JUN 2 1 1990

REGNET
REGULATORY NETWORK, INC.

June 18, 1990

Dr. Richard Niemeier
Director
Division of Standards Development
and Technology Transfer
NIOSH
4676 Columbia Parkway
C-14
Cincinnati, Ohio 45226

Dear Dr. Niemeier:

The Chlorinated Paraffins Industry Association (CPIA) is pleased to respond to NIOSH's request for comment and secondary data relevant to occupational exposure to cutting fluids (55 Fed. Reg. 20637). CPIA is trade association of the domestic producers of chlorinated paraffins.

CPIA's interest in the activities of NIOSH regarding cutting fluids is based on the fact that approximately 50% of all chlorinated paraffins produced domestically are used as additives to metalworking fluids. Chlorinated paraffins have a variety of other industrial applications, including use as primary and secondary plasticizers, and as flame retardants. The industrial uses of chlorinated paraffins are more fully described in the enclosed 1990 Chlorinated Paraffins Status Report.

CPIA's 1990 Status Report on chlorinated paraffins also provides a summary of the chlorinated paraffins toxicological and environmental data base, and describes the labeling, warning and safe handling practices for chlorinated paraffins. I trust that you will find much useful information in this report. I have also enclosed a paper by David M. Serrone, entitled "Toxicology of Chlorinated Paraffins," which was in the Journal of Food and Chemical Toxicology.

If additional information becomes available regarding the issue identified in the Federal Register notice, I will forward it to you. In the meantime, CPIA would appreciate receiving any further information NIOSH has regarding this request for data. Please do not hesitate to contact me if you have further questions or require clarification of any of the information presented.

Sincerely,

Robert J. Fensterheim
Executive Director, CPIA

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# CHLORINATED PARAFFINS:

## A STATUS REPORT

JANUARY 1990

CPIA

**Chlorinated Paraffins Industry Association**
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Suite 1000
Washington, DC 20006
202-857-0117

## CONTENTS



*This Status Report has been developed by the Chlorinated Paraffins Industry Association (CPIA), a trade association of the domestic producers of chlorinated paraffins.*[1] *Its purpose is to summarize the existing information on the chemistry, uses, health and environmental effects, safe handling practices and regulatory considerations for chlorinated paraffins. This report updates CPIA's September, 1988 Status Report.*

[1] The members of the CPIA are: Dover Chemical Corporation; ICI Americas Incorporated; Keil Chemical Division/Ferro Corporation; Occidental Chemical Corporation; and Argus Division/Witco Corporation.

*CHLORINATED PARAFFINS (CPs) are a class of chlorinated hydrocarbons widely used in industry. Commercial products containing blended chlorinated paraffins include: industrial lubrication additives, secondary plasticizers and flame retardants in rubber, and plasticizers in paints, adhesives, sealants and caulks. The greatest use of chlorinated paraffins is in metalworking fluids, particularly those used during the manufacture of automobiles, automobile parts and appliances.*

*Chlorinated paraffins have been safely used in industry since their introduction over 50 years ago. There is virtually no direct exposure of the general public to CPs from these products and there have been no confirmed reports of illness, injuries or disabilities caused by exposure to, or contact with, CPs.*

## ■ PRODUCTION

There are currently four major manufacturers of chlorinated paraffins in the United States.

**MAJOR PRODUCERS OF CHLORINATED PARAFFINS**

| Company | Location |
|---|---|
| Occidental Chemical | Deer Park, TX |
| Keil Chemical Div., Ferro Corporation | Hammond, IN |
| ICC Industries, Inc. Dover Chemical Corp. | Dover, OH |
| Argus Division, Witco Corporation | Phillipsburg, NJ |

Manufacturers have continued to modernize processes for the production of chlorinated paraffins since their introduction into commerce. All CP production is now in essentially closed systems, leaving very little possibility of exposure for workers or releases to the environment.

# CHEMISTRY AND PROPERTIES OF CHLORINATED PARAFFINS

Chlorinated paraffins are chlorinated hydrocarbons that have the general formula $C_xH_{(2x-y+2)}Cl_y$. They are made by chlorinating paraffin fractions obtained from petroleum distillation. The three most common commercial feedstocks used are straight chain paraffins with carbon number ranges of:

- Short: $C_{10}$ to $C_{13}$
- Intermediate: $C_{14}$ to $C_{19}$
- Long: $C_{20}$ to $C_{30}$.

These hydrocarbons are reacted with chlorine resulting in chlorinated paraffins of different carbon chain lengths with varying degrees of chlorination. For example, a $C_{12}$, 60% chlorine CP actually refers to a CP with an average carbon chain length of 12 and these carbon chains contain an average of 60% chlorine; some carbon chains are chlorinated to more than 60% and some chlorinated to less than 60 percent. The majority of CP products can be depicted in a 9-cell matrix, as shown in Figure 1.

**Figure 1**
**Classification of Chlorinated Paraffins by Percent of Chlorination and Carbon Chain Length[2]**

| | Percent of Chlorination (by weight) 40-50 | 50-60 | 60-70 |
|---|---|---|---|
| C 10-13 ($C_{12}$ Feed Stock) | A1 | A2 | A3 |
| C 14-19 ($C_{15}$ Feed Stock) | B1 | B2 | B3 |
| C 20-30 ($C_{24}$ Feed Stock) | C1 | C2 | C3 |

2 This graphic was originally developed by industry and was submitted to the EPA in 1980. The matrix is now used by EPA to depict the different types of chlorinated paraffins.

The performance characteristics of chlorinated paraffin products are a function of their carbon chain length and degree of chlorination. Generally, the viscosity of the chlorinated paraffin increases as either the chlorine content increases or the carbon chain lengthens. Thus, short chain CPs ($C_{10-13}$) with lower percentages of chlorination (40-50 percent by weight) are the least viscous. Reciprocally, long chain CPs ($C_{20-30}$), that are highly chlorinated (60-70 percent by weight), are solids at room temperature. In addition, the percentage of chlorine influences chlorinated paraffins' ability to inhibit combustion. The higher the percentage of chlorination, the more effective the compound is as a flame retardant.

Because of their high molecular weight, chlorinated paraffins have low vapor pressure when used in a normal working environment. Generally, chlorinated paraffins are water insoluble, but emulsifiable. CPs can be blended with a wide variety of petroleum lubricating basestocks and other organic solvents.

During the manufacturing process, the paraffins react exothermically with gaseous chlorine at 80° C to 120° C. The corrosive nature of the chlorine and the byproduct, hydrogen chloride, require the use of glass-lined reactors.

## USES OF CHLORINATED PARAFFINS

Chlorinated paraffins are used where the demand for chemical stability is high. At high temperatures they react to form low melting inorganic lubricant films on metal surfaces. This film prevents unwanted welding of metal parts, which makes CPs useful additives in cutting oils and high pressure lubricating oils.

Chlorinated paraffins are used in their present applications because they are safer, perform better, and are more cost-effective than any of the possible substitutes. The performance characteristics of chlorinated paraffins have led to their use in applications that range from extreme pressure additives in lubricants, to secondary plasticizers in paints and plastics, to flame retardants in various plastics and textiles.

Approximately 50 percent of the chlorinated paraffins produced domestically are used as additives to metalworking lubricants. About twenty percent of the amount consumed are used as plastics additives, while another 12 percent are used as additives to rubber. Nine percent of chlorinated paraffin production serves as additives to paints with the remaining volume used in adhesives, caulks and sealants. More detailed information on the major uses is provided in Table 1.

**Table 1**
**Primary Uses Of Chlorinated Paraffins In The U.S.**

| Use | Percent of Use | Application |
|---|---|---|
| Lubricating additives | 50 | Extreme-pressure additives and anti-wear agents for cutting oils (metal machinery) and other lubricants. |
| Plastics | 20 | Primary and secondary plasticizers, flame retardant plasticizers for flexible vinyl in the housing and automobile industries, flame retardants in acrylonitrilebutadiene-styrene resins (ABS), unsaturated polyester resins, polyethylene, polypropylene and urethane foam. |
| Rubber | 12 | Flame retardant for styrene-butadiene-rubber (SBR), nitrile and neoprene. |
| Paints | 9 | Plasticizer in alkyd enamels, chlorinated rubber coatings, polyurethane and vinyl. |
| Adhesives, caulks, sealants | 6 | Plasticizers |
| Miscellaneous | 3 | Flame retardant and water repellents for various applications |

## EPA'S CALL FOR AN ASSESSMENT OF CHLORINATED PARAFFINS

The U.S. Environmental Protection Agency (EPA) began inquiring as to the toxicity of chlorinated paraffins in 1977 when chlorinated paraffins were nominated for toxicologic testing by the Interagency Testing Committee (ITC). During the following few years, an International Consortium of Chlorinated Paraffin (ICCP) manufacturers met with EPA and obtained Agency agreement that the testing program ICCP had initiated in 1972, in combination with the National Toxicology Program's (NTP) testing of CPs, would fulfill the Agency's needs for toxicologic data on these substances. EPA announced its approval of the program as a substitute for mandating any health or environmental effects testing in the *Federal Register* on January 8, 1982 (47 Fed. Reg. 1017).

Four representative CPs were chosen for testing in batteries of both environmental and health studies. A two-tier approach was adopted for the toxicity program. Phase 1 was designed to assess differential toxicity, if any, among the selected grades of CPs. Based on the Phase 1 results, at least one CP was to be evaluated in Phase 2.

The environmental studies conducted included 60-day tests of mussels and rainbow trout. The health studies included Phase I single dose pharmacokinetics, 90-day subchronic, metabolism, mutagenicity and teratology tests. A Phase II multigeneration reproductive study was originally called for, but EPA subsequently determined such a study was not needed.

The ICCP conducted the environmental and health studies at laboratories in the U.S. and England. The studies have all been completed; the results have been transmitted to EPA, and most of the studies have already been published in the peer-reviewed literature.

EPA's Office of Toxic Substances has been reviewing all available CP health and environmental effects data. In assessing the human health risks of CPs, EPA is focusing on the implications of the NTP cancer bioassay studies. Preliminary indications from EPA suggest that the Agency does not believe human health risks are significant. This conclusion is largely based on EPA's recognition that CP manufacturing, and most CP use, is conducted in closed systems and that consumers have virtually no exposure. Even if humans were to have dermal contact, CPs do not appear to be rapidly absorbed through human skin.

Accordingly, it is unlikely that EPA will find a need to issue Toxic Substances Control Act (TSCA) regulations to address human health risks of

CPs. The Agency could, however, recommend at some later date that the Occupational Safety and Health Administration (OSHA) review this issue as it pertains more specifically to occupational exposures.

# ASSESSMENT OF THE TOXICOLOGIC AND ENVIRONMENTAL DATA BASE

## Toxicology

Since the inception of testing, an extensive body of information on the toxicity of chlorinated paraffins has been developed. A complete summary of the toxicology of chlorinated paraffins was recently published by Serrone, *et al.* *(Fd Chem. Toxic.* 25:7, 553-562 (1987); see also Bucher *et al.* FAT 9:454-468, (1987)). The following discussion highlights the main findings of this testing program.

The acute toxicity of chlorinated paraffins has been tested in a large variety of animal species and is consistently found to be very low.

In subchronic studies in mice, rats and dogs, the liver was determined to be a primary target organ for CPs. No-observed-effect levels were estabished with consdierably higher values found for longer chain CPs. Mutagenicity studies of CPs, as well as reproductive and teratology tests, all showed negative results.

Results of the National Toxicology Program's (NTP) cancer testing of two CPs--$C_{12}$ chain length, 60 percent chlorine CP; and a $C_{23}$ chain length, 43 percent chlorine CP--were announced in August 1985. NTP interpreted these studies to show:

1) For the short-chain material, clear evidence of carcinogenicity in both sexes of rats and mice; and,

2) For the long-chain material, no evidence of carcinogenicity in male rats, equivocal evidence in female rats, equivocal evidence in female mice, and clear evidence in male mice.

On the basis of these cancer studies, the NTP has listed only the $C_{12}$, 60 percent chlorinated material as a suspect carcinogen in the *Fifth Annual Report on Carcinogens*, which was released in late 1989. The NTP concluded that "[t]here is sufficient evidence for the carcinogenicity of chlorinated paraffins ($C_{12}$, 60% chlorine) in experimental animals."

In determining the relevance of these studies to human risk assessment it is important to consider a number of significant toxicologic issues including:

- data have been generated that suggest the mechanism for tumor formation in rodents may not occur in, and is thus not relevant to, humans;
- the NTP studies were conducted by the corn oil gavage method; and,
- the doses administered in the rodent studies greatly exceeded human exposure levels and likely also exceeded the animals' maximum tolerated dosage.

The International Agency for Research on Cancer (IARC) also reviewed the NTP studies. In February 1989, IARC concluded that:

> Chlorinated paraffins of average carbon chain length $C_{12}$ and average degree of chlorination approximately 60% are possibly carcinogenic to humans (Group 2B).

The IARC Group 2B rating reflects the dual consideration of the absence of any human data suggesting CPs cause cancer and the sufficiency of evidence for carcinogenicity in experimental animals exposed to $C_{12}$, 60 percent chlorinated CP.

The Group 2B classification is limited to the short chain, $C_{12}$, 60% material. IARC concluded that there was "limited evidence" for the carcinogenicity of a commercial chlorinated paraffin product of average carbon chain length $C_{23}$ and average degree chlorination 43% in *experimental animals*. IARC did not suggest any conclusions regarding the carcinogenic potential to *humans* of the $C_{23}$ material or to any other chlorinated paraffin compound. The IARC report is scheduled for publication in 1990.

## Environmental Fate and Effects

In the aquatic environment, CPs are generally associated with sediment or suspended particles because they are of limited solubility in water. The shorter carbon chain length CPs are slightly soluble in water, with a maximum solubility of around 0.1 mg/liter (100 parts per billion). In order to conduct laboratory tests, CPs were made into fine suspensions with the aid of acetone to permit testing at concentrations above the solubility level.

Only when studies were extended to 60 days could the toxicity of CPs be shown in the rainbow trout and mussels and then only with the short chain CP ($C_{10-13}$). Longer chain CPs did not demonstrate toxicity in a 60-day study. Concentrations of CPs ($C_{10-13}$) between 12 and 30 parts-per-billion (ppb) reduced the growth of mussels and were lethal to some trout; however, higher levels of the same CP (up to 280 ppb) had no effect on the growth or viability of the sheepshead minnow. The maximum acceptable concentration (*i.e.*, a concentration which did not produce significant adverse effects in the test species) was determined to be 100 parts-per-billion for the midge (an organism that lives in sediment on the bottoms of streams and ponds). Studies with the short chain CP also showed slight bioconcentration in mussels and the rainbow trout.

CPs were also found to affect adversely the reproduction of certain small crustacean species. Concentrations of CP ($C_{10-13}$) in water under laboratory conditions at or about 10 ppb adversely affected reproduction of the water flea (Daphnia) and the mysid shrimp.

EPA has expressed concern about the relatively low concentration of short chain CPs found to be toxic in the environmental laboratory studies. However, the Agency has also recognized that CPs at such levels are not generally found in aquatic media.

## EPA's Field Studies Report

In 1986/1987, the EPA designed and conducted a study monitoring CPs in river water, sediment and aquatic life. Conduct of the study required the development of a monitoring method sensitive enough to both detect CPs at part-per-billion levels and to distinguish the three chain length grades of CPs (i.e., long, intermediate and short). Water and sediment samples were collected from rivers into which a CP manufacturer and a CP user discharge.

EPA's report[3] of the analyses of these samples indicates CPs, mostly long-chain, were found at low parts-per-billion levels in the river sediment and water near the manufacturer. CPs were also detected in the fat tissue of mussels taken from this river. CPs could not be detected, however, in the waterways or sediments into which the CP user discharges.

The results from these field studies will be combined with other environmental and health data and collectively contribute to EPA's environmental risk assessment for CPs.

[3] U.S. EPA, *Chlorinated Paraffins: A Report on the Findings from Two Field Studies — Sugar Creek, Ohio and Tinkers Creek, Ohio.* Office of Pesticides and Toxic Substances. January, 1988.

# LABELING, WARNINGS AND SAFE HANDLING PRACTICES

## CAS Numbers

The Chemical Abstract Services (CAS) assigns Registry Numbers to compounds listed in the Chemical Abstracts (CA) *Chemical Substance Index*. These numbers are frequently used as identifiers for chemical substances.

Various CAS numbers have been assigned to chlorinated paraffins. These CAS numbers may represent specific CP isomers or may reflect large categories of CPs. The CAS # 63449-39-8 is often used to denote chlorinated paraffin waxes of unspecified carbon chain length and degree of chlorination.

Most of the CAS numbers that have been assigned to chlorinated paraffins are listed in Table 2. The last two numbers listed were issued in 1987 to represent specifically the two chlorinated paraffins tested by the National Toxicology Program. The percentage of chlorination is not specified because the Chemical Abstract Service's naming convention does not provide for degree of chlorination to be indicated. The last two CAS numbers were, however, assigned based on the NTP descriptions of the tested materials, which specifies degree of chlorination.

**Table 2**

| CAS No. | CAS Name | CAS No. | CAS Name |
|---|---|---|---|
| 63449-39-8 | Paraffin waxes and hydrocarbon waxes, chloro | 85535-84-8 | Alkanes, $C_{10-13}$, chloro |
| | | 85535-85-9 | Alkanes, $C_{14-17}$, chloro |
| | | 85535-86-0 | Alkanes, $C_{18-28}$, chloro |
| 85422-92-0 | Paraffin oils and hydrocarbon oils, chloro | 85536-22-7 | Alkanes, $C_{12-14}$, chloro |
| | | 85681-73-8 | Alkanes, $C_{10-14}$, chloro |
| 61788-76-9 | Alkanes, chloro | 97659-46-6 | Alkanes, $C_{10-26}$, chloro |
| 68920-70-7 | Alkanes, $C_{6-18}$, chloro | 97553-43-0 | Paraffins (petroleum), normal C>10, chloro |
| 71011-12-6 | Alkanes, $C_{12-13}$, chloro | | |
| 84082-38-2 | Alkanes, $C_{10-21}$, chloro | 106232-85-3 | Alkanes, $C_{18-20}$, chloro |
| 84776-06-7 | Alkanes, $C_{10-32}$, chloro | 106232-86-4 | Alkanes, $C_{22-40}$, chloro |
| 84776-07-8 | Alkanes, $C_{16-27}$, chloro | 108171-26-2 | Alkanes, $C_{10-12}$, chloro |
| 85049-26-9 | Alkanes, $C_{16-35}$, chloro | 108171-27-3 | Alkanes, $C_{22-26}$, chloro |

## OSHA's Hazard Communication Standard

CP manufacturers have for many years made Material Safety Data Sheets (MSDSs) available to their customers. Since 1983, OSHA has imposed additional worker training and communication requirements for all hazardous chemicals. Pursuant to the OSHA Hazard Communication Standard, hazardous chemicals must be labeled with the appropriate hazard warning, and MSDSs detailing hazards must be available to workers.

**Health Effects Warnings** - OSHA's interpretive guidelines for hazard communication require a cancer warning on the labels of compounds identified as carcinogens or potential carcinogens by: 1) the NTP in its *Annual Report of Carcinogens;* 2) the International Agency for Research on Cancer; or, 3) OSHA itself. In addition, each manufacturer is required to evaluate existing data and label compounds for which available evidence indicates human toxicity. More complete health effects information is called for on MSDSs.

The IARC classification and inclusion in the *NTP Fifth Annual Report on Carcinogens* of the CP average $C_{12}$ chain length and average 60% chlorine content, necessitates that this CP be *labeled* as cancer-causing. At the same time, because the findings for the $C_{23}$ chain length 43% chlorine CP are equivocal and IARC and NTP did not classify this compound as a potential human carcinogen, labeling requirements are not triggered for this CP. In preparing MSDSs, manufacturers must make an informed judgment as to the meaning and significance of the full range of results, including those by NTP, as they may apply to other than the tested material.

**Safe Handling Practices** - Material Safety Data Sheets contain a section that addresses safe handling practices. Although a specific use of a CP may necessitate special handling requirements, the control measures recommended by the various manufacturers are similar. The information provided below briefly summarizes the safe handling recommendations provided in the Material Safety Data Sheets from the CPIA members:

| | |
|---|---|
| Respiratory Protection | - Normally not needed; for oil-type mist, use NIOSH approved respirator |
| Ventilation | - Generally, special ventilation not required under normal conditions of use |
| Protective Gloves | - Use impervious (rubber, nitrile, neoprene) gloves |
| Eye Protection | - Use chemical safety goggles or face shield |
| Other Protective Measures | - Clean clothes; where splash can occur, use apron or chemical suit. |

## DISPOSAL OF CHLORINATED PARAFFINS

Chlorinated paraffins are not regulated hazardous wastes under the Federal Resource Conservation Recovery Act (RCRA) system. Nonetheless, because many chlorinated compounds have been the focus of RCRA attention, questions have occasionally been raised about proper disposal practices for used CPs.

Under RCRA, wastes are deemed "hazardous" in two ways: a waste can be hazardous because (1) it meets one of four general characteristics; or because (2) EPA has included it in a list of hazardous wastes. There are currently four general characteristics that can cause a waste to be hazardous: Ignitability, Corrosivity, Reactivity and EP Toxicity. Used CPs, unless possibly mixed with other substances, do not generally meet any of these hazardous waste characteristics. EPA has proposed expanding, by addition of 38 organic chemicals, the list of substances that would, if found above specified concentrations in a specially designed leaching procedure (i.e., TCLP), classify a waste hazardous (51 Fed. Reg. 21648, June 13, 1986). A final rule is expected in 1990. These additional toxic chemicals do not, however, include chlorinated paraffins or any of their typical components.

Through rulemaking EPA has also listed a number of wastes from both specific and non-specific sources as "hazardous" (i.e., 40 C.F.R. Sections 261.31, 261.32, 261.33.) Chlorinated paraffins are not included on any of these lists and wastes likely to derive from chlorinated paraffin use also do not appear on these lists.

Chlorinated paraffins are also not on the Appendix VIII list of hazardous chemicals whose presence EPA must consider when reviewing a particular waste to determine if it should be listed as hazardous.

The Agency has banned land disposal of liquid hazardous wastes containing certain halogenated organic compounds (HOCs) in concentrations above 1,000 mg/kg (0.1%). (40 C.F.R. Section 268.32). This land ban, however, only applies to wastes that are already listed by regulation as hazardous; i.e., being above 0.1% HOC does not by itself make a waste hazardous. (See 52 Fed. Reg. at 25770; July 8, 1987). EPA's list of hazardous HOCs does not include chlorinated paraffins among compounds that count toward the 0.1% concentration limit. (See 40 C.F.R. Part 268 Appendix III.)

EPA at one time proposed listing all used oil as a RCRA hazardous waste (50 Fed. Reg. 49258, Nov. 29, 1985). That proposal specifically indicated that metalworking fluid including cutting, grinding, machining, rolling, stamping, quenching, and tempering oils would be included in the definition of used oils. Id. at 49261. The Agency subsequently decided not to list used oils has hazardous wastes, but this decision was challenged in litigation (*Hazardous Waste Treatment Council v. EPA*, 861 F.2d 270 (D.C. Cir, 1988). Although the Court directed EPA to reevaluate its decision not to list used oil as hazardous waste, other legislative initiatives mandating management standards for used oils may obviate the need for such a RCRA listing.

Used oil that is burned for energy recovery is subject to regulation under 40 C.F.R. Part 266 if it is contaminated by physical or chemical impurities as a result of its use. These regulations provide for less comprehensive requirements for such used oil, than for hazardous waste, provided it has not been mixed with a hazardous waste. If used oil contains more than 1000 ppm total halogens, it is necessary to rebut the presumption that the used oil was mixed with a hazardous waste. Although CP additives may cause used oil to exceed 1000 ppm total halogens, EPA has acknowledged that the presumption can be rebutted by showing that the high halogen levels come from chlorinated paraffins, which are not hazardous constituents under the RCRA regulations. 50 Fed. Reg. 49177 (Nov. 29, 1985). These regulations should be consulted before any arrangement is made to burn used oil containing CPs for energy recovery.

## ■ CALIFORNIA'S PROPOSITION 65

Considerable concern for a wide variety of chemicals has arisen in California in the last year as its Proposition 65 has become effective. Proposition 65 imposes strict rules on discharges of, and exposures to, chemicals known to the State to cause cancer or to be reproductive toxicants.

In April 1989, the California Science Advisory Panel (SAP) added to its list of chemicals subject to these requirements the chlorinated paraffin "$C_{12}$, 60% chlorine". This is the same CP that was listed by IARC and the NTP. Other CPs have not been listed by the SAP.

As a result of the listing of the $C_{12}$ 60% chlorinated paraffin, the public is to be notified of any significant exposures to this compound. In addition, discharges of significant amounts of this compound to drinking water are prohibited. California has yet to determine what is to be considered a significant exposure to $C_{12}$ 60% chlorine CP. Users of chlorinated paraffins should consult their Material Safety Data Sheets to determine whether the product contains a Proposition 65 chemical.

It should also be noted that some chlorinated paraffin products may be affected by Proposition 65 because they contain other chemical substances that are found on the California list. For example, resinous chlorinated paraffins, which are generally highly chlorinated (approximately 70%), often contain residual concentrations of carbon tetrachloride. Since carbon tetrachloride is on the California list, products containing carbon tetrachloride may be affected.

If you have any further questions or would like to receive additional information, please contact your product manufacturer or:

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*Fd Chem. Toxic.* Vol 25, No. 7, pp. 553–562, 1987
Printed in Great Britain

0278-6915/87 $3.00 + 0.00
Pergamon Journals Ltd

*Summaries of Toxicological Data*

# TOXICOLOGY OF CHLORINATED PARAFFINS*

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(*Received* 7 *November* 1986)

## Introduction

Chlorinated paraffins are a group of complex mixtures, the extremes of which are *n*-paraffins of 10–30 carbon atoms chlorinated 40–70% by weight. The starting hydrocarbon material contains mostly *n*-paraffins but small amounts of isoparaffins or aromatics may be present. There are many grades of chlorinated paraffin, each representing a small spectrum within the ranges of carbon chain length and percentage chlorination. Each grade has specific physical and chemical properties, which make the compounds useful in a variety of industrial applications from extreme pressure additives in lubricants to secondary plasticizers in plastics and paint.

The chlorinated paraffins of short and medium chain length are oily liquid materials at ambient temperature. The long-chain highly chlorinated paraffins are solid waxy materials. The chlorinated paraffins are highly soluble in oils and fats and most are practically insoluble in water. Those of shorter chain length, however, are slighly soluble in water (maximum around 0.1 mg/litre).

The widespread use of chlorinated paraffins and their detection at low concentrations in the aquatic and terrestrial environments, as well as the lack of toxicological information, were prime reasons for conducting this programme (Campell & McConnell, 1980; Madeley & Birtley, 1980). Since more than 200 chlorinated paraffins are produced on a world-wide basis by European and American companies, the Working Party felt that grades at the middle and extremes of the range should be tested so that any effects due to changes in chlorine content and carbon chain length would become apparent. Therefore, evidence of differential toxicity was sought by evaluation of the following four selected chlorinated paraffins:

58% chlorination of short-chain ($C_{10-13}$) *n*-paraffins (liquid); 52% chlorination of intermediate-chain ($C_{14-17}$) *n*-paraffins (liquid); 43% chlorination of long-chain ($C_{20-30}$) *n*-paraffins (liquid); 70% chlorination of long-chain ($C_{22-26}$) *n*-paraffins (solid).

In January 1982, the Environmental Protection Agency reviewed the Consortium's testing programme and found it acceptable (Experimental Protection Agency, 1982).

## Acute toxicity

Chlorinated paraffins have very low acute mammalian toxicity (Birtley *et al.* 1980). The acute oral

*The work summarized here was conducted by The Working Party of the Chlorinated Paraffin Manufacturers Toxicology Testing Consortium on behalf of Atochem France, Caffaro Italy, Diamond Shamrock Chemical USA, Dover Chemical USA, Dynamit-Nobel AG Germany, Hercules Inc. USA, Hoechst AG Germany, Huls AG Germany, Imperial Chemical Industries plc UK, Keil Chemical USA, Neville Chemical USA, Rhone-Poulenc France and Witco Chemical USA. Full reports giving details of the studies conducted by the Consortium at International Research and Development Corporation (IRDC) and Wildlife International Ltd may be obtained from D. M. Serrone, Ricerca, Inc., Painesville, OH 44077, USA. These reports are cited in the text under the IRDC or Wildlife International number and are identified on p. 558.

†To whom correspondence and reprint requests should be addressed.

$LD_{50}$ of all grades tested exceeded 4 g/kg. Most chlorinated paraffins produced some degree of skin irritation in animal tests in which the skin was kept covered with an occlusive dressing for 24 hr. Mild-to-moderate skin irritation was produced by grades derived from *n*-paraffins containing 10–13 and 14–17 carbon atoms; the response was independent of the degree of chlorination, but the irritation decreased with the longer chain lengths ($C_{20-30}$). The short-chain ($C_{10-13}$) *n*-paraffins produced a mild and transient irritation when placed in the eye of a rabbit. No eye irritation was observed with the longer-chain *n*-paraffins.

## Subchronic toxicity in rats

Dosages for the 14-day studies are given in Table 1 and for the 90-day studies in Table 2.

### *Chlorinated paraffin, ($C_{10-13}$) and 58% chlorination*

The chlorinated paraffin containing 10–13 carbon atoms and chlorinated to 58% was administered to Fischer 344 rats as part of the diet, in studies lasting either 14 or 90 days (IRDC 438-002; IRDC 438-022/035). In similar studies, the same chlorinated paraffin was dissolved in corn oil and given to male and female rats by gavage (IRDC 438-006; IRDC 438-022/029).

The 14-day studies identified the liver as a target organ for this chlorinated paraffin. Both male and female rats given the test material either in the diet or by gavage at dose levels of 100 mg/kg/day or above had increased liver weights. Hepatocellular hypertrophy was observed when the livers were examined microscopically. The no-observable-effect level was considered to be 30 mg/kg/day.

The 90-day studies showed the kidney and thyroid–parathyroid glands as target organs in addition to the liver. No overt signs of toxicity were observed in these studies. Body-weight gains were slightly reduced in male rats at high dosages and a slight skin atonia was observed, as well as changes in water consumption. The major effects were increases in the weights of the liver and the kidneys of both sexes at doses of 100 mg/kg/day and above (Table 3). Thyroid–parathyroid weights were increased at a dose of 625 mg/kg/day (Table 3). Microscopic findings included increased incidences of hepatocellular hypertrophy in both males and females at the mid and high doses. Thyroid hypertrophy and hyperplasia were observed in males at the mid and high doses and in females at the high dose (Table 4). High incidences of trace-to-mild chronic nephritis were observed in the kidneys of male rats at the mid and high doses and increased pigmentation of the renal tubules occurred in high-dose females (Table 4). No treatment-related microscopic changes were found in any tissues from rats in the 10-mg/kg/day group.

Administration of chlorinated paraffin containing $^{14}C$-labelled chlorinated undecane as a marker demonstrated that some of the dose was absorbed after oral administration but most was excreted in the faeces. The kinetics of absorption and tissue concentrations were similar following administration of the radiolabelled material to naive rats or to rats that had received chlorinated paraffins for 90 days prior to the administration of the radiolabelled material. This may suggest that sites of interaction were not saturated. The highest tissue concentrations of radiolabelled material were seen in the liver, kidney, adipose tissue and ovary. The high levels of radioactivity in liver and kidney may be related to the effects seen in these organs, but may also represent processing of the compounds by biotransformation, distribution or elimination. The high concentration of radioactivity found in the ovary was not associated with any morphological changes in this organ.

The chlorinated paraffin containing 10–13 carbon atoms and chlorinated to 58% produced similar effects in the target organs whether administered as a part of the diet or dissolved in corn oil and given by gavage (Table 4). The no-observable effect level by either route of administration was 10 mg/kg/day (Table 5).

Table 1. Dose levels used in 14-day subchronic toxicity studies on chlorinated paraffins administered in the diet or by gavage

| Dose levels of chlorinated paraffin: | | | | |
|---|---|---|---|---|
| 58% Cl ($C_{10-13}$) | | 52% Cl ($C_{14-17}$) | 43% Cl ($C_{20-30}$) | 70% Cl ($C_{22-26}$) |
| Dietary (ppm in diet) | Gavage (mg/kg body weight/day) | Dietary (ppm in diet) | Gavage (mg/kg body weight/day) | Dietary (ppm in diet) |
| 900 | 30 | 150 | 30 | 150 |
| 2700 | 100 | 500 | 100 | 500 |
| 9100 | 300 | 1500 | 300 | 1500 |
| 27,300 | 1000 | 5000 | 1000 | 5000 |
| — | 3000 | 15,000 | 3000 | 15,000 |

Table 2. Dose levels used in 90-day subchronic toxicity studies on chlorinated paraffins administered in the diet or by gavage

| Dose levels (mg/kg body weight/day) of chlorinated paraffin: | | | |
|---|---|---|---|
| 58% Cl ($C_{10-13}$) | 52∘ Cl ($C_{14-17}$) | 43% Cl ($C_{20-30}$) | 70% Cl ($C_{22-26}$) |
| Route . . . D & G | D | G | D |
| 10 | 10 | 100 | 100 |
| 100 | 100 | 900 | 900 |
| 625 | 625 | 3750 | 3750 |

D = Administered in diet G = Administered by gavage

Table 3. Organs showing increases in absolute or relative weight in 90-day subchronic studies on chlorinated paraffins

| Chlorinated paraffin | Route | Dose (mg/kg body weight) | Males: Absolute | Males: Relative* | Females: Absolute | Females: Relative* |
|---|---|---|---|---|---|---|
| 58% Cl ($C_{10-13}$) | D | 10 | — | — | — | — |
| | | 100 | Liver<br>Kidney | Liver<br>Kidney | Liver<br>Kidney | Liver<br>Kidney |
| | | 625 | Liver<br>Kidney<br>Thyroid | Liver<br>Kidney<br>Thyroid | Liver<br>Kidney<br>Thyroid | Liver<br>Kidney<br>Thyroid |
| 58% Cl ($C_{10-13}$) | G | 10 | — | — | — | — |
| | | 100 | Liver<br>Kidney | Liver<br>Kidney | Liver | Liver<br>Kidney |
| | | 625 | Liver<br>Kidney<br>Thyroid | Liver<br>Kidney<br>Thyroid | Liver | Liver<br>Kidney |
| 52% Cl ($C_{14-17}$) | D | 10 | — | Liver | — | — |
| | | 100 | Liver<br>Kidney | Liver<br>Kidney | Liver<br>Kidney | Liver<br>Kidney |
| | | 625 | Liver<br>Kidney<br>Thyroid<br>Adrenal | Liver<br>Kidney<br>Thyroid<br>Adrenal | Liver<br>Kidney<br>Adrenal | Liver<br>Kidney<br>Adrenal |
| 43% Cl ($C_{20-30}$) | D | 100 | — | — | Liver | — |
| | | 900 | — | — | Liver | Liver |
| | | 3750 | — | — | Liver | Liver |
| 70% Cl ($C_{22-26}$) | G | 100 | — | — | — | — |
| | | 900 | — | — | — | — |
| | | 3750 | — | Liver | Liver | Liver |

D = Administered in diet G = Administered by gavage

*Expressed as a percentage of body weight.

### *Chlorinated paraffin, $C_{14-17}$ and 52% chlorination*

The chlorinated paraffin containing 14–17 carbon atoms and chlorinated to 52% was administered to Fischer 344 rats as part of the diet, in studies lasting either 14 or 90 days (IRDC 438-003; IRDC 438-023/026).

Liver weights were increased in both male and female rats following the 14-day dietary administration of this chlorinated paraffin at 5000 and 15,000 ppm and liver weight relative to body weight was increased in females given 1500 ppm. Microscopic examination of the livers showed mild diffuse hepatocellular hypertrophy in all rats receiving the two highest dose levels. A dietary level of 500 ppm was considered to be a no-observable-effect level.

In the 90-day studies, the weights of livers and kidneys of both sexes were increased at doses of 100 mg/kg/day and above (Table 3). An increase in relative liver weight at the 10-mg/kg/day level occurred only in males and was not supported by microscopic findings, so it was not considered biologically significant. At 625 mg/kg/day, thyroid–parathyroid weights were increased in male rats and adrenal weights were increased in both males and females (Table 3). Microscopic findings included increased hepatocellular hypertrophy in the livers of both males and females at the high dose (Table 6), while thyroid hypertrophy and hyperplasia were observed in males at the high dose (Table 6). Also at the high dose, trace-to-mild chronic nephritis occurred in males, and renal tubular pigmentation was observed exclusively in the females (Table 6). There were no detectable morphological changes in the adrenal glands.

Some of a $^{14}C$-labelled dose was absorbed following oral administration, but most was excreted in the faeces. Faecal excretion may represent both unabsorbed material and labelled material excreted in the bile. The kinetics of absorption and tissue concentrations were similar following administration of radiolabelled material to naive rats or to rats that had received chlorinated paraffin test material for 90 days prior to the administration of radiolabelled material. Tissue concentrations were highest initially in the liver and kidney and later in adipose tissue and the

Table 4. Microscopic findings in 90-day subchronic studies in which 58% chlorinated ($C_{10-13}$) paraffin was administered to rats in the diet or by gavage*

| Dose (mg/kg body weight/day) | Liver | Kidney | Thyroid |
|---|---|---|---|
| **Males** | | | |
| 10 | — | — | — |
| 100 | Hepatocellular hypertrophy | Chronic nephritis | Hypertrophy, hyperplasia |
| 625 | Hepatocellular hypertrophy | Chronic nephritis | Hypertrophy, hyperplasia |
| **Females** | | | |
| 10 | — | — | — |
| 100 | Hepatocellular hypertrophy | — | — |
| 625 | Hepatocellular hypertrophy | Renal tubule pigmentation | Hypertrophy, hyperplasia |

*Results of both studies considered.

Table 5. No-observable-effect levels (NOEL) in 90-day subchronic studies on chlorinated paraffins

| Chlorinated paraffin | NOEL (mg/kg body weight/day): Males | Females |
|---|---|---|
| 58% Cl ($C_{10-13}$) | 10 | 10 |
| 52% Cl ($C_{14-17}$) | 10 | 10 |
| 43% Cl ($C_{20-30}$) | >3750 | <100 |
| 70% Cl ($C_{22-26}$) | 900 | 900 |

ovary. The high liver and kidney levels of radioactivity may be related to changes seen in these organs. Despite the high levels in the ovary, no morphological changes were observed in that organ.

Dietary administration of the chlorinated paraffin containing 14–17 carbon atoms and chlorinated to 52% identified several target organs. The no-observable-effect level was 10 mg/kg/day (Table 5).

*Chlorinated paraffins, $C_{20-30}$ and 43% chlorination*

The chlorinated paraffin containing 20–30 carbon atoms and chlorinated to 43% was dissolved in corn oil and given by gavage to Fischer 344 rats in studies lasting either 14 or 90 days (IRDC 438-005; IRDC 438-021/028).

No compound-related effects were found in either male or female rats during regular observations, in organ weights or in the tissues examined microscopically in the 14-day study.

There were no significant adverse effects on body-weight gain, water or food consumption, haematology or clinical biochemistry measurements during the 90-day study. There was a treatment-related effect on the liver of female rats at all dose levels, but no effect was observed in the livers of males (Table 3). Female liver weights were increased and a multifocal granulomatous hepatitis characterized by inflammatory changes and necrosis was seen on microscopic examination of the liver (Table 7). [Bucher et al. (1984) reported similar hepatic lesions in female rats in 90-day studies and in male rats receiving much larger doses for 6–12 months in a 2-yr chronic toxicity and carcinogenicity study]. Nephrosis was observed in the kidneys of male rats and mineralization in the kidneys of female rats at the high dose (Table 7).

Similarity in the concentrations of radioactivity in the tissues of male and female rats given $^{14}C$-labelled test material suggested that the total amount of test material absorbed was similar in both sexes. The level of radioactivity was higher in the livers of female rats, however, than in the livers of males. A higher level of radioactivity was found in the ovary than in the blood or adipose tissue during the first 7 days after administration of the radioactivity test material. As with the other chlorinated paraffins, no morphological change in the ovary was associated with this level of accumulation of labelled material. The retention in adipose tissue and subsequent slow rate of elimination of radioactivity was not unexpected for such a highly lipophilic chemical.

**Table 6. Microscopic findings in a 90-day subchronic study in which 52% chlorinated $C_{14-17}$ paraffin was administered to rats in the diet**

| Dose (mg/kg body weight/day) | Changes detected in: Liver | Kidney | Thyroid |
|---|---|---|---|
| | **Males** | | |
| 10 | — | — | — |
| 100 | — | — | — |
| 625 | Hepatocellular hypertrophy | Chronic nephritis | Hypertrophy, hyperplasia |
| | **Females** | | |
| 10 | — | — | — |
| 100 | — | — | — |
| 625 | Hepatocellular hypertrophy | Renal tubule pigmentation | |

Table 7. Microscopic findings in a 90-day subchronic study in which 43% chlorinated $C_{20-30}$ paraffin was administered to rats by gavage

| Dose (mg/kg body weight/day) | Changes detected in: Liver | Kidney |
|---|---|---|
| | **Males** | |
| 100 | — | — |
| 900 | — | — |
| 3750 | — | Nephrosis |
| | **Females** | |
| 100 | Multifocal granulomatous hepatitis, inflammation & necrosis | |
| 900 | Multifocal granulomatous hepatitis, inflammation & necrosis | |
| 3750 | Multifocal granulomatous hepatitis, inflammation & necrosis | Mineralization |

No effects were seen in the thyroid.

A toxicological no-effect level for female rats was not established in this 90-day study (Table 5). No adverse observable effects apart from a mild nephrosis were found for male rats up to and including 3750 mg/kg/day.

*Chlorinated paraffins, $C_{22-26}$ and 70% chlorination*

The chlorinated paraffin containing 22–26 carbon atoms and chlorinated to 70% was administered to Fischer 344 rats in the diet in studies lasting either 14 or 90 days (IRDC 438-004; IRDC 438-024/027).

No compound-related effects were found in the 14-day study in either male or female rats.

Slight, but statistically significant, decreases in the rate of body-weight gain were observed at the high dose level in both male and female rats in the 90-day study. Food consumption was slightly increased in males at all treatment levels. Increases in alanine aminotransferase (ALT) activity were recorded in both males and females in the high-dose group, indicating a treatment-related effect on liver function. Aspartate aminotransferase (AST) was also increased in females at this high dose. The increase in liver weights found at the high-dose level in both males and females was considered to be treatment-related, as hepatocellular hypertrophy and cytoplasmic fat vacuolation were accompanying histopathological findings (Tables 3 & 8). A slight incidence of chronic nephritis was seen in kidneys of high-dose males (Table 8).

A small part of the $^{14}C$-labelled dose was absorbed following oral administration. The highest tissue concentration of radioactivity was in the liver and was similar for males and females. Radioactive material did not appear to concentrate in the ovary as with other chlorinated paraffins. The retention in adipose tissue and the subsequent slow rate of elimination of radioactivity was expected for a highly lipophilic material.

On the basis of the findings in the liver, the no-observable effect level was 900 mg/kg/day (Table 5).

*Summary*

The subchronic studies indicated, in general, a higher toxicity for the shorter-chain chlorinated paraffins, $C_{10-13}$ and $C_{14-17}$ than for the $C_{20-30}$ material. The liver and kidney appeared to be the primary

Table 8. Microscopic findings in a 90-day subchronic study in which 70% chlorinated $C_{22-26}$ paraffin was administered to rats in the diet

| Dose (mg/kg body weight/day) | Liver | Kidney |
|---|---|---|
| | **Males** | |
| 100 | — | — |
| 900 | — | — |
| 3750 | Hepatocellular hypertrophy, cytoplasmic vacuolation (fat) | Chronic nephritis |
| | **Females** | |
| 100 | — | — |
| 900 | — | — |
| 3750 | Hepatocellular hypertrophy, cytoplasmic vacuolation (fat) | — |

No effects were seen in the thyroid.

target organs for the toxicity of the chlorinated paraffins. Studies with radiolabelled marker compounds demonstrated some absorption of the materials from the gastro-intestinal tract. Interestingly, little difference in the toxicity was observed between the $C_{10-13}$ chlorinated paraffin given in the diet and that given by gavage.

### Teratology in rats and rabbits

Dose levels for these studies are given in Table 9. Rats were treated on days 6–19 and rabbits on days 6–27 of gestation.

*Chlorinated paraffin, $C_{10-13}$ and 58% chlorination*

The chlorinated paraffin containing 10–13 carbon atoms and chlorinated to 58% was dissolved in corn oil and administered to pregnant Charles River rats (IRDC 438-016; IRDC 438-019) and to artificially inseminated Dutch Belted rabbits (IRDC 438-031; IRDC 438-037).

In the rat study, eight of 25 pregnant dams (32%) from the high-dose group died following the administration of the chlorinated paraffin. Signs of maternal toxicity were observed in both the mid-dose and high-dose groups. An increased number of post-implantation losses, increased early and late resorptions and a decrease in viable foetuses per dam, in addition to adactyly and/or shortened digits, were observed at the high dose. The digital malformations observed at a dose that produced significant mortality in treated dams cannot be interpreted as a direct

Table 9. Dose levels used in teratology studies on chlorinated paraffins in rats and rabbits

| Dose levels (mg/kg body weight/day) of chlorinated paraffin | | | | | | | |
|---|---|---|---|---|---|---|---|
| 58% ($C_{10-13}$) | | 52% ($C_{14-17}$) | | 43% ($C_{20-30}$) | | 70% ($C_{22-26}$) | |
| Rat | Rabbit | Rat | Rabbit | Rat | Rabbit | Rat | Rabbit |
| 100 | 10 | 500 | 10 | 500 | 500 | 500 | 100 |
| 500 | 30 | 2000 | 30 | 2000 | 2000 | 2000 | 300 |
| 2000 | 100 | 5000 | 100 | 5000 | 5000 | 5000 | 1000 |

Test material was administered by gavage to rats on days 6 to 19 and to rabbits on days 6 to 27 of gestation.

Table 10. Doses used for the cytogenetic evaluation of chlorinated paraffins in the bone-marrow cells of male rats treated by gavage for 5 days

| Chlorinated paraffin | Vehicle | Dose (mg/kg body weight/day) | Observations |
|---|---|---|---|
| 58% Cl ($C_{10-13}$) | Corn oil | 250 | |
| | | 750 | Reduced body-weight gain |
| | | 2500 | Death of 7/8 rats |
| 52% Cl ($C_{14-17}$) | Corn oil | 500 | |
| | | 1500 | |
| | | 5000 | |
| 43% Cl ($C_{20-30}$) | Corn oil | 500 | |
| | | 1500 | |
| | | 5000 | |
| 70% Cl ($C_{22-26}$) | 1% CMC | 500 | |
| | | 1500 | |
| | | 5000 | Reduced body-weight gain |

CMC = Carboxymethylcellulose

teratogenic effect; they are more likely to be a secondary response due to maternal toxicity. No effects on dams or foetuses were observed at the lowest dose level.

Pregnant rabbits were more sensitive to this chlorinated paraffin than were pregnant rats, as judged by the doses that could be tolerated. Embryotoxicity was seen in both the mid-dose and high-dose groups in the rabbit teratology study. No effect was observed on the occurrence of malformations at any dose level.

*Chlorinated paraffin, $C_{14-17}$ and 52% chlorination*

The chlorinated paraffin containing 14–17 carbon atoms and chlorinated to 52% was dissolved in corn oil and administered to pregnant Charles River rats (IRDC 438-017; IRDC 438-034; IRDC 438-047) and to artificially inseminated Dutch Belted rabbits (IRDC 438–020; IRDC 438-032; IRDC 438-036).

Maternal toxicity was observed in the rat study at the high dose. One female in the mid-dose group died on day 16 of gestation from an undetermined cause. There were no biologically meaningful or relevant statistically significant differences in Caesarean section observations or in the incidence of foetal malformations in the litters of treated groups when compared to the control.

Again pregnant rabbits were more sensitive to the chlorinated paraffin than were pregnant rats. Although no maternal toxicity was observed in the rabbit study, mean maternal body-weight losses were seen during treatment at the high dose level in a range-finding study. This preliminary result was the basis for the selection of the high dose in the main study. There were no biologically meaningful differences in the numbers of litters/foetuses with malformations or in developmental and genetic variations when the treated groups were compared to the control.

*Chlorinated paraffin, $C_{20-30}$ and 43% chlorination*

The chlorinated paraffin containing 20–30 carbon atoms and chlorinated to 43% was dissolved in corn oil and administered to pregnant Charles River rats (JRDC 438-015; IRDC 438-033) and to artificially inseminated Dutch Belted rabbits (IRDC 438-018; IRDC 438-030).

Maternal toxicity was observed in rats at the high dose. One female from this group died on day 18 of gestation. No differences in the incidence of foetal malformations were observed when treated groups were compared to the control.

Rabbits were not more sensitive to this chlorinated paraffin and were able to tolerate the same doses as the rats. Two of 12 dams at the high dose and one of 13 dams at the mid-dose aborted. In the high-dose group, there was a slight increase in mean post-implantation loss and a slight decrease in the mean number of viable foetuses when compared to the control. The data did not indicate a teratogenic response.

*Chlorinated paraffin, $C_{22-26}$ and 70% chlorination*

The chlorinated paraffin containing 22–26 carbon atoms and chlorinated to 70% was suspended in 1% aqueous carboxymethylcellulose and administered to pregnant Charles River rats (IRDC 438-045; IRDC 438-046) and to artificially inseminated Dutch Belted rabbits (IRDC 438-038; IRDC 438-039, IRDC 438-040).

No maternal toxicity was observed in any of the pregnant rats that were given this chlorinated paraffin. There were no biologically meaningful differences in the incidence of developmental variations and malformations in the treated groups when compared to the control.

In preliminary rabbit studies, an increase in post-implantation loss was observed at a dose of 1000 mg/kg/day and above, but this effect was not seen in the main teratology study. Two high-dose does died on day 9 and 10 of gestation because of an intubation error; one mid-dose doe died on day 16 from an undetermined cause. No biologically meaningful differences were observed in maternal appearance, behaviour or body-weight gain or in the occurrence of genetic and developmental variation in the treated groups when compared to the control. There were no adverse treatment-related differences in Caesarean section observations or in the incidence of foetal malformations in the litters of the treated groups when compared to control values.

*Summary*

None of the four chlorinated paraffins tested produced an effect that could be concluded to be teratogenic in either rats or rabbits.

**Cytogenetic evaluation in rat bone-marrow cells**

The four chlorinated paraffins described above were administered orally by gavage to groups of eight sexually mature male Fischer 344 rats for five consecutive days (IRDC 438-012; IRDC 438-013; IRDC 438-014; IRDC 438-043). Dose levels, vehicles and observations are shown in Table 10. Cyclophosphamide, given to a group of rats as a positive control, induced a significant number of chromosomal aberrations (primarily chromatid type). None of the chlorinated paraffins increased the frequency of chromosomal or chromatid aberrations in bone-marrow cells. Therefore, the chlorinated paraffins were not considered to be clastogenic in this test system.

**Dominant lethal study in rats**

The chlorinated paraffin containing 10–13 carbon atoms and chlorinated to 58% was dissolved in corn oil and administered orally by gavage on five consecutive days to groups of 15 sexually mature male Charles River rats at doses of 0, 250, 750 and 2000 mg/kg body weight/day (IRCD 438-011). Cyclophosphamide was given to a group of 15 male rats as a positive control. Two days after the end of treatment each of the males was paired with two females for 5 days. Following 2 days of rest, the pairing was repeated with two new females per male. This cycle was repeated ten times (20 females in total per male). Uterine examinations were carried out on each female 15 days after the introduction of the male. Cyclophosphamide produced a dominant lethal mutation affecting the post-meiotic stage of spermatogenesis. The chlorinated paraffin did not induce any increase in early foetal deaths or a decrease in viable embryos during the ten matings of the study. Thus it was concluded that this chlorinated paraffin was negative in the dominant lethal assay.

## Reproduction

*Chlorinated paraffin, $C_{10-13}$ and 58% chlorination—ducks*

The chlorinated paraffin containing 10–13 carbon atoms and chlorinated to 58% was fed for 22 wk at levels of 0, 28, 166 and 1000 ppm in the diet to young adult mallard ducks approaching their first breeding season (Wildlife International Ltd, Project No. 188–101). Each group consisted of 20 pens, each containing one pair (a drake and a hen). Eggs were collected daily during the 10-wk egg-laying period. They were incubated and hatched, and the offspring were maintained on basal diet for 14 days.

No effects of the chlorinated paraffin were seen in adults or hatchlings at any of the feeding levels. There appeared to be a reduction in egg fertility at the high-dose level. This effect was not statistically significant when the number of viable embryos of eggs set was compared to controls over the entire study, but when weekly comparisons were made a significant difference was found for two of the 10-wk collection periods (wk 3 and 6). A slight decrease in eggshell thickness was also observed at the high-dose level (control 0.375 mm *v.* high dose 0.355 mm). Although the difference was statistically significant, biological significance was considered questionable as the mean was within the range of normal values (0.34–0.39 mm) given in the EPA-Environmental Effects Test Guidelines (560/6-82-002) and no increase in cracked shells was observed in the study. No treatment-related differences in embryo viability or eggshell thickness were noted in the 28 or 166 ppm groups when compared with the control. No effects on egg weight, eggshell cracks, eggs laid, 21-day embryos or hatchability were observed in any of the treatment groups.

The no-observable-effect dietary concentration was considered to be 166 ppm.

*Chlorinated paraffin, $C_{14-17}$ and 52% chlorination—rats*

The chlorinated paraffin containing 14–17 carbon atoms and chlorinated to 52% was fed in the diet to Charles River rats at levels of 0, 100, 1000 and 6250 ppm (IRDC 438-049). 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. Pups were given the same diet as their parents from weaning until the offspring were 70 days of age.

No differences were seen in appearance, fertility, body-weight gain, food consumption or reproductive performance in the parent generation. No adverse effects on pups were observed prior to lactation day 7. Litter size, weight, and survival showed no adverse effects at birth or on lactation day 4. A significant decrease in pup survival was apparent in the high-dose group on lactation day 10. None of the high-dose pups survived to weaning. Survival in pups from the mid-dose group was decreased by lactation day 21. Observations in pups included bruised areas, decreased activity, laboured breathing, pale discoloration and/or blood around the orifices. Necropsy findings in pups that died during the study included pale liver, kidneys and lungs, and blood in the cranial cavity, brain, stomach and intestines. Male and female pup weights were lower in the low- and mid-dose groups than in the control group on lactation day 21. The reduced weight continued after weaning in the females, whereas with the males the difference from the control group became less pronounced as the study progressed.

One possible explanation for such an observation could be the concentration and passage of relatively high levels of chlorinated paraffins from the mother to the pups in the milk. Preliminary results of a cross-fostering study showed a greater mortality in pups exposed via milk than in pups exposed only *in utero* (R. D. N. Birtley, personal communication, 1986). The haematological effects appeared to be a dysfunction in the vitamin K-dependent elements of the extrinsic component of the clotting process.

## Summary and conclusions

The studies reported here demonstrated that toxicity of the chlorinated paraffins was related to carbon chain length and possibly to the degree of chlorination. Each chlorinated paraffin tested had a different toxicological profile. The two materials of shorter chain length and chlorinated to 58 and 52% were more toxic than longer-chain materials, in that they produced effects on the liver and kidney at lower daily doses and also had effects on the thyroid. Part of this difference may be due to the fact that the longer-chain grades were less well absorbed from the rat gut than the shorter-chain grades. Previous studies on chlorinated alkanes in mice and quail have shown that absorption and metabolism were apparently related to the degree of chlorination and most probably to the length of the carbon chain (Biessman *et al.* 1983; Darnerud *et al.* 1982; Darnerud & Brandt, 1982). The chlorinated paraffin containing 20–30 carbon atoms and chlorinated to 43% produced a multifocal granulomatous hepatitis in the livers of only the female rats in the 90-day study. The chlorinated paraffin containing 22–26 carbon atoms and chlorinated to 70% induced changes in serum enzymes indicative of liver damage, an indication supported by microscopic findings of hepatocellular hypertrophy and cytoplasmic fat vacuolation in both male and female rats. The two shorter-chain grades produced hepatocellular hypertrophy in both sexes but with no corresponding elevation of serum enzymes.

The National Toxicology Program (NTP, 1986a) showed what was termed clear evidence of carcinogenicity for the chlorinated paraffin containing 10–13 carbon atoms and chlorinated to 58%. This conclusion was based on increased incidences of hepatocellular neoplasms in male and female rats, of adenomas or adenocarcinomas (combined) of the kidney tubular cells in male rats, and of follicular cell adenomas or carcinomas (combined) of the thyroid gland in female rats. The tumours occurred in the target tissues identified in the subchronic study reported here. The dosages used in the NTP study were 312 and 625 mg/kg/day—extremely large doses which were sufficient to produce histopathological changes in the target tissues in 90 days. The no-observable-effect level in the subchronic study reported here for this chlorinated paraffin was 10 mg/kg/day. The doses selected by NTP may have been at too high a level to provide adequate information on the shape of the dose-response curve. Since genotoxicity studies conducted with this chlorinated paraffin were negative, one must postulate non-genotoxic mechanisms for tumour induction and conclude that this grade of chlorinated paraffin should be considered in a worst case scenario as a 'promoter'.

A chlorinated paraffin in the category of 20–30 carbon atoms and chlorinated to approximately 43% was also studied by the National Toxicology Program (NTP, 1986b). In rats, there was no evidence of carcinogenicity in males while in females what NTP termed equivocal evidence of carcinogenicity was provided by an increased incidence of adrenal gland medullary phaeochromocytomas. The subchronic study had identified the liver as the target organ for toxicity in female rats, but no increased incidence of liver tumours was reported in the bioassay (NTP, 1986b). No toxicity was reported for the male rats in the 90-day study. An increased incidence of malignant lymphomas was reported for male $B6C3F_1$ mice given this chlorinated paraffin (NTP, 1986b). Mice are prone to the development of lymphomas, however, with a range of tumour incidence of 2–73%. Viruses may be the actual causative agent of the lymphomas and these viruses are ubiquitous among laboratory strains of mice. Thus the induction of lymphomas in mice as an index of carcinogenic activity is, in our opinion, not valid. One would conclude, therefore, on the basis of the bioassay results, that the chlorinated paraffin containing 20–30 carbon atoms and chlorinated to 43% provided no clear evidence of carcinogenicity.

The chlorinated paraffins demonstrated limited absorption from the gastro-intestinal tract and had as their main target organs those systems involved with metabolism and excretion (liver and kidney). The shorter-chain grades, $C_{10-13}$ and $C_{14-17}$, appeared to act as do many xenobiotics by inducing adaptive changes in the liver, as indicated by an increase in weight and by hepatocellular hypertrophy. Excretion of the parent compound and/or metabolites in the bile may also have occurred. Kidney changes may have been produced by either parent-compound or metabolite overload.

The material of longer chain length ($C_{20-30}$) but a lower degree of chlorination (43%) can apparently be more easily handled by male rats, but produced changes (granulomatous hepatitis) in the liver of the female rat. The more highly chlorinated (70%) grade produced effects in the livers of both male and female rats. Hepatocellular hypertrophy, which was a response similar to that seen with the shorter-chain grades, as well as a fatty cytoplasmic vacuolation were observed with this grade of chlorinated paraffin.

Only the chlorinated paraffin containing 10–13 carbon atoms and chlorinated to 58% produced what NTP termed evidence of carcinogenicity in rats and mice when given by gavage in large doses suspended in corn oil (NTP, 1986a). Administration of chlorinated paraffins by gavage is, in our opinion, an inappropriate method of administration as it is not relevant to man. Use of corn oil as a vehicle alters the normal nutritional status of the test animals and this, in turn, may influence the carcinogenic response. Dose levels in the rat bioassay were excessive, producing marked toxicity of the liver and kidney within 6 months. As conducted, the experiment provided little information relevant to a carcinogenic assessment for man.

A chlorinated paraffin of longer chain length ($C_{20-30}$) and a lower degree of chlorination (43%) did not produce clear evidence of carcinogenicity when tested in rats and mice (NTP, 1986b).

The chlorinated paraffins did not produce malformations in offspring indicative of a teratogenic response. Concentration of radiolabel in the ovary was a consistent finding, but no morphological changes were observed. Reproductive studies in both the rat and duck failed to demonstrate impairment of reproductive function.

Chlorinated paraffins are complex mixtures and should not be regarded as homogeneous. As a group, they are difficult to characterize chemically. There is variation in the percentage and localization of chlorine, as well as in the consistency of distribution of the *n*-paraffins. Evaluation of biological data from studies with complex mixtures must consider the possibility that toxic responses may be due to a single constituent within the mixture. Studies with unleaded gasoline, a complex mixture, have attributed the renal toxicity produced in male rats to saturated branched-chain aliphatic compounds such as 2,2,4-trimethylpentane. One cannot rule out the possibility that the effects observed with chlorinated paraffins or, for that matter, with any complex mixture are due to specific fractions of the complex mixture tested or even to contaminants with the mixture when no data for individual constituents are available.

In most applications, chlorinated paraffins become an integral part of the compounds in which they are used (e.g. plastics) and consequently the general public is not directly exposed to these materials. Human exposure to chlorinated paraffins is minimal and limited to the workplace, and therefore, any risk assessment should consider the established no-effect levels and in-plant exposures. The existing toxicological data would seem to be adequate for determining a 'safe' workplace concentration.

*Acknowledgement*—The authors thank Alice K. Lemin for preparation of the manuscript.

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