinated paraffins Witaclor 50 (50% Cl) and Cereclor S52 (52% Cl) were > 5 g/L and > 10 g/L, respectively and for the C_{22-26} chlorinated paraffin Cereclor 42 (42% Cl) it was > 5 g/L. As stated above, little detail was given to evaluate these data, however the concentrations used were well above the water solubility of chlorinated paraffins.

The toxicity over 60 days to the rainbow trout (*Oncorhynchus mykiss*) in a dynamic system at 12°C was determined for 52% chlorinated intermediate chain and 43% and 70% chlorinated long chain (C_{22-26}) CP (Madeley and Maddock, 1983c, 1983b and 1983e).

In the study on the 52% chlorinated intermediate chain CP, the measured concentrations tested were 1050 and 4800 µg/L (Madeley and Maddock, 1983c). Acetone (500 ppm v/v) was required to maintain the CP in suspension. At the highest concentration, the water was cloudy indicating problems with water solubility. No mortality of the fish occurred at either concentration. Residues in fish at the end of the test period were 34 µg/g (wet weight) in fish exposed to 1050 µg/L and 190 µg/g in fish exposed to 4800 µg/L. Bioconcentration factors were therefore 32 and 39, respectively.

In the study on the 43% chlorinated long chain CP, the measured concentrations tested were 970 and 4000 µg/L (Madeley and Maddock, 1983b). Acetone (500 ppm v/v) was required to maintain the CP in suspension. At the highest concentration, the water was cloudy indicating problems with water solubility. This was not overcome by using acetone at 1000 ppm. No mortality of the fish occurred at either concentration. Residues in fish at the end of the test period were 3.5 µg/g (wet weight) in fish exposed to 970 µg/L and 36 µg/g in fish exposed to 4000 µg/L. Bioconcentration factors were therefore 3.6 and 9, respectively.

In the study on the 70% chlorinated long chain CP, acetone (1000 ppm v/v) was required to maintain the CP powder in suspension. Measured concentrations tested were 840, 1900 and 3800 µg/L. Fish exposed to the highest concentration found it was difficult to find their food in the cloudy suspension. This occurred to a lesser extent with the middle concentration. All fish populations behaved abnormally in the first 2 weeks of the study. Bioconcentration factors were variable, with the BCF ranging from 42.8 to 53.8 for 840 µg/L, 1.0 to 5.7 for 1900 µg/L and 31.6 to 32.5 for 3800 µg/L (Madeley and Maddock, 1983e).

11.1.5 Amphibians and Reptiles

No studies were identified on the toxicity of chlorinated paraffins to amphibians and reptiles.

TABLE 11.1 Aquatic toxicity of short chain paraffins.

Species	Test Substrate, %Cl	Test	Response Conc. (μg/l)	Reference
marine algae *(Skeletonema costatum)*	58%	48-h EC_{50}, growth	31.6	Thompson & Madeley, 1983b
		96-h EC_{50}, growth	55.0	
		48-h NEOC, growth	12.1	
freshwater algae *(Selenastrum capricornutum)*	58%	96-h EC_{50}, cell density	3.69	Thompson & Madeley, 1983a
		168-h EC_{50}, cell density	1.55	
		240-h EC_{50}, cell density	1.31	
water flea *(Daphnia magna)*	58%	48-h EC_{50}, static, immobilization	530.0	Thompson & Madeley, 1983c
		48-h NOEC, static, immobilization	12.0	
		72-h LC_{50}, flow-through	24.0	
		96-h LC_{50}, flow-through	18.0	
		120-h LC_{50}, flow-through	14.0	
		144-h LC_{50}, flow-through	12.0	
		21-d NOEC, survival, reproduction or growth	5.0	
marine mysid shrimp *(Mysidopsis bahia)*	58%	24-h LC_{50}, flow-through	>84.4	Thompson & Madeley, 1983d
		48-h LC_{50}, flow-through	22.3	
		72-h LC_{50}, flow-through	16.7	
		96-h LC_{50}, flow-through	15.5	
		96-h NOEC, mortality	7.1	
		28-d, no significant effects on survival, sexual maturation, reproduction or final size	7.3 (highest concentration tested)	
2nd instar midge larvae *(Chironomus tentans)*	58%	48-h LC_{50}, static	>162.0	EG&G Bionomics, 1983
		49-d lifecycle study (decrease in adult emergence)	≥121.0	

TABLE 11.1 Continued

Species	Test Substrate %Cl	Test	Response Conc. (μg/l)	Reference
copepod	Cereclor, 49%	96-h LC_{50}	100.0	Tarkpea *et al.*, 1981 (as
(Nitocra spinipes)	Cereclor, 70%	96-h LC_{50}	< 300.0	cited in Svanberg, 1983)
	Chloroparaffin	96-h LC_{50}	< 5000.0	
	70%	96-h LC_{50}	60.0	
	Witaclor, 49%			
crustacean		96-h LC_{50}	> 1000.0	Tarkpea, 1982 (as cited in
(*Leander adspersus*)	Witaclor, 49%			Svanberg, 1983)
mussel	58%	12-wk, dynamic, growth reduction	9.3	Thompson & Shillabeer,
(Mytilus edulis)		12-wk, NOEC, growth reduction	2.3	1983
		60-d LC_{50}, dynamic	74.0	Madeley & Thompson,
		Reduced feeding activity	13.0	1983c
sheepshead minnow embryo & larvae	58%	28-d NOEC, hatchability, survival, development	> 620.5	Hill & Maddock, 1983a, 1983b
(Cyprinodon variegatus)		larvae size > control	2.4 to 71	
		larvae size < control	620.5	
rainbow trout	58%	24-wk, no significant mortality or growth inhibition	3.4	Madeley & Maddock, 1983a
(Oncorhynchus mykiss)		24-wk, enhancement of growth	17.2	

TABLE 11.1 Continued

Species	Test Substrate %Cl	Test	Response Conc. (μg/l)	Reference
rainbow trout	58%	60-day LC_{50}	340	Madeley & Maddock, 1983d
		LT_{50}, 350 μg/L	44.7 days	
		LT_{50}, 1070 μg/L	31.0 days	
		LT_{50}, 3050 μg/L	30.4 days	
		60-day NOEC	<33	
flounder (*Platichthys flesus*)	Witaclor, 49%	♀ more sensitive than ♂ sublethal hematological effects, induced MFO (P-448) & hypoglycemia	1000 (mg/kg-bw), oral dose	Haux *et al.*, 1982
	Hulz 70C, 70%	Caused hyperglycemia, increased steroid metabolizing enzymes	1000 (mg/kg-bw), oral dose	Haux *et al.*, 1982
bleak *(Alburnus alburnus)*	Chloroparaffin 70C, 70%	29-d, semistatic, neurotoxic	after 14 d at 1000 μg/L and later at 100 μg/L	Svanberg *et al.*, 1978
	Witaclor 149, 49%; Witaclor 159, 59%; Witaclor 171, 71%	14-d, semi-static, 125 μg/L	abnormal movements, posture and shoaling behaviour for all substrates	Bengtsson *et al.*, 1979
	Witaclor 149, 49%	91-d, $\leq$ 5800 μg/g-diet	behaviour change-wk 5	Bengtsson and Ofstad, 1982
	Witaclor 171, 71%	91-d, $\leq$ 5800 μg/g-diet	behaviour change-wk 12	
	5 shortchains, various %Cl	96-h LC_{50} static	All > 5 (g/L)	Linden *et al.*, 1979

TABLE 11.1 Continued

Species	Test Substrate %Cl	Test	Response Conc. (μg/l)	Reference
rainbow trout fingerling	Chlorowax 500C, 60%	82-day, 10 mg/kg-diet	Decreased weight gain from day 9	Lombardo *et al.*, 1970
bluegill sunfish (*Lepomis macrochirus*)	Chlorowax 500C, 59%	96-h LC_{50}	>300 (mg/L)	Johnson, 1975 (as cited in Howard, 1975)
channel catfish (*Ictalurus punctatus*)	Chlorowax 500C, 59%	96-h LC_{50}	>300 (mg/L)	
fathead minnow (*Pimephales promelas*)	Chlorowax 500C, 59%	96-h LC_{50}	>100 (mg/L)	

Table 11.2 Aquatic toxicity of medium chain paraffins.

Species	Test substrate, %Cl	Test	Response Conc. (μg/L)	Reference
copepod	Cereclor, 45%	96-h LC_{50}	9000	Tarkpea *et al.*, 1981 (as cited
(Nitocra spinipes)	Cereclor, 52%	96-h LC_{50}	>10 000 000	in Svanberg, 1983)
mussel	52%	60-day exposure -no mortality, reduced feeding activity	3800	Madeley & Thompson, 1983b
(*Mytilus edulis*)		60-day NOEC	220	
bleaks	Witaclor, 50%	14-d, semi-static, 125 μg/L	Abnormal posture and shoaling behaviour	Bengtsson *et al.*, 1979
(*Alburnus alburnus*)	Witaclor, 50%	96-h LC_{50}	>5000	Linden *et al.*, 1979
	Cereclor, 52%	96-h LC_{50}	>10,000	

Table 11.3 Aquatic toxicity of long chain paraffins.

Species	Test substrate, %Cl	Test	Response Conc. (μg/L)	Reference
copepod	Cereclor, 42%	96-h LC_{50}	>1,000,000	Tarkpea *et al.*, 1981 (as cited
(*Nitocra spinipes*)	Cereclor, 49%	96-h LC_{50}	>10,000,000	in Svanberg, 1983)
water flea	Chlororwax, 45%	24-h LC_{50}	6900	Analytical Biochemistry
(*Daphnia magna*)		48-h LC_{50}	120	Laboratories Inc., 1986c
		48-h NOEC (sublethal effects)	<75	
mussel	43%	60-day, no mortality, reduced feeding activity	2180	Madeley & Thompson, 1983a
(*Mytilus edulis*)		60-day NOEC	120	
	70%	60-day, no mortality, reduced feeding activity	1330	Madeley & Thompson, 1983d
		60-day NOEC	460	
rainbow trout	43%	60-day, sublethal or behavioural effects	4000	Madeley & Maddock, 1983b
(*Oncorhynchus mykiss*)				
	70%	60-day, sublethal or behavioural effects	3800	Madeley & Maddock, 1983e
	Chlorowax, 45%	96-h LC_{50}	>5000	Analytical Biochemistry
		96-h NOEC, static, sublethal effects	600	Laboratories Inc., 1986b
	Cereclor, 42%	96-h LC_{50}, CPs prepared as emulsions	>770	Madeley & Birtley, 1980
		49-day no effect	47 & 385 mg/kg-dw, oral	
bluegill sunfish	Chlorowax, 45%	96-h LC_{50}, static	>10,000	Analytical Biochemistry
(*Lepomis macrochirus*)		96-h NOEC, static, sublethal effects	5000	Laboratories Inc., 1986a
bleaks	Cereclor, 42%	96-h LC50	>5000	Linden *et al.*, 1979
(*Alburnus alburnus*)				
	Witaclor, 49%	14-day semi-static, 124 μg/L	abnormal posture and shoaling behaviour	Bengtsson *et al.*, 1979
	Witaclor, 49%	91-day, 340 μg/g diet	behaviour change in balance and swimming	Bengtsson & Ofstad, 1982

11.1.6 Ecosystem Effects Modelling

The effects of stress on individuals occur in an ecosystem context. Bartell (1990) used a model to extrapolate the results of single-species toxicity assays to expected effects in a complex pelagic ecosystem from exposure to short chain CPs. The model simulated patterns of seasonal production dynamics in northern dimictic lakes, using ten populations of phytoplankton, five populations of zooplankton, three populations of planktivorous fish, and one population of piscivorous fish. The bioenergetics of individual fish growth provided the basis for the physiological-process equations. Zooplankton and fish populations grew as a function of their feeding rates, minus losses to respiration, natural mortality and predation. Rates of photosynthesis minus combined losses to respiration, mortality, and grazing determined phytoplankton growth. Each model population was ecologically distinct. Available toxicity data were assigned to the model populations. As assignment of toxicity data to model populations influences the resulting risk estimates, several possible scenarios with different assignments of assay data to the pelagic system populations were simulated. Ecological risks were estimated for four exposure concentrations: 0.0001, 0.001, 0.01 and 0.1 mg/L, spanning reported chlorinated paraffin concentrations in surface waters.

Bioassay data used in four of the scenarios were as follows:

- phytoplankton populations 1-5 (spring blooming taxa) were assigned a toxicity value based on the EC_{50} for the diatom *Skeletonema costatum* of 0.0316 mg/L;
- phytoplankton populations 6-10 (mid- to late-summer phytoplankton) were assigned a toxicity value based on the 96-h EC_{50} for the green alga *Selenastrum capricornutum* of 3.69 mg/L;
- zooplankton toxicity was based on EC_{50} for *Daphnia magna* of 0.046 mg/L;
- planktivore population 1 was assigned a value of 100 mg/L based on the fathead minnow (*Pimephales promelas*);
- planktivore population 3 was assigned a value of 300 mg/L based on the bluegill sunfish (*Lepomis macrochirus*);
- planktivore population 2 was assigned a value of 200 mg/L, the midpoint between the fathead minnow and bluegill benchmarks; and
- the piscivorous fish population was assigned a value of 100, 300 or 0.046 mg/L, depending on the scenario. The latter value, the LC_{50} for *Daphnia magna*, was assigned due to the suspect values for fish toxicity.

Results of the model were consistent with an intuitive expectation of risk. The risks of decreased piscivore and planktivore population size were negligible at the lowest exposure concentration and increased as concentration increased. For example, the risk of a 25% reduction in total annual piscivore production was 0.05 at 0.0001 mg/L and 0.64 at 0.001 mg/L. At concentrations approaching those that have been measured in the environment (0.001 mg/L) the risk of a 200% increase in blue-green algal production ranged between 0.70 and 0.76. The probability was 0.33 at 0.0001 mg/L. In a fifth scenario, Bartell (1990) used some chronic bioassay data and showed the probability of risk to fish populations to be 1. Indirect food web effects were the primary cause of modelled reductions in fish populations.

As this model was for a dimictic lake, risk estimates for other systems may be different. Given the low solubility of chlorinated paraffins and tendency of these compounds to accumulate in sediments, there is a potential risk to benthic populations which are not considered in this model.

11.1.7 Summary of Aquatic Effects

Under the limited test conditions and limited test durations studied, the short chain (C_{10-13}) CPs were more toxic than the other CPs studied, although chronic effects were noted for all four of the formulations tested by the Consortium. For the short chain CPs, adverse effects occurred at the lowest concentration tested (i.e. 0.5 μg/L), thus a NOEL was not determined.

One study showed the importance of test duration on toxicity of short chain chlorinated paraffins. Fish may require long exposure periods to demonstrate the actual toxicity of chlorinated paraffins. This may be particularly important for longer chain length CPs with slower uptake rates. Studies of several months duration might yield lower effect levels than reported in these studies.

11.2 Terrestrial Environment

11.2.1 Plants

No data were identified on the toxicity of chlorinated paraffins to terrestrial plants.

11.2.2 Invertebrates

No data were identified on the toxicity of chlorinated paraffins to terrestrial invertebrates.

11.2.3 Mammals

No studies were identified on the toxicity of CPs to wild mammals, thus the data available on laboratory mammals (Section 9) can be used to evaluate toxicity to wild mammals. The reader is referred to that section.

11.2.4 Birds

No field studies were identified on the toxicity of chlorinated paraffins to wild birds. Studies on metabolism of CPs by birds are discussed in Section 8.3. The following effects were noted in laboratory studies.

11.2.4.1 Short Chain CPs

No studies were found on the acute toxicity of short chain CPs to birds. A one generation reproductive study on the effects of a 58% chlorinated short chain CP was done using Mallard Ducks (*Anas platyrhynchos*) (Serrone *et al.*, 1987). Concentrations of test substrate of 28, 166 and 1000 mg/kg-diet were administered. No treatment related effects on survival, physical condition, body weight or food consumption were observed in either adults or hatchlings. A slight decrease in eggshell thickness and 14-day embryo viability was observed in the 1000 mg/kg group. No effects on egg weight, eggshell cracks, eggs laid, 21-day embryos or hatchability were observed in any treatment group. The NOEL of the study was estimated to be 166 mg/kg-diet.

11.2.4.2 Medium and Long Chain CPs

Based on limited studies, chlorinated paraffins have low acute and subacute toxicity to birds. No studies on chronic toxicity to birds were found.

Madeley and Birtley (1980) studied the acute and subacute toxicity of Cereclor S52 (C_{14-17}, 52% Cl) to Ring-necked Pheasants (*Phasianus colchicus*) and Mallard Ducks (*Anas platyrynchos*). In the acute oral LD_{60} studies, doses up to 24,606 mg/kg (Pheasant) and 10,280 mg/kg (Mallard Duck) failed to produce any abnormal clinical signs or mortality in any bird. Thus the acute oral LD_{60} is in excess of those values for Cereclor S52. Similarly birds receiving 24,063 mg/kg-diet remained in good health throughout the experiment. The subacute dietary LC_{60} to Ring-necked Pheasants and Mallard Ducks is >24,063 mg/kg.

Three days following a single oral dose of 10 g/kg, Cereclor 42 (C_{20-30}, 42% Cl), adult Mallard Ducks had levels of 2.4 mg/kg (wet weight) in liver, 15 mg/kg in the gut, 7 mg/kg in heart 2.2 mg/kg in muscle, 67 mg/kg in fat and 115 mg/kg in feathers (Madeley and Birtley, 1980). The high level in feathers may have been an artifact.

11.2.5 Summary of Terrestrial Effects

No information was available to evaluate the effects of chlorinated paraffins on terrestrial plants and invertebrates. The medium chain CPs are of low toxicity to birds. Although there were no data on the acute toxicity of short chain CPs, given the low toxicity of the medium chain and the low acute toxicity of the short chain paraffins to mammals, toxicity to birds is expected to be low. No effects on avian reproduction were noted except at very high doses.

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Appendix 1 - Quantitative Estimates of Cancer Risk

Quantitative estimates of cancer risk were derived on the basis of the NTP carcinogenesis bioassay in mice in which adequate numbers of animals were exposed for a large proportion of the lifespan to several concentrations of a short chain CP (C_{12}, 60% Cl) by gavage in corn oil. Increases in tumour incidence in rats observed in the NTP bioassay were not considered appropriate for quantitative risk estimation since the maximum tolerated dose may have been exceeded. Quantitative estimates were developed only for tumours for which there was a statistically significant increase in incidence for at least one dose, and evidence of a dose-response relationship. Owing to the lack of information about the extent of metabolism to unidentified possibly active metabolite(s) and the possible role of such metabolites in carcinogenicity, a surface area to body weight correction was incorporated. The unit risks $(mg/kg\ b.w./day)^{-1}$ for each of the tumour types in mice in the NTP carcinogenicity bioassay, estimated using the robust linear extrapolation model (Krewski *et al.*, 1991) and incorporating the surface area to body weight correction and a factor for conversion of the 5 day per week exposure regimen to daily exposure, are as follows:[1]

Females

Follicular cell adenomas or carcinomas (combined) - 1.1×10^{-2}
Hepatocellular adenomas or carcinomas (combined) - 8.0×10^{-2}

Males

Hepatocellular adenomas or carcinomas (combined) - 7.1×10^{-2}

Though owing to the possible exceedence of the MTD in the NTP bioassay in rats, the unit risks $(mg/kg\ b.w./day)^{-1}$ estimated for the tumour types observed in this species are not presented here, it is of interest to note that they are less than those presented above for mice.

Because the model used to generate the estimated unit risks is based on linear extrapolation, these values are regarded as being relatively conservative i.e. it is unlikely that the risk is underestimated. This conservatism is considered to be appropriate when dealing with such a potentially serious outcome as cancer, particularly in light of the large uncertainties in extrapolating the results of high-dose animal experiments to the much lower exposures of humans in the general population.

Owing to the lack of available information on concentrations of short chain CPs in environmental media to which humans are exposed and to the lack of suitability of fugacity modelling to estimate levels in the environment, it is not possible to quantitatively estimate the total daily intake of short chain CPs by the general population in Canada. It is, therefore, not possible at this time, to estimate on the basis of the unit risks presented above, calculated excess lifetime cancer risks due to exposure to short chain chlorinated paraffins in the general environment in Canada.

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[1] The unit risk is the largest additional probability (that is consistent with the data) of developing cancer above background per unit of exposure, based on a dose-response model that is linear at low doses.