CHLORINATED PARAFFINS

1. Chemical and Physical Data

Chlorinated paraffins are manufactured by the chlorination of specified normal paraffin fractions (straight-chain hydrocarbons) obtained from petroleum refining. Ordinary commercial chlorinated paraffins are not single compounds but are mixtures, each containing several homologous *n*-alkanes corresponding to their manufacture from *n*-paraffin fractions with several different degrees of chlorination.

Chlorinated paraffins are characterized to a first approximation by the carbon-chain length range of their *n*-alkanes and by the chlorine content of the product. An average chain length for the hydrocarbon feedstock or an average molecular weight is often stated as well. For example, a chlorinated paraffin referred to as C_{12}, 60% chlorine, would be a product with an average chain length of 12 carbons with approximately 60% chlorine.

A general classification of chlorinated paraffins by carbon-chain length and degree of chlorination is presented in Table 1.

Table 1. Chlorinated paraffin categories[a]

Carbon-chain length	Feedstock	Chlorination by weight (%)		
		40–50	50–60	60–70
C_{10-13}	C_{12}	A1	A2	A3
C_{14-19}	C_{15}	B1	B2	B3
C_{20-30}	C_{24}	C1	C2	C3

[a]From Chlorinated Paraffins Industry Association (1988)

1.1 Synonyms

Chem. Abstr. Services Reg. Nos and Chem Abstr. Services Names:

63449-39-8 Paraffin waxes and hydrocarbon waxes, chloro
85422-92-0 Paraffin oils and hydrocarbon oils, chloro
61788-76-9 Alkanes, chloro
68920-70-7 Alkanes, C_{6-18}, chloro
71011-12-6 Alkanes, C_{12-13}, chloro

84082-38-2	Alkanes, C_{10-21}, chloro
84776-06-7	Alkanes, C_{10-32}, chloro
84776-07-8	Alkanes, C_{16-27}, chloro
85049-26-9	Alkanes, C_{16-35}, 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
85536-22-7	Alkanes, C_{12-14}, chloro
85681-73-8	Alkanes, C_{10-14}, chloro
97659-46-6	Alkanes, C_{10-26}, chloro
97553-43-0	Paraffins (petroleum), normal C > 10, chloro
106232-85-3	Alkanes, C_{18-20}, chloro
106232-86-4	Alkanes, C_{22-40}, chloro
108171-26-2	Alkanes, C_{10-12}, chloro
108171-27-3	Alkanes, C_{22-26}, chloro

Synonyms: Alkanes, chlorinated; alkanes (C_{10-12}), chloro (60%); alkanes (C_{10-13}), chloro (50–70%); alkanes (C_{14-17}), chloro (40–52%); alkanes (C_{18-28}), chloro (20–50%); alkanes (C_{22-26}), chloro (43%); C_{12}, 60% chlorine; C_{23}, 43% chlorine; chlorinated alkanes; chlorinated hydrocarbon waxes; chlorinated paraffin waxes; chlorinated waxes; chloroalkanes; chlorocarbons; chloroparaffin waxes; paraffin, chlorinated; paraffins, chloro; paraffin waxes, chlorinated; paroils, chlorinated; polychlorinated alkanes; polychloro alkanes

1.2 Molecular formula

$$C_xH_{(2x-y+2)}Cl_y$$

1.3 Chemical and physical properties of chlorinated paraffins

Chlorinated paraffins that have been manufactured from pure *n*-paraffins are generally unreactive and stable during storage at normal temperatures.

Depending on their chain length and degree of chlorination, chlorinated paraffins are colourless or yellowish, mobile to highly viscous liquids or waxy to glassy solidified substances.

Chlorinated paraffins are practically insoluble in water, although they can form emulsions and/or suspensions (Schenker, 1979).

Selected chemical and physical properties of some chlorinated paraffin products are summarized in Table 2.

Table 2. Chemical and physical properties of representative chlorinated paraffins[a]

Paraffin feedstock	Average chain length	Chlorine content (%)	Density (25°C, g/ml)	Refractive index	Viscosity (25°C, P)	Pour-point[b] (°C)	Heat stability (% HCl after 4 h at 175°C)
C_{10}–C_{13}	C_{12}	60	1.36	1.516	35	-10	0.10
C_{13}–C_{17}	C_{15}	52	1.25	1.510	16	-10	0.10
C_{17}–C_{30}	C_{24}	39	1.12	1.501	7	-20	0.20
		42	1.17	1.505	30	0	0.20
		48	1.23	1.516	125	10	0.25
		70	1.65	-	Solid	NA	0.15

[a]From Schenker (1979)

[b]Lowest temperature at which a substance flows under specified conditions

–, not reported; NA, not applicable

1.4 Technical products and impurities

Trade names: The following generic trade names are usually accompanied by a suffix indicating a specific product: A 70; A 70 (wax); Adekacizer E; Arubren; Cereclor; Chlorcosane; Chlorez; Chlorofin; Chloroflo; Chlorparaffin; Chlorowax; Cloparin; Cloparol; Clorafin; CW; Derminolfett; Derminolöl; EDC-tar; Electrofine; Enpara; Hordaflam; Hordaflex; Hordalub; Hulz; KhP; Meflex; Monocizer; Paroil; Poliks; Tenekil; Toyoparax; Unichlor

Chlorinated paraffins are marketed in a variety of mixtures comprising a combination of different carbon-chain lengths with varying degrees of chlorination. Products may be classified according to the scheme in Table 1.

The chain lengths of commercial paraffin products are between ten and 38 carbon atoms and chlorine contents between 10 and 72%. The chlorinated paraffins most frequently used are those with chain lengths of C_{10-17} and a chlorine content of 45–55% (40–70%; Schenker, 1979). Very few products contain less than 35% chlorine. At a chlorine content of approximately 72%, all of the carbon atoms are singly chlorinated and further chlorination is very difficult (Strack, 1986). For a given average chlorine content, the distribution of individual chlorinated homologues is distributed around this average value. For example, Zitko (1974) described the distribution of chlorinated paraffins in a commercial chlorinated paraffin product (C_{20}–C_{30}, 26% chlorine) as shown in Table 3.

Analysis of a C_{26} paraffin chlorinated in the laboratory showed that with a chlorine content or more than about 40%, less than 1% of the chloroparaffins contained fewer than three chlorine atoms per molecule (Könnecke & Hahn, 1962).

Isoparaffins (usually less than 1%), aromatic compounds (usually less than 100 ppm) and low levels of metal contamination may be present in technical products (Schenker, 1979).

Table 3. Distribution of chlorinated homologues in a commercial chlorinated paraffin[a]

No. of chlorine atoms per molecule	Vol. %
0	1.1
1	3.7
2	11.0
3	14.2
4	24.1
5	25.2
6	12.2
More than 6	8.2

[a]From Zitko (1974)

Chlorinated paraffins are relatively inert materials, but prolonged exposure to heat and light or the presence of aluminium, zinc or iron can result in dehydrochlorination, resulting in a darkening of the material. Stabilizers are therefore usually added for storage. The most common stabilizers used are epoxidized soya bean oils. Others used in the past include pentaerythritol, organometallic tin compounds, and certain lead and cadmium compounds (Schenker, 1979; see IARC, 1976, 1980).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Chlorinated paraffins have been produced commercially since the 1930s. These mixtures of chlorinated *n*-alkanes are produced by reacting normal paraffin fractions obtained from petroleum distillation with gaseous chlorine exothermically at 80–120°C in the liquid phase (Chlorinated Paraffins Industry Association, 1988). Ultraviolet light is often used to promote chlorination, particularly at higher chlorine levels. The linings of the reactor vessels must be inert (e.g., glass or steel; Strack, 1986) to avoid the formation of metal chlorides, which cause darkening of the product by decomposition. Production of resinous chlorinated paraffins (70% chlorine content) requires the use of a solvent such as carbon tetrachloride during chlorination. Additional procedures include solvent stripping and grinding of the products as necessary (Zitko, 1974; Schenker, 1979).

Approximately 45 000 tonnes of chlorinated paraffins were produced in the USA in 1987 (US International Trade Commission, 1988). In 1985, 95 000 tonnes were produced in western Europe (SRI International, 1986) and more than 300 000 tonnes worldwide (Strack, 1986).

Chlorinated paraffins are produced in Argentina, Australia, Brazil, Bulgaria, Canada, Czechoslovakia, China, the Federal Republic of Germany, France, the German Democratic Republic, India, Italy, Japan, Mexico, Poland, Romania, Spain, South Africa, Taiwan, the UK, the USA and the USSR.

(*b*) *Use*

Data are from the European Chemical Industry Ecology and Toxicology Centre (1989), unless otherwise specified.

Chlorinated paraffins are used as secondary plasticizers for polyvinyl chloride (PVC) in applications such as electrical cables when the inherent low inflammability of PVC would be impaired by primary plasticizers (e.g., dioctyl phthalate). Chlorinated paraffins are used on a large scale as extreme-pressure additives in metal-machining fluids, e.g., in the automobile industry, precision engineering industry and in machinery construction. As additives to paints, coatings and sealants, chlorinated paraffins improve resistance to water and chemicals. Systems of this kind are especially suitable for marine paints, as coatings for industrial flooring, vessels and swimming pools (e.g., rubber and chlorinated rubber coatings), and as road marking paints. The flame-retarding properties of highly chlorinated paraffins are important for their use in plastics, fabrics, paints and coatings. Chlorinated paraffins are also used with decabromodiphenyl oxide and antimony trioxide in polyester fabrics for tents (Priha *et al.*, 1988).

Approximately 50% of the chlorinated paraffins consumed in the USA is used as extreme-pressure lubricant additives in the metal working industry. The remainder is used in plastics, fire-retardant and water-repellent fabric treatments, and in paint, rubber, caulks and sealants. In contrast, 50% of the chlorinated paraffins consumed in western Europe is as secondary plasticizers in PVC and other plastics (Schenker, 1979).

The chlorinated paraffins most frequently used as plasticizers for plastics are those with a medium chain length (C_{14-17}), with chlorine contents between 45 and 52% (40 and 50%; Zitko, 1974). C_{10-13} or $C_{>20}$ paraffins are also used, depending on the PVC or plastics type. C_{10-13} chlorinated paraffins are suitable for water- and chemical-resistant, low-inflammability and abrasion-resistant paints, either as plasticizer or as a constituent of the binder. Special medium-chain length C_{14-17} grades are used for sealants. Chlorinated paraffin grades with good solubility in mineral oils (C_{10-17}) and chlorine contents of 40–60% are preferred for use as extreme-pressure additives to metal machining fluids, pastes, emulsions and lubricants. For flame-retardant applications, chlorinated paraffins with approximately 70% chlorine are used; the chain length depends on the substrate: C_{10-13} for rubber and soft plastics and C_{18-30} for rigid plastics such as polyesters and polystyrene (Zitko, 1974).

(*c*) *Regulatory status and guidelines*

No regulatory standard or guideline has been established for chlorinated paraffins.

2.2 Occurrence

(a) *Natural occurrence*

Chlorinated paraffins are not known to occur as natural products.

(b) *Occupational exposure*

Approximately 1 500 000 workers were potentially exposed to chlorinated paraffins in the USA in 1972–74 (National Institute for Occupational Safety and Health, 1977).

No data on levels of exposure to chlorinated paraffins were available to the Working Group.

(c) *Water and sediment*

Chlorinated paraffins have been identified in marine and fresh water and in sediments in the UK. Concentrations ranged from < 0.5 to 4 μg/l (w/w) in water and from < 0.05 to 10 mg/l in sediments. Near industrialized areas, maximal levels of 6 mg/l (water) and 15 mg/l (sediment) have been detected (Campbell & McConnell, 1980).

(d) *Biological samples*

Short-chain chlorinated paraffins were found at levels of 6–12 mg/kg in mussels from waterways contaminated with chlorinated paraffins close to the point of discharge. In contrast, the values in seals, marine shellfish and fresh- and salt-water fish from unpolluted areas were less than 0.2 mg/kg C_{20-30} and 0.4 mg/kg C_{10-20}. Seabird eggs contained up to 2 mg/kg C_{10-20} and up to 0.1 mg/kg C_{20-30} (detection limit, 0.05 mg/kg). C_{20-30} chlorinated paraffins were detected in only a few samples of human food, whereas 70% of the samples contained up to 0.5 mg/kg C_{10-20}, with up to 0.3 mg/kg in milk products, 0.15 mg/kg in vegetable oils and 0.025 mg/kg in fruit and vegetables. Liver samples from sheep that had been pastured near a chlorinated paraffin factory contained up to 0.2 mg/kg. Chlorinated paraffins were also found in human tissues *post mortem*: C_{10-20} compounds were often found in liver, adipose tissues and kidneys, whereas long-chain chlorinated paraffins were found in only a few samples. The maximal value was 1.5 mg/kg in a liver sample; most values were below 0.09 mg/kg (Campbell & McConnell, 1980).

2.3 Analysis

Selected methods for the analysis of chlorinated paraffins in various matrices are presented in Table 4.

Table 4. Analytical methods for the determination of chlorinated paraffins in various matrices

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Adipose tissue	Homogenize in dichloromethane; percolate through anhydrous Na_2SO_4; remove solvent; dissolve residue in pentane; wash, dry and concentrate; purify by alumina chromatography	GC/MS	5 ng	Schmid & Müller (1985)
Sediment	Extract with acetone:hexane (1:1, v:v); wash, dry and concentrate; purify by alumina chromatography	GC/MS	5 ng	Schmid & Müller (1985)
Sewage sludge	Homogenize with acetone; extract with pentane; wash, dry and concentrate; purify by alumina chromatography	GC/MS	5 ng	Schmid & Müller (1985)
Environmental and biota samples	Clean up by irradiating extracts with high-intensity UV light (90 min, $<20°C$) in aliphatic hydrocarbons	GC/CD	NR	Friedman & Lombardo (1975)
	Introduce extract directly into mass spectrometer	NICIMS	NR	Gjos & Gustavsen (1982)
Air	Adsorb on charcoal; desorb with carbon disulfide	GC/FID	0.01 mg/sample	Eller (1985)

[a]Abbreviations: GC/MS, gas chromatography/mass spectrometry; GC/CD, gas chromatography/coulometric detection; NICIMS, negative-ion chemical ionization mass spectrometry; NR, not reported; GC/FID, gas chromatography/flame ionization detection

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

(i) *Chlorinated paraffin; average carbon-chain length, C_{12}; average degree of chlorination, 60%*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, eight to nine weeks of age, were treated by gavage with 0, 125 or 250 mg/kg bw of a commercial-grade chlorinated paraffin product dissolved in corn oil on five days a week for 103 weeks. All survivors were killed at 112–114 weeks of age. Body weights of treated females were about 10% lower than those of controls during the second year. Survival of treated males was not significantly different from that of controls, but fewer high-dose females were still alive after week 100 as compared to controls. The incidences of tumours at various sites that are significantly greater than those in controls are shown in Table 5. The incidences of hepatocellular adenomas and of hepatocellular adenomas and carcinomas combined were significantly increased in treated mice. The incidence of alveolar/bronchiolar carcinomas was significantly increased in males, and the combined incidence of follicular-cell adenomas and carcinomas of the thyroid in females was significantly elevated. The incidences of adenomas of the Harderian gland in females were 1/50 controls, 6/50 in low-dose animals and 2/50 in high-dose animals; the trend with dose is not significant (National Toxicology Program, 1986a; Bucher *et al.*, 1987).

Table 5. Incidences of tumours in mice administered C_{12}, 60% chlorine chlorinated paraffin

Dose (mg/kg bw)	Hepatocellular adenomas	Hepatocellular adenomas and carcinomas	Alveolar/bronchiolar carcinomas	Follicular-cell tumours of the thyroid
Males				
Control	11/50	20/50	0/50	
125	20/50	34/50	3/50	
250	29/50	38/50	6/50	
	$p < 0.001$[a]	$p < 0.001$[a]	$p < 0.011$[a]	
Females				
Control	0/50	3/50		8/50
125	18/50	22/50		12/49
250	22/50	28/50		13/49
	$p < 0.001$[a]	$p < 0.001$[a]		$p < 0.024$[a]

[a]Incidental tumour test for trend

Rat: Groups of 50 male and 50 female Fischer 344/N rats, six to seven weeks of age, were treated by gavage with 0, 312 or 625 mg/kg bw of a commercial-grade chlorinated paraffin product dissolved in corn oil on five days a week for 104 weeks. All survivors were killed at 111–113 weeks of age. Body weights of high-dose males were 10–23% lower than those of controls after week 37, and survival of treated males was shorter than that of controls after about week 90; survival of low-dose females was shorter than that of controls after week 92. The incidences of tumours that are significantly greater than those in controls are shown in Table 6. The incidences of hepatic neoplastic nodules [adenomas; Maronpot *et al.*, 1986] and of hepatic neoplastic nodules and hepatocellular carcinomas combined was significantly increased in treated animals. Hepatocellular carcinomas occurred in 0/50 control males and in 3/50 at the low dose and 2/48 at the high dose. The combined incidences of renal tubular-cell adenomas and adenocarcinomas in males were 0/50 controls and 9/50 low-dose and 3/49 high-dose animals; two of the tumours in the low-dose group were carcinomas. The

Table 6. Incidences of tumours in rats administered C_{12}, 60% chlorine chlorinated paraffin

Dose (mg/kg bw)	Hepatocellular carcinomas	Hepatocellular adenomas and carcinomas	Follicular-cell adenomas and carcinomas of the thyroid	Mononuclear cell leukaemia
Males				
Control	0/50	0/50		7/50
312	10/50	13/50		12/50
625	16/48	16/48		14/50
	$p < 0.001$[a]	$p < 0.001$[a]		$p = 0.001$[b]
Females				
Control	0/50	0/50	0/50	
312	4/50	5/50	6/50	
625	7/50	7/50	6/50	
	$p = 0.005$[a]	$p = 0.008$[a]	$p = 0.02$[a]	

[a]Incidental tumour test for trend
[b]Life table test

combined incidence of follicular-cell adenomas and carcinomas of the thyroid was significantly increased in treated females; three in the high-dose group were carcinomas. The incidence of mononuclear-cell leukaemia was significantly increased in treated males; in females, mononuclear-cell leukaemia was observed in 11/50 controls and 22/50 low-dose and 16/50 high-dose animals. The combined incidences of acinar-cell adenomas and adenocarcinomas of the pancreas in males were 11/50 controls and 22/50 low-dose and 17/49 high-dose animals; two of the pancreatic tumours in the high-dose group were carcinomas (National Toxicology Program, 1986a; Bucher *et al.*, 1987).

(ii) *Chlorinated paraffin; average carbon length, C_{23}; average degree of chlorination, 43%*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, eight to nine weeks of age, were treated by gavage with 0, 2500 or 5000 mg/kg bw of a commercial-grade chlorinated paraffin product dissolved in corn oil on five days a week for 103 weeks. All survivors were killed at 113–114 weeks of age. Low-dose males and females had lower weight gains than controls or high-dose animals. Survival in treated and control groups was similar for animals of each sex, but median survival was shorter in females (90–95 weeks) than in males (more than 105 weeks). The authors commented that the lower survival in females may have decreased the potential of the study to detect a carcinogenic effect. The incidence of malignant lymphomas was significantly increased in males: they occurred in 6/50 controls and in 12/50 low-dose and 16/50 high-dose animals ($p = 0.009$, life-table test for trend; $p = 0.011$, incidental tumour test for trend). The combined incidences of hepatocellular adenomas and carcinomas in females were 4/50 controls, 3/49 low-dose and 10/50 high-dose animals (trend not significant; National Toxicology Program, 1986b; Bucher *et al.*, 1987).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, six to seven weeks of age, were treated by gavage with 0, 1875 or 3750 mg/kg bw (males) and 0, 100, 300 or 900 (females) mg/kg bw of a commercial-grade chlorinated paraffin product dissolved in corn oil on five days a week for 103 weeks. All survivors were killed at 111–112 weeks of age. No significant difference in body weight gain or survival was observed between treated and control animals. The incidence of phaeochromocytomas of the adrenal medulla was significantly increased in females: control, 1/50; low-dose, 4/50; mid-dose, 6/50; high-dose, 7/50 ($p = 0.046$, incidental tumour test for trend; National Toxicology Program, 1986b; Bucher *et al.*, 1987).

3.2 Other relevant data

(a) Experimental systems

The Working Group noted the lack of systematic investigation of the influence of carbon-chain length and degree of chlorination in the reported studies on toxicokinetics and toxic effects.

(i) *Absorption, distribution, excretion and metabolism*

The Working Group noted that in these studies labelled material was isolated from tissues or excreta but was not characterized, and the kinetics of parent compounds and metabolites were not studied; thus, the metabolic pathways involved in the degradation of chlorinated paraffins remain largely unknown.

Percutaneous absorption of two ^{14}C-labelled paraffins (C_{18}, 50–53% chlorine; C_{28}, 47% chlorine) was evaluated in Sprague-Dawley rats; absorption of the C_{18} paraffin over four days was 0.7% of the applied radioactivity in males and less than 0.7% in females and that of the C_{28} paraffin was less than 0.1% (Yang *et al.*, 1987).

Studies in which the disposition of radiolabel was determined following intravenous or oral administration to C57Bl mice of three ^{14}C-labelled chlorododecanes of different chlorine content (17.5%, 55.9% and 68.5%) demonstrated marked uptake of label on all three paraffins in liver, fat, salivary glands, bone marrow and thymus. The concentration of radioactivity in the tissues and the amount of exhaled ^{14}C-CO_2 were inversely related to the degree of chlorination of the paraffins (Darnerud *et al.*, 1982).

In C57Bl mice, a ^{14}C-C_{16}, 34% chlorine paraffin in a fat emulsion was readily absorbed after oral administration and the label was distributed to tissues that exhibit high metabolic activity, e.g., intestinal mucosa, bone marrow and exocrine glands. Exhaled CO_2 contained 33% of the ^{14}C-label within 12 h of administration, compared with 44% of the label when the material was given by intravenous administration (Darnerud & Brandt, 1982).

By following the disappearance of radioactivity after feeding a ^{36}Cl-labelled C_{14-17}, 52% chlorine paraffin to Wistar rats for ten weeks, the half-life for its elimination was estimated to be less than one week from the liver and approximately eight weeks from fat (Birtley *et al.*, 1980).

Injection of a ^{14}C-C_{16}, 65% chlorine paraffin into the portal vein of Sprague-Dawley rats *via* cannulated bile ducts resulted in excretion of conjugates of the paraffin with *N*-acetylcysteine and glutathione into the bile. The parent compound constituted less than 3% of the total label excreted (Åhlman *et al.*, 1986).

In studies in C57Bl mice with a ^{14}C-labelled C_{12}, 68.5% chlorine paraffin, exhaled ^{14}C-CO_2 was quantified following administration of inducers and inhibitors of cytochrome P450. Pretreatment with the inhibitors piperonyl butoxide and metyrapone inhibited CO_2 production by 84 and 60%, respectively. Induction with phenobarbital stimulated the peak exhalation rate to 152% of that in controls. Studies with differently chlorinated dodecanes (17.4, 55.9 and 68.5% chlorine) suggested a more prominent role for cytochrome P450 in the metabolism of more heavily chlorinated paraffins (Darnerud, 1984). These studies suggest that cytochrome P450 catalyses a de-chlorination reaction which is followed by β-oxidation and incorporation of the carbon chain into cellular metabolism.

(ii) *Toxic effects*

The toxicity of chlorinated paraffins in fish and birds has been studied extensively (Howard *et al.*, 1975; Lombardo *et al.*, 1975; Svanberg *et al.*, 1978; Madeley & Birtley, 1980). The acute toxicity of chlorinated paraffins is low; in rats the oral LD_{50} value for a C_{12}, 59% chlorine paraffin was reported to be greater than 21.5 ml/kg bw, and no death resulted from oral dosing of rats with 10 ml/kg bw of a C_{24}, 40% chlorine paraffin or with 50 g/kg bw of a C_{24}, 70% chlorine paraffin (Howard *et al.*, 1975).

It has been reported that in 14-day and 90-day feed and gavage studies in Fischer 344 rats with a C_{10-13}, 58% chlorine paraffin, livers were enlarged and showed hepatocellular hypertrophy at doses of 100 mg/kg bw per day and above; in 90-day studies, chronic nephropathy and thyroid hyperplasia [unspecified] were also observed with doses of 100 mg/kg bw per day and above (Serrone *et al.*, 1987).

In 16-day studies with a C_{12}, 60% chlorine paraffin, deaths and reduced body weight gains occurred in male and female rats at doses of 7500 mg/kg bw per day, and all mice receiving doses of 3750 mg/kg bw per day or above died. Livers were enlarged in all groups of treated rats (low dose, 469 mg/kg bw per day) and mice (low dose, 938 mg/kg bw per day). In 90-day gavage studies, no death was considered to be related to treatment (highest doses, 5000 mg/kg bw per day for rats and 2000 mg/kg bw per day for mice). Liver weights were increased in treated rats and mice, and hypertrophy of hepatocytes was evident microscopically; focal hepatic necrosis was observed in mice. Nephrosis was more severe in high-dose rats than in controls. In two-year studies in rats (see also section 3.1), non-neoplastic lesions, including minimal necrosis, hypertrophy and angiectasis of the liver, were associated with treatment. Severe chronic renal disease with secondary parathyroid hyperplasia and subsequent fibrous osteodystrophy and inflammation and hyperkeratosis of the forestomach were seen in male rats. Nephropathy was also increased in incidence in female rats. In similar studies in mice, the incidence of nephrosis was slightly increased in females (National Toxicology Program, 1986a; Bucher *et al.*, 1987).

Liver enlargement was reported in 14- and 90-day dietary studies (at up to 15 000 and 625 ppm, respectively), and chronic nephropathy and thyroid hyperplasia [unspecified] were observed in 90-day dietary studies in Fischer 344 rats administered a C_{14-17}, 52% chlorine paraffin (Serrone *et al.*, 1987).

In 90-day studies in which Wistar rats were fed diets containing up to 5000 ppm of a C_{14-17}, 52% chlorine paraffin, no effect on survival, clinical signs, haematological measurements or efficiency of food utilization was noted; however, liver and kidney weights were elevated, and microscopic examination of the liver showed proliferation of smooth endoplasmic reticulum. Similar results were observed in male beagle dogs fed diets providing up to 100 mg/kg bw per day of the same paraffin for up to 90 days, but no effect was seen in females (Birtley *et al.*, 1980).

In 14- and 90-day gavage studies in Fischer 344 rats with a longer-chain paraffin (C_{20-30}, 43% chlorine), no compound-related effect was reported in the 14-day study, but females in the 90-day study showed an increase in liver weight and lesions described as multifocal granulomatous hepatitis at doses of 100 mg/kg bw per day and above. Males showed increased nephrosis and females increased kidney mineralization at 3750 mg/kg bw per day (Serrone *et al.*, 1987)

A C_{23}, 43% chlorine paraffin was evaluated in 16-day, 90-day and two-year studies by oral gavage in corn oil in Fischer 344 rats and B6C3F$_1$ mice of each sex. No significant toxicity was observed in the 16-day or 90-day studies at doses of up to 3750 mg/kg bw per day in rats and 7500 mg/kg bw per day in mice, with the exception of granulomatous inflammation of the livers in female rats in the 90-day study. In the two-year studies (see also section 3.1), non-neoplastic lesions in rats of each sex included lymphocytic infiltration and granulomatous inflammation of the liver and mesenteric and pancreatic lymph nodes, with associated lymphoid hyperplasia and splenic congestion. Increased kidney-tubule pigmentation and nephropathy occurred in female rats. No significant non-neoplastic lesion was seen in mice treated with up to 5000 mg/kg bw per day (National Toxicology Program, 1986b; Bucher *et al.*, 1987).

Feeding of Fischer 344 rats with a C_{22-26}, 70% chlorine paraffin was reported to induce no toxicity in 14-day studies but slight increases in serum enzyme levels, liver weight, hepatocellular hypertrophy and cytoplasmic fat vacuolization at 3750 mg/kg bw per day in the 90-day studies (Serrone *et al.*, 1987).

The effects of chlorinated paraffins of varying chain lengths (C_{10-13}, 49% chlorine, 59% chlorine, 71% chlorine; C_{14-17}, 50% chlorine; C_{18-26}, 49% chlorine) on proliferation of hepatocyte smooth endoplasmic reticulum and induction of various forms of cytochrome P450 have been examined in rats by intraperitoneal injection. Cytochrome P450 induction and proliferation of smooth endoplasmic reticulum were stimulated to a greater extent by shorter-chain than by longer-chain paraffins (Nilsen & Toftgård, 1981; Nilsen *et al.*, 1981). An increase in the occurrence of lipid droplets followed by proliferation of peroxisomes and mitochondria was observed in the livers of the rats given the C_{10-13}, 49% chlorine and C_{18-26}, 49% chlorine paraffins (Nilsen *et al.*, 1980). Administration of a highly chlorinated mixture of paraffins (C_{10-23}, 70% chlorine) to C57Bl/6 mice resulted in an increase in the level of hepatic cytosolic epoxide hydrolase (Meijer & DePierre, 1987).

As reported in an abstract, administration by gavage for 14 days of 2 g/kg bw per day to male rats and of 1 g/kg bw per day to female rats and male and female mice of C_{12}, 60% chlorine, C_{10-12}, 56% chlorine or C_{14-17}, 40% chlorine caused increases in liver weight and proliferation of hepatocellular smooth endoplasmic reticulum and peroxisomes. A C_{23}, 40% chlorine compound did not induce similar effects on peroxisome proliferation (Elcombe *et al.*, 1990).

(iii) *Effects on reproduction and prenatal toxicity*

In a series of studies on chlorinated paraffins (C_{10-13}, 58% chlorine; C_{14-17}, 52% chlorine; C_{20-30}, 43% chlorine; and C_{22-26}, 70% chlorine), pregnant Charles River rats and pregnant rabbits were treated by gavage on gestation days 6–19 and 6–27, respectively. No teratogenic effect was reported (Serrone *et al.*, 1987). [The Working Group noted that the data given did not allow an evaluation of the study for reproductive effects.]

(iv) *Genetic and related effects* (see Appendix 1)

Chlorinated paraffins C_{10-13}, 50% chlorine (Birtley *et al.*, 1980); C_{12}, 60% chlorine (National Toxicology Program, 1986a); C_{14-17}, 52% chlorine (Birtley *et al.*, 1980); C_{20-30}, 42% chlorine (Birtley *et al.*, 1980); C_{23}, 43% chlorine (National Toxicology Program, 1986b); and C_{10-23}, 70% chlorine (Meijer *et al.*, 1981) were not mutagenic to several strains of *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system from Aroclor 1254-induced rat liver (Birtley *et al.*, 1980; Meijer *et al.*, 1981; National Toxicology Program, 1986a,b) or Syrian hamster liver (National Toxicology Program, 1986a,b).

Chlorinated paraffins (C_{14-17}, 52% chlorine; C_{20-30}, 43% chlorine; C_{22-26}, 70% chlorine; C_{10-13}, 58% chlorine) were reported not to cause chromosomal aberrations in rat bone marrow when given by gavage at toxic doses of up to 5 g/kg bw per day for five days. A C_{10-13}, 58% chlorine chlorinated paraffin at up to 2 g/kg bw per day did not cause dominant lethal mutations in rats (Serrone *et al.*, 1987). [The Working Group noted that the data reported did not allow an evaluation of the study with regard to genetic and related effects.]

(*b*) *Humans*

No data relevant to an evaluation of carcinogenicity were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Chlorinated paraffins are mixtures of polychlorinated *n*-alkanes produced by the reaction of chlorine with specific normal paraffin fractions from petroleum distillation. Carbon-chain lengths of commercial products are generally between C_{10} and C_{30}, and the chlorine content is typically between 40 and 70%. Chlorinated paraffins are used as plasticizers for polyvinyl chloride, as extreme-pressure additives in metal-machining fluids, as additives to paints, coatings and sealants to improve their resistance to chemicals and to water, and as flame retardants for plastics, fabrics, paints and coatings. No data on occupational exposure levels were available. Chlorinated paraffins have been detected in water and sediments, in tissues of marine animals, in human foods and in human tissues *post mortem*.

4.2 Experimental carcinogenicity data

A commercial chlorinated paraffin product of average carbon-chain length C_{12} and average degree of chlorination 60% was tested for carcinogenicity by oral administration in one strain of mice and in one strain of rats. In mice, it increased the incidence of hepatocellular tumours in animals of each sex and of alveolar/bronchiolar carcinomas in males and of follicular-cell tumours of the thyroid gland in females. In rats, it increased the incidences of hepatocellular tumours in animals of each sex, of follicular-cell tumours of the thyroid in females and of mononuclear-cell leukaemia in males.

A commercial chlorinated paraffin product of average carbon-chain length C_{23} and average degree of chlorination 43% was tested for carcinogenicity by oral administration in one strain of mice and in one strain of rats. It increased the incidence of malignant lymphomas in male mice. In rats, it induced phaeochromocytomas of the adrenal medulla in females.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

Administration of some chlorinated paraffins to rodents resulted in nephrotoxicity and proliferation of smooth endoplasmic reticulum and peroxisomes in hepatocytes.

None of six chlorinated paraffins tested was mutagenic to bacteria either in the presence or absence of an exogenous metabolic system

4.5 Evaluation[1]

There is *sufficient evidence* for the carcinogenicity of a commercial chlorinated paraffin product of average carbon-chain length C_{12} and average degree of chlorination 60% in experimental animals.

[1]For description of the italicized terms and criteria for making the evaluation, see Preamble, pp. 25–29.

Summary table of genetic and related effects of chlorinated paraffins

Nonmammalian systems													**Mammalian systems**																											
Prokaryotes		Lower eukaryotes				Plants			Insects				*In vitro*																*In vivo*											
													Animal cells								Human cells								Animals							Humans				
D	G	D	R	G	A	D	G	C	R	G	C	A	D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
	-																																							

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the table, the following symbol indicates the consensus of the Working Group with regard to the results for each endpoint:

- considered to be negative

There is *limited evidence* for the carcinogenicity of a commercial chlorinated paraffin product of average carbon-chain length C_{23} and average degree of chlorination 43% in experimental animals.

No data were available from studies in humans on the carcinogenicity of chlorinated paraffins.

Overall evaluation

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

5. References

Åhlman, M., Bergman, Å., Darnerud, P.O., Egestad, B. & Sjövall, J. (1986) Chlorinated paraffins: formation of sulphur-containing metabolites of polychlorohexadecane in rats. *Xenobiotica, 16,* 225–232

Birtley, R.D.N., Conning, D.M., Daniel, J.W., Ferguson, D.M., Longstaff, E. & Swan, A.A.B. (1980) The toxicological effects of chlorinated paraffins in mammals. *Toxicol. appl. Pharmacol., 54,* 514–525

Bucher, J.R., Alison, R.H., Montgomery, C.A., Huff, J., Haseman, J.K., Farnell, D., Thompson, R. & Prejean, J.D. (1987) Comparative toxicity and carcinogenicity of two chlorinated paraffins in F344/N rats and $B6C3F_1$ mice. *Fundam. appl. Toxicol., 9,* 454–468

Campbell, I. & McConnell, G. (1980) Chlorinated paraffins and the environment. 1. Environmental occurrence. *Environ. Sci. Technol., 14,* 1209–1214

Chlorinated Paraffins Industry Association (1988) *Chlorinated Paraffins: Status Report,* Washington DC

Darnerud, P.O. (1984) Chlorinated paraffins: effects of some microsomal enzyme inducers and inhibitors on the degradation of 1–^{14}C–chlorododecanes to $^{14}CO_2$ in mice. *Acta pharmacol. toxicol., 55,* 110–115

Darnerud, P.O. & Brandt, I. (1982) Studies on the distribution and metabolism of a ^{14}C-labelled chlorinated alkane in mice. *Environ. Pollution (Ser. A), 27,* 45–56

Darnerud, P.O., Biessmann, A. & Brandt, I. (1982) Metabolic fate of chlorinated paraffins: degree of chlorination of [1–^{14}C]chlorododecanes in relation to degradation and excretion in mice. *Arch. Toxicol., 50,* 217–226

Elcombe, C.R., Watson, S.C., Soames, A.R. & Foster, J.R. (1990) Hepatic effects of chlorinated paraffins. *Arch. Toxicol.* (in press)

Eller, P.M. (1985) *NIOSH Manual of Analytical Methods,* 3rd ed. (*DHHS (NIOSH) Publ. No. 84–1000*), Washington DC, US Government Printing Office, pp. 5013-1–5013-5

European Chemical Industry Ecology and Toxicology Centre (1989) *Chlorinated Paraffins,* Brussels

Friedman, D. & Lombardo, P. (1975) Photochemical technique for the elimination of chlorinated aromatic interferences in the gas-liquid chromatographic analysis for chlorinated paraffins. *J. Assoc. off. anal. Chem., 58,* 703–706

Gjos, N. & Gustavsen, K.O. (1982) Determination of chlorinated paraffins by negative ion chemical ionization mass spectrometry. *Anal. Chem., 54,* 1316–1318

Howard, P.H., Santodonato, J. & Saxena, J. (1975) *Investigation of Selected Potential Environmental Contaminants: Chlorinated Paraffins (EPA-560/2-75-007*; PB248 634), Washington DC, US Environmental Protection Agency

IARC (1976) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 11, *Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics*, Lyon, pp. 39–74

IARC (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 23, *Some Metals and Metallic Compounds*, Lyon, pp. 325–415

Könnecke, H.-G. & Hahn, P. (1962) Chromatographic separation of chloroalkanes obtained by chlorination of hexakontane (Ger.). *J. prakt. Chem.*, *16*, 37–41

Lombardo, P., Dennison, J.L. & Johnson, W.W. (1975) Bioaccumulation of chlorinated paraffin residues in fish fed Chlorowax 500C. *J. Assoc. off. anal. Chem.*, *58*, 707–710

Madeley, J.R. & Birtley, R.D.N. (1980) Chlorinated paraffins and the environment. 2. Aquatic and avian toxicology. *Environ. Sci. Technol.*, *14*, 1215–1221

Maronpot, R.R., Montgomery, C.A., Jr, Boorman, G.A. & McConnell, E.E. (1986) National Toxicology Program nomenclature for hepatoproliferative lesions of rats. *Toxicol. Pathol.*, *14*, 263–273

Meijer, J. & DePierre, J.W. (1987) Hepatic levels of cytosolic, microsomal and 'mitochondrial' epoxide hydrolases and other drug-metabolizing enzymes after treatment of mice with various xenobiotics and endogenous compounds. *Chem.-biol. Interactions*, *62*, 249–269

Meijer, J., Rundgren, M., Åström, A., DePierre, J.W., Sundvall, A. & Rannug, U. (1981) Effects of chlorinated paraffins on some drug-metabolizing enzymes in rat liver and in the Ames test. *Adv. exp. Med. Biol.*, *136*, 821–828

National Institute for Occupational Safety and Health (1977) *National Occupational Hazard Survey (NOHS)*, Cincinnati, OH

National Toxicology Program (1986a) *Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C_{12}, 60% Chlorine) (CAS No. 63449-39-8) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies) (Tech. Rep. Ser. No. 308)*, Research Triangle Park, NC

National Toxicology Program (1986b) *Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C_{23}, 43% Chlorine) (CAS No. 63449-39-8) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies) (Tech. Rep. Ser. No. 305)*, Research Triangle Park, NC

Nilsen, O.G. & Toftgård, R. (1981) Effects of polychlorinated terphenyls and paraffins on rat liver microsomal cytochrome P-450 and in vitro metabolic activities. *Arch. Toxicol.*, *47*, 1–11

Nilsen, O.G., Toftgård, R. & Glaumann, H. (1980) Changes in rat liver morphology and metabolic activities after exposure to chlorinated paraffins. *Dev. Toxicol. environ. Sci.*, *8*, 525–528

Nilsen, O.G., Toftgård, R. & Glaumann, H. (1981) Effects of chlorinated paraffins on rat liver microsomal activities and morphology: importance of the length and the degree of chlorination of the carbon chain. *Arch. Toxicol.*, *49*, 1–13

Priha, E., Vuorinen, R., Schimberg, R. & Ahonen, I. (1988) *Tekstiilien Viimeistysaineet* (Textile Finishing Agents) (*Series on Working Conditions No. 65*) (Finn.), Helsinki, Institute of Occupational Health

Schenker, B.A. (1979) Chlorocarbons, -hydrocarbons (paraffins). In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 5, New York, John Wiley & Sons, pp. 786–791

Schmid, P.P. & Müller, M.D. (1985) Trace level detection of chlorinated paraffins in biological and environmental samples, using gas chromatography/mass spectrometry with negative-ion chemical ionization. *J. Assoc. off. anal. Chem.*, *68*, 427–430

Serrone, D.M., Birtley, R.D.N., Weigand, W. & Millischer, R. (1987) Toxicology of chlorinated paraffins. *Food chem. Toxicol.*, *25*, 553–562

SRI International (1986) *Chemical Economics Handbook*, Menlo Park, CA

Strack, H. (1986) Chlorinated paraffins. In: *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A6, 5th ed., Weinheim, VCH Verlagsgesellschaft, pp. 323–330

Svanberg, O., Bengtsson, B.-E. & Lindén, E. (1978) Chlorinated paraffins — a case of accumulation and toxicity to fish. *Ambio*, *7*, 64–65

US International Trade Commission (1988) *Synthetic Organic Chemicals, US Production and Sales, 1987* (*USITC Publ. 2118*), Washington DC, US Government Printing Office, pp. 15-7, 15-29

Yang, J.J., Roy, T.A., Neil, W., Krueger, A.J. & Mackerer, C.R. (1987) Percutaneous and oral absorption of chlorinated paraffins in the rat. *Toxicol. ind. Health*, *3*, 405–412

Zitko, V. (1974) *Chlorinated Paraffins: Properties, Uses and Pollution Potential* (*Environ. Canada, Fish. Mar. Serv. tech. Rep. No. 491*), St Andrews, New Brunswick, Fisheries and Marine Services, pp. 1–38