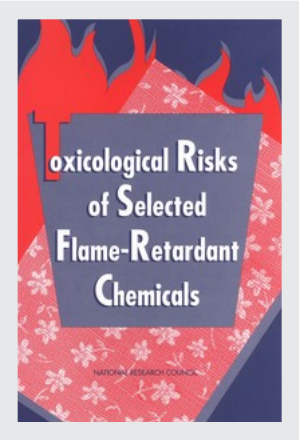

Toxicological Risks of Selected Flame-Retardant Chemicals (2000)

DETAILS

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Chlorinated Paraffins

THIS chapter reviews the physical and chemical properties, toxicokinetics, toxicological, epidemiological, and exposure data on chlorinated paraffins.[1] The subcommittee used that information to characterize the health risk from exposure to chlorinated paraffins. The subcommittee also identified data gaps and recommended research relevant for determining the health risk from exposure to chlorinated paraffins.

PHYSICAL AND CHEMICAL PROPERTIES

The term "chlorinated paraffins" is commonly applied to chlorinated *n*-alkanes manufactured from straight-chain hydrocarbons (*n*-paraffins). Commercial chlorinated paraffins are mixtures that contain chlorinated paraffins of several carbon chain lengths with varying degrees of chlorination. Commercial chlorinated paraffins have carbon chain lengths between 10 and 38 carbon atoms and percent chlorination between 10% and 72%.

Chlorinated paraffins are named according to their average n-paraffin chain length and percent chlorination. For instance, a chlorinated paraffin that has an

[1]Category includes chlorinated α-olefins which do not differ significantly from chlorinated paraffins with regard to structure, physical characteristics, or toxicity (EPA 1994).

average carbon chain length of 24 carbons and is 70% chlorine would be referred to as "C_{24}, 70% chlorine." The name may also include the range of carbon chains used in the manufacture of the mixture (e.g. $C_{10–13}$, 58% chlorine). Chlorinated paraffins with average carbon chain lengths of 10–13 carbons ($C_{10–13}$) are referred to as short-chain chlorinated paraffins. $C_{14–20}$ chlorinated paraffins are categorized as medium-chain paraffins, while $C_{20–30}$ chlorinated paraffins are referred to as long-chain paraffins. If chlorinated paraffins are used as flame retardants in residential furniture, long-chain chlorinated paraffins with 70% chlorination by weight are most likely to be used in a fabric backcoating application (Dr. Gary Stevens, University of Surrey, personal communication).

The physical and chemical properties of chlorinated paraffins vary depending on their carbon chain length and degree of chlorination (see Table 19–1). Chlorinated paraffins are insoluble in water or lower alcohols but can form emulsions or suspensions (EPA 1975). Chlorinated paraffins with low chlorine content (i.e., 35%) are usually mobile liquids. Chlorinated paraffins with higher degrees of chlorination (i.e., 40–60%) are viscous oils, while even higher chlorination of n-paraffins results in a waxy solid with a glassy sheen.

Commercial-grade chlorinated paraffins contain several contaminants. Alkenes (i.e., olefins) are unavoidably formed during dehydrohalogenation of chlorinated paraffins. Isoparaffins comprise about 1% of a chlorinated paraffin mixture; aromatic compounds are present at levels usually less than 100 ppm. Carbon tetrachloride, methylene chloride, chloroform, perchloroethylene, and metals have been detected in trace amounts (0.1–7.4 ppm) in chlorinated paraf

TABLE 19–1 Physical and Chemical Properties of Representative Chlorinated Paraffins (adapted from IARC 1990)

Paraffin feedstock	Average chain length	Chlorine content (%)	Density (25° C, g/mL)	Viscosity (25° C, P)	Pour-point[a] (°C)	Heat stability (% HCl after 4 hr at 175°C)
C_{10}-C_{13} (short-chain)	C_{12}	60	1.36	35	−10	0.10
C_{13}-C_{17} (medium chain)	C_{15}	52	1.25	16	−10	0.10
C_{17}-C_{30} (long-chain)	C_{24}	39	1.12	7	−20	0.20
		42	1.17	30	0	0.20
		48	1.23	125	10	0.25
		70	1.65	Solid	NA	0.15

[a]Lowest temperature at which a substance flows under a specific condition.

fins (EPA 1975). Epoxidized soya bean oils, pentaerythritol, organometallic tin compounds, lead oxide, and cadmium compounds are added as stabilizers to chlorinated paraffins (IARC 1990).

OCCURRENCE AND USE

Approximately 70 million pounds of chlorinated paraffins were produced in the U.S. in 1998 (Chlorinated Paraffins Industry Association 1999). About half of all chlorinated paraffins consumed in the U.S. are used as extreme-pressure lubricant additives in the metal working industry (IARC 1990). Chlorinated paraffins have been used as flame retardants in commercial furniture, particularly in automobile upholstery. Chlorinated paraffins ($C_xH_{(2x-y+2)}Cl_y$) have been proposed as possible candidates for use as flame retardants in residential upholstered furniture in the U.S. (Fire Retardant Chemicals Association 1998). A recent survey of North American chlorinated paraffin industry did not identify textiles as a major area for use of chlorinated paraffins as flame retardants (Chlorinated Paraffins Industry Association 1999). Currently, chlorinated paraffins are not used as flame retardants in residential furniture in the U.S. (Fire Retardant Chemicals Association 1998) but are used as a flame-retardant backcoating for residential furniture upholstery in the United Kingdom.

For flame-retardant applications, chlorinated paraffins with approximately 70% chlorine are used. The carbon chain length of chlorinated paraffins used in flame retardants is dependent on the commercial application. $C_{10–13}$, 70% chlorine, is typically used as a flame retardant (FR) in rubber and soft plastics. $C_{18–30}$, 70% chlorine, is used in rigid plastics such as polyesters and polystyrene (IARC 1990). Long-chain, 70% chlorinated paraffins are used in upholstery backcoating in combination with antimony trioxide.

TOXICOKINETICS

Absorption

Short-chain Chlorinated Paraffins

No absorption data were located for any short-chain chlorinated paraffin following exposure by the dermal, oral, or inhalation routes.

Medium-chain Chlorinated Paraffins

$C_{14–17}$, 52% chlorine, was not absorbed through human skin in vitro at any detectable level after 56 hr of continuous contact (Scott 1989). About 0.70%

(Standard deviation [SD]=0.15%) was recovered in excreta, expired air, and tissues of male Sprague-Dawley rats 96 hr after dermal application of 66 mg/cm^2 (≈2.0 g/kg body weight) of C_{18}, 50–53% chlorine (Yang et al. 1987). About 25% of an oral dose of 500 mg/kg C_{18}, 50% chlorine, was recovered after 24 hr in the excreta and 86% at 96 hr in Sprague-Dawley rats indicating that medium-chain chlorinated paraffin is absorbed to some extent through the rat GI tract.

Long-chain Chlorinated Paraffins

Less than 0.1% of a topically applied dose of C_{28}, 47% chlorine (66 mg/cm^2 or 2.0 g/kg body weight), was recovered after 96 hr in the excreta of Sprague-Dawley rats (Yang et al. 1987).

Distribution and Excretion

Short-chain Chlorinated Paraffins

Serrone et al. (1987)[2] reported that the highest levels of radioactivity in rats were found in the liver, kidney, adipose tissue, and the ovary following oral administration of $C_{10–13}$, 58% chlorine. Most of the dose was excreted in the feces.

Radiolabeled C_{12}, 17.4%, 55.9%, and 68.5% chlorination, were found to distribute to the liver, body fat, intestinal mucosa, bone marrow, salivary glands, and thymus within 24 hr of intravenous injection or oral gavage in C57Bl mice (Darnerud et al. 1982). Radioactivity continued to be detected in the liver, fat, adrenal cortex, and gonads after 4–12 d of exposure and retention in the liver and body fat increased with degree of chlorination. Intravenous injection of C_{12}, 17.4% and 55.9% chlorine, resulted in the retention of radioactivity in the central nervous system 30–60 d after injection. About 52% of C_{12}, 17.4% chlorination, was converted to CO_2 12 hr after administration and about 32% and 8% of the administered doses of C_{12}, 55.9% chlorination, and C_{12}, 68.5% chlorination, respectively, were converted to CO_2 over the same time period (Darnerud et al. 1982).

[2]Summary of studies conducted by International Research Development Corporation for the Chlorinated Paraffin Manufacturers Toxicology Testing Consortium (Aochem 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).

Medium-chain Chlorinated Paraffins

Birtley et al. (1980) reported that radio-labeled chlorinated paraffin was distributed to the body fat and liver of Wistar rats fed either 0.4 or 40 ppm of $C_{14–17}$, 52% chlorine, in their diet for 10 or 8 wk, respectively. Equilibrium was reached in the liver and body fat within 1 and 7 wk, respectively. No radioactivity was detected in the brain or adrenal glands. Radioactivity decreased to below background levels in the livers of the 0.4-ppm dose group within 3 wk after discontinuation of exposure. The half-life for radioactivity in the abdominal fat was estimated to be 8 wk. No attempts were made to chemically characterize the radioactivity in any tissue.

^{14}C-C_{16}, 34% chlorination, was readily absorbed and distributed to the intestinal mucosa, bone marrow, and exocrine glands when fed to C57B1 mice (Darnerud and Brandt 1982). When ^{14}C-C_{16}, 34% chlorination was given by intravenous administration, 33% of the dose was exhaled as CO_2 within 12 hr and 44% thereafter after administration.

Radiolabeled C_{16}, 69% chlorine (1.6 μmol/kg), was distributed to the bile, liver, kidney, and intestinal contents in C57B1 mice and quail within 24 hr after oral administration (Biessmann et al. 1983). Radioactivity was retained in the fat for >12 d and >30 d for quail and mice, respectively. In mice, radioactivity accumulated in the corpora lutea 1–4 d after exposure. In both species, 66 and 43 percent of radioactivity was eliminated in the feces following intravenous and oral administration, respectively, within 96 hr of administration. About 1% of an administered dose of C_{16}, 69% chlorination, was converted to CO_2 by C57B1 mice within 8 hr after gavage or intravenous injection. Urinary excretion was 3% in both cases. In quail, a combined 58% of the administered dose was eliminated in the urine and feces.

Radioactivity was detected in the liver, kidney, adipose tissue, and ovary in F-344 rats administered radio-labeled $C_{14–17}$, 52% chlorine, by oral gavage (Serrone et al. 1987). Most of the administered dose was excreted in the feces.

Poon et al. (1995) reports that radioactivity accumulated in both the liver and fat of rats fed 5–5,000 ppm (0.3–300.0 mg/kg-d, estimated dose levels) $C_{14–17}$, 52% chlorine, in their food for 90 d. Levels in the liver were approximately 20–60 times higher than in feed while radioactivity levels in fat were equal to those in the diet when measured at d 90 of the study.

Yang et al. (1987) found that about 3.3% of the radioactivity from a single oral dose of medium-chain paraffin (500 mg/kg) was distributed to the liver, intestines, and the fat 96 hr after dosing. About 0.12% of the radioactivity of a topically applied dose of 66 mg/cm^2 (≈2.0 g/kg body weight) of [^{14}C]-labeled C_{18}, 50–53% chlorine, was present in intestines, liver, and fat, of male and female rats 96 hr after exposure.

Long-chain Chlorinated Paraffins

Radioactivity was detected in the liver, ovaries, blood, and adipose tissue in F-344 rats administered $C_{20–30}$, 43% chlorine, or $C_{22–26}$, 70% chlorine, by oral gavage (Serrone et al. 1987). Radioactivity levels were highest in the liver in both males and females. Radioactivity (i.e., the radio-labeled compound) was slowly eliminated from these animals, but no elimination rates or half-lives were determined.

Metabolism

No studies were found that attempted to identify the primary urinary metabolites of chlorinated paraffins formed in rodents or humans following exposure by any route. Ahlman et al. (1986) reported that injection of the radio-labeled short-chain chlorinated paraffin C_{16}, 65% chlorine, into the portal vein of Sprague-Dawley rats resulted in the excretion into the bile of N-acetylcysteine and glutathione conjugates. Less than 3% of the radioactivity that was excreted into the bile represented the unchanged parent compound.

Darnerud (1984) found that pretreatment of C57B1 mice with P450 inhibitors 30 min before administration of [^{14}C]-C_{12}, 69% chlorine, significantly decreased the rate and the amount of degradation of this compound to $^{14}CO_2$. Pretreatment of mice with the P450 inducer phenobarbital significantly increased the rate and the amount of $^{14}CO_2$ formed. Pretreatment with P450 inducers 3-methylcholanthrene or Arochlor 1254 did not increase [^{14}C]-C_{12}, 69% chlorine, degradation to $^{14}CO_2$. Administration of $C_{14–17}$, 52% chlorine, to C57B1 mice for 3 consecutive days enhanced the metabolism of $C_{14–17}$, 52% chlorine, to $^{14}CO_2$. Pretreatment with $C_{10–13}$ did not significantly affect the rate of metabolism of $C_{14–17}$, 52% chlorine. Further studies showed that piperonyl butoxide-induced P450 enzymes may be important in the metabolism of highly chlorinated paraffins.

Enzyme Induction

Induction of enzyme activity in rats following administration of chlorinated paraffin has been reported by a number of authors. Epoxide hydrolase and glutathione transferase activity was induced in male Sprague-Dawley rats injected with $C_{14–17}$, 58% chlorination; $C_{10–23}$, 70% chlorination; or C_{23}, 70% chlorination; but not $C_{22–26}$, 42% chlorination, 1 g/kg-d for 5 d (Meijer et al. 1981). Hepatic uridine diphosphate (UDP)-glucuronosyltransferase and amino

pyrine *N*-demethylase activities were increased in male and female Sprague-Dawley rats fed 5,000 ppm $C_{14–17}$, 52% chlorination, in feed for 13 wk (Poon et al. 1995). However, no significant alterations in arylhydrocarbon hydroxylase and 7-ethoxyresorufin O-deethylation activities were observed in either sex.

Nilsen et al. (1980, 1981) and Nilsen and Toftgard (1981) found that hepatic P450 protein content and liver weights were increased and deethylation activity was inhibited in rats 24 hr after intraperitoneal injection of short-chain chlorinated paraffin (Table 19–2). These effects were not observed for medium- or long-chain chlorinated paraffins.

Microsomal glucuronidation of thyroxin (T_4) was significantly increased in male rats treated with chlorinated paraffins by oral gavage (1 g/kg-d) for 14 d (Wyatt et al. 1993). The observed increase corresponded directly with statistically significant increases in plasma thyroid stimulating hormone (TSH) and enzyme activity characteristic of peroxisome proliferation. Mice receiving similar treatment were comparably more sensitive for these effects than rats. The authors concluded that increased T_4 glucuronidation levels could have caused the thyroid neoplasia observed in rodents exposed to C_{12}, 60% chlorination for 2 years (NTP 1986a).

Elcombe et al., Zeneca Central Toxicology Laboratory (1999, unpublished material) reported that oral administration of $C_{10–13}$, 56%chlorine; $C_{10–13}$, 58% chlorine; or $C_{14–17}$, 40% chlorine, for 14 d at 1 g/kg-d caused the induction of hepatic enzymes in male and female F-344 rats and B6C3F1 mice. Specifically, P450 4A1, 2B1, and 2B2 protein levels were elevated in treated animals. Ethoxycoumain-O-deethylation (ECOD), pentoxyresorufin-O-depentylation (PROD), lauryl acid hydroxylation (LAH), and liver β-oxidation activities were also increased following treatment. Increases in liver weight, hepatocellular hypertrophy, peroxisome proliferation, and proliferation of the smooth endoplasmic reticulum occurred in both rats and mice. In mice, PROD activities were not induced and only P450 4A1 protein levels were increased. No liver effects including enzyme induction were observed in male guinea pigs after oral administration of the aforementioned chlorinated paraffins for 14 consecutive days at 2 g/kg-d. Oral exposure to $C_{20–30}$, 43% chlorine, did not increase hepatic microsomal P450 content or hepatic enzyme activities in mice or rats. The effects of oral administration of $C_{20–30}$, 43% chlorine, was not assessed in male guinea pigs.

S.C.Hasmall et al., Zeneca Central Toxicology Laboratory (1999, unpublished material), provided further evidence that male guinea pigs respond differently to $C_{10–13}$, 58% chlorine, as compared with rats or mice. A statistically significant increase in hepatic *p*-nitrophenol-glucuronosyl transferase activity was observed in male guinea pigs given 1,000 mg/kg daily for 14 d. However,

neither liver β-oxidation nor T_4-glucuronosyl transferase activities were affected as compared with nonexposed controls. Similar results were reported for cultured guinea pig hepatocytes exposed to $C_{10–13}$, 58% chlorine (Williams et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material).

TABLE 19–2 Effect of Carbon Chain Length and Percent Chlorination on Liver Weight, P450 Content, and O-Deethylation of 7-Ethoxyresorufin in Rats Treated with Chlorinated Paraffins by Intraperitoneal Injection

Substance	Liver Weight/Body Weight Ratio	nmol P450/mg Liver Protein	O-Deethylation of 7-Ethoxyresorufin
Short-chain chlorinated paraffins			
$C_{10–13}$, 49% chlorine	0.048±0.002[a]	0.65±0.07	80±6
$C_{10–13}$, 59% chlorine	0.046±0.002[a]	0.73±0.09[a]	39±5[a]
$C_{10–13}$, 71% chlorine	0.042±0.001[a]	0.71±0.05[a]	37±4[a]
Medium-chain chlorinated paraffins			
$C_{14–17}$, 50% chlorine	0.038±0.001[a]	0.62±0.08	84±6
Long-chain chlorinated paraffins			
$C_{18–26}$, 49% chlorine	0.034±0.001	0.65±0.08	86±13
Controls	0.034±0.001	0.55±0.07	80±8

[a]$p<0.05$.
Source: Adapted from Nilsen et al. 1980, 1981.

HAZARD IDENTIFICATION[3]

Chlorinated paraffins are complex mixtures that are expected to differ with respect to their chemical content between "batches" or "runs" and between manufacturers. Chlorinated paraffins may differ in the number of carbons in the chain, chlorine content, and trace contaminants. Therefore, any toxicological risk assessment should be based on toxicological data generated for the specific commercial chlorinated paraffin to be used as an FR in residential furniture. Ideally, separate risk assessments should be conducted for each commercial chlorinated paraffin using toxicological data specific for that particular mixture.

[3]In this section, the subcommittee reviewed toxicity data on chlorinated paraffins, including the toxicity assessment prepared by the U.S. Consumer Product Safety Commission (Hatlelid 1999).

Dermal Exposure

Irritation

Birtley et al. (1980) assessed the dermal irritancy of seven classes of chlorinated paraffins in female Wistar rats (see Table 19–3). Topical application of 0.1 mL of chlorinated paraffin every other day for up to 6 d produced varying degrees of skin irritation in most cases. Chlorinated paraffins containing 10–13 and 14–17 carbons produced mild skin irritation independent of the degree of chlorination. Moderate skin irritation was inconsistently observed for $C_{10–13}$, 70% chlorination. Irritating chlorinated paraffins also produced mild erythema and desquamation responses by the third application. These responses improved with continued application. The authors noted that skin irritation may have been partly caused by chemical stabilizers. All chlorinated paraffins of longer chain length were characterized as nonirritating.

In studies summarized by EPA (1975), Abasov (1970) reported that KhP 470 produced no marked effect when applied to the skin.

Systemic Effects

No subchronic or chronic toxicity studies were identified for chlorinated paraffins following dermal exposure.

Available LD_{50} data for dermal application of chlorinated paraffins are summarized in Table 19–4. The dermal LD_{50} in rabbits for Chlorowax 500C (C_{12}, 59% chlorine) was reported to be greater than 10 g/kg body weight (Diamond Chemical Co. 1975, as cited in EPA 1975).

Birtley et al. (1980) reported no evidence of systemic toxicity in female Wistar rats topically treated with chlorinated paraffins (0.1 mL) every other day for up to 6 d with the chlorinated paraffins described in Table 19–3. However,

TABLE 19–3 Summary of Chlorinated Paraffins Assessed for Dermal Toxicity by Birtley et al. (1980) in Female Wistar Rats

Number of Carbon Atoms in *n*-Paraffin Chain	Extent of Chlorination of *n*-Paraffin (by weight)		
	41–50%	51–60%	61–70%
10–13	X	X	X
14–17		X	
20–30	X	X	X

the report does not specify which chlorinated paraffins were tested for systemic toxicity.

Injection of male Sprague-Dawley rats with short- or medium-chain chlorinated paraffins produced various clinical and hepatic effects, mainly peroxisome proliferation (Nilsen et al. 1980, 1981; Nilsen and Toftgard 1981; Meijer et al. 1981). These studies are summarized in the Metabolism section.

Neurological Effects

Intravenous injection of mice with $C_{10–13}$, 49% chlorination (300 mg/kg) produced a statistically significant decrease in motor capacity as compared with vehicle control mice (Eriksson and Kihlström 1985). Motor capacity was not significantly decreased in mice injected with this chlorinated paraffin at 30, 97.5, 165, or 232.5 mg/kg. Decreases in motor activity apparently did not occur in mice injected with $C_{10–13}$, 70% chlorine, at 30, 97.5, 165, 232.5, or 300 mg/kg. The authors noted that at higher dose levels, both chlorinated paraffins caused an unwarranted cessation of movement (one forepaw in the air during walking). No other studies were found regarding the effects of chlorinated paraffins on the nervous system.

Other Systemic Effects

No studies were identified that investigated the immunological, reproductive, developmental, or carcinogenic effects of chlorinated paraffins following dermal exposure.

Inhalation Exposure

There were no clinical signs of toxicity in rats exposed to Chlorowax 500C at exposure concentration of 3.3 mg/L for one hr (Diamond Shamrock Chemical Company 1975, as reviewed by EPA 1975). No other studies were located that investigated the systemic toxicity of chlorinated paraffins following inhalation exposure.

No studies were identified that investigated the immunological, neurological, reproductive, developmental, or carcinogenic effects of chlorinated paraffins following inhalation exposure.

TABLE 19–4 Acute and Short-term Toxicity Studies of Chlorinated Paraffins

Duration, Route	Effects	NOAEL/LOAEL	Reference
Short-chain chlorinated paraffins			
$C_{10–13}$, 56% Cl_2			
14 d, gavage[a]	Significant increase in relative liver weights. Peroxisome proliferation, hepatocyte hypertrophy. Increase in total microsome P450 content. Increased hepatic P450 4A1, 2B1, and 2B2 protein levels. Induction of ECOD, PROD, LAH, and liver β-oxidation activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
14 d, gavage[a]	Significant increase in relative liver weights, peroxisome proliferation, and hepatocyte hypertrophy. Total P450 microsomal content increased. Increased hepatic P450 4A1 protein levels. Induction of ECOD, LAH, and liver β-oxidation activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
14 d, gavage[a]	Increase in relative liver weight. No changes in liver morphology. No enzyme activity induction (ECOD, PROD, EROD, LAH, β-oxidation).	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
14 d, gavage[a]	Statistically significant decreases in body weight gain, relative liver weight. Increase in p-nitrophenol-glucuronosyl transferase activity at 1,000 mg/kg-d. Neither liver β-oxidation nor T_4-glucuronosyl transferase activities were affected at either dose levels as compared with nonexposed controls.	ND	S.C.Hasmall et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material

15 d, gavage[a]	Relative liver weights, liver β-oxidation activity, and T_4- and p-nitrophenol glucuronidation activity levels increased in males and females. Increases in relative kidney weights in males. T_4 levels decreased in both dose groups, both sexes. Centrilobular hypertrophy.	ND	Wyatt et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
14 d, gavage[a]	Significant increase in absolute liver weight. Peroxisome proliferation. T_4 levels were significantly decreased and TSH levels significantly increased in animals exposed at 1,000 mg/kg-d.	Liver weight LOAEL: 10 mg/kg-d Peroxisome proliferation NOAEL: 500 mg/kg-d; LOAEL: 1,000 mg/kg-d	Wyatt et al. 1993
14 d, gavage[a]	Significant increase in absolute liver weight at 100 mg/kg-d. Peroxisome proliferation. T_4 levels significantly decreased and TSH levels significantly increased in animals exposed at 1,000 mg/kg-d.	Liver weight NOAEL: 50 mg/kg-d; LOAEL: 100 mg/kg-d Peroxisome proliferation NOAEL: 100 mg/kg-d; LOAEL: 250 mg/kg-d	Wyatt et al. 1993
$C_{10–13}$, 58% Cl_2			
14 d, gavage[a]	Significant increase in relative liver weights. Peroxisome proliferation, hepatocyte hypertrophy. Total P450 microsomal content and hepatic P450 4A1, 2B1, and 2B2 protein levels increased. Induction of ECOD, PROD, LAH, and liver β-oxidation activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
14 d, gavage[a]	Significant increase in relative liver weights, peroxisome proliferation and hepatocyte hypertrophy. Total P450 microsomal content and hepatic P450 4A1 protein levels increased. Induction of ECOD, LAH, and β-oxidation activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material

Duration, route	Effects	NOAEL/LOAEL	Reference
14 d, gavage[a]	Slight increase in relative liver weight. No changes in liver morphology. No induction of total P450 microsomal content or ECOD, PROD, EROD, LAH, or liver β-oxidation activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
14 d, gavage[a]	No increase in absolute liver weight starting at 100 mg/kg-d. Peroxisome proliferation. T_4 levels were significantly decreased and TSH levels significantly increased in animals exposed at 1,000 mg/kg-d.	Liver weight NOAEL: 50 mg/kg-d; LOAEL: 100 mg/kg-d Peroxisome proliferation NOAEL: 100 mg/kg-d; LOAEL: 250 mg/kg-d	Wyatt et al. 1993
14 d, gavage[a]	Significant increase in absolute liver weight at≥500 mg/kg-d. Peroxisome proliferation. T_4 levels were significantly decreased and TSH levels significantly increased in animals exposed at 1,000 mg/kg-d.	Liver weight NOAEL: 100 mg/kg-d; LOAEL: 250 mg/kg-d Peroxisome proliferation NOAEL: 100 mg/kg-d; LOAEL: 250 mg/kg-d	Wyatt et al. 1993
14 d, gavage[a]	Animals inactive after dosing. No deaths or toxicty observed.	Toxicity NOAEL: 13,600 mg/kg-d	NTP 1986a
14 d, gavage[a]	Animals inactive after dosing. No deaths or toxicty observed.	Toxicity NOAEL: 27,200 mg/kg-d	NTP 1986a

16 d, gavage[b]	One of five males and two of five females of the 7,500 mg/kg-d group died. High-dose rats had diarrhea, body-weight gains decreased. Livers enlarged in three of five animals of all dose groups except 469-mg/kg-d female rats.	Liver effects LOAEL: 469 mg/kg-d	NTP 1986a
16 d, gavage[b]	Deaths at≥3,750. Final mean body weights of survivors were not different from controls; diarrhea occurred in all dosed mice. Livers were enlarged in dosed mice that survived the study.	Liver effects LOAEL: 938 mg/kg-d	NTP 1986a
14 d, diet	Increased liver weight accompanied by hepatocellular hypertrophy.	Liver effects NOAEL: 30 mg/kg-d; LOAEL: 100 mg/kg-d	IRDC 1983, as reviewed by Serrone et al. 1987 (438–002)[c]
14 d, gavage[a]	Increased liver weight accompanied by hepatocellular hypertrophy.	Liver effects NOAEL: 30 mg/kg-d; LOAEL: 100 mg/kg-d	IRDC 1981, as reviewed by Serrone et al. 1987 (438–006)[c]
Medium-chain chlorinated paraffins			
$C_{14–17}$, 40% Cl_2			
14 d, gavage[a]	Significant increase in relative liver weights. Peroxisome proliferation, hepatocyte hypertrophy. Increased total P450 microsomal content and hepatic P450 4A1, 2B1, and 2B2 protein levels. Induction of ECOD, PROD, LAH, and liver β-oxidation activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
14 d, gavage[a]	Significant increase in relative liver weights, peroxisome proliferation, and hepatocyte hypertrophy. Total P450 microsomal content and P450 4A1 protein levels increased. Induction of ECOD, LAH, and liver β-oxidation activities. No induction PROD or EROD activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material

Duration, route	Effects	NOAEL/LOAEL	Reference
14 d, gavage[a]	No increase in relative liver weight. No changes in liver morphology observed. No induction of total P450 microsomal content or ECOD, PROD, EROD, LAH, or liver β-oxidation activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
15 d, gavage[a]	Relative liver weights, liver β-oxidation activity, and T_4- and p-nitrophenol glucuronidation activity levels increased in all dosed animals. Increases in relative kidney weights in males of both dose groups. T_4 levels were decreased in both dose groups. Centrilobular hypertrophy.	ND	Wyatt et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
14 d, gavage[a]	Significant increase in absolute liver weight, but no consistent dose-response. Peroxisome proliferation. T_4 levels significantly decreased and TSH levels significantly increased in animals exposed at 1,000 mg/kg-d.	Liver weight LOAEL: 10 mg/kg-d Peroxisome proliferation NOAEL: 250 mg/kg-d; LOAEL: 500 mg/kg-d	Wyatt et al. 1993
14 d, gavage[a]	Significant increase in absolute liver weight at 1,000 mg/kg-d. Peroxisome proliferation. T_4 levels significantly decreased and TSH levels significantly increased in animals exposed at 1,000 mg/kg-d.	Liver weight NOAEL: 500 mg/kg-d; LOAEL: 1,000 mg/kg-d Peroxisome proliferation NOAEL: 250 mg/kg-d; LOAEL: 500 mg/kg-d	Wyatt et al. 1993

$C_{14–17}$, 52% Cl_2			
14 d, diet	Increased liver weight accompanied by mild, diffuse hepatocellular hypertrophy..	Liver effects NOAEL: 500 ppm; LOAEL: 1,500 ppm for F, 5,000 ppm for M	IRDC 1981, as reviewed by Serrone et al. 1987 (438–003)[c]
14 d, gavage[a]	No compound-related effects.	Toxicity NOAEL: 30 mg/kg-d	IRDC 1981, as reviewed by Serrone et al. 1987 (438–005)[c]
Long-chain chlorinated paraffins			
C_{23}, 43% Cl_2			
14 d, gavage[d]	No significant increase in relative liver weights or changes in liver morphology. No change in total P450 microsomal content or hepatic P450 4A1, 2B1, and 2B2 protein levels. No increase in ECOD, EROD, PROD, LAH, and liver β-oxidation activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
14 d, gavage[d]	No significant increase in relative liver weights or changes in liver morphology. No change in total P450 microsomal content or hepatic P450 4A1, 2B1, and 2B2 protein levels. No increase in activity levels for ECOD, EROD, PROD, LAH, and liver β-oxidation activities.	ND	Elcombe et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
Gavage	Animals inactive after dosing. No deaths or toxicty observed.	Toxicity NOAEL: 23,400 mg/kg-d	NTP 1986b
16 d, gavage[b]	No deaths occurred and no clinical signs of toxicity were observed in treated animals. Body weights of dosed animals were not different from those of controls.	Toxicity NOAEL: 3,750 mg/kg-d	NTP 1986b

Duration, route	Effects	NOAEL/LOAEL	Reference
16 d, gavage[b]	No deaths occurred and no clinical signs of toxiciry were observed in treated animals. Body weights of dosed animals were not different from those of controls.	Toxicity NOAEL: 7,500 mg/kg-d	NTP 1986b
$C_{22–26}$, 70% Cl_2			
14 d, diet	No compound-related effects were found in the 14-d study in either male or female rats.	Toxicity NOAEL: 15,000 pp	IRDC 1981, as reviewed by Serrone et al. 1987 (438–004)[c]

ECOD, ethoxycoumain-o-deethylase; EROD, ethoxyresorufin-o-deethylase; F, female; LAH, lauryl hydroxylation; M, male; PROD, pentoxyresofu-o-depentylation.

[a]Test compound administered as a single dose on d 1 in corn oil unless noted otherwise.

[b]Animals were exposed at $C_{20–30}$, 43% chlorination.

[c]Study results summarized in Serrone et al. (1987).

[d]Repeat dose studies. Test compounds were administered daily for 16 d. Highest doses for mice were administered as split doses, 5 hr apart, twice a day.

Oral Exposure

Systemic Effects

Gosselin et al. (1976) report that chlorinated paraffins are "practically nontoxic" in humans with a probable oral lethal dose above 15 g/kg, or greater than 2.2 pounds, for a 70-kg person.

Table 19–4 provides a summary of oral acute and short-term toxicity data for chlorinated paraffins. Based on these data, it appears that chlorinated paraffins are not very toxic with gross toxic effects (i.e., death, clinical signs of toxicity) occurring at doses greater than 469 mg/kg-d. Increases in liver weights occur at doses greater than 10–30 mg/kg-d.

Additional oral acute toxicity studies in rats conducted by Birtley et al. (1980) of $C_{10–13}$, $C_{14–17}$, or $C_{20–30}$ containing either 41–50%, 51–60%, or 61–70% chlorine found that only $C_{10–13}$ caused clinical toxicity and at dose levels of 4 g/kg or greater. All animals exhibiting signs of toxicity usually recovered within 7 d of treatment. EPA (1975) reviewed the LD_{50} data for a variety of commercial chlorinated paraffins administered by various routes of administration. No compound-related mortality was reported in these studies. Doses tested ranged from 5 to 60 g/kg. Some of these studies only reported the amounts of chlorinated paraffins used in the tests; these amounts ranged between 0.464 and 21.4 mL/kg chlorinated paraffin.

Table 19–5 provides a summary of the subchronic and chronic toxicity data available for short-, medium-, and long-chain chlorinated paraffins.

Short-chain Chlorinated Paraffins

Subchronic and chronic (90-d, 6-mo, 12-mo, and 2-yr) oral toxicity studies have been carried out for short-chain chlorinated paraffins by the U.S. National Toxicology Program (NTP 1986a). Subchronic studies have been carried out by IRDC (as reviewed by Serrone et al. 1987) and Wyatt et al., Zeneca Central Toxicology Laboratory (1999, unpublished material). Major toxic effects associated with subchronic or chronic oral exposure to short-chain chlorinated paraffins include a statistically significant increase in relative liver weights in rats (NTP 1986a; Serrone et al. 1987; Wyatt et al. 1993), and mice (NTP 1986a). Microscopic examination revealed hepatocyte hypertrophy in rats (NTP 1986a; Serrone et al. 1987; Wyatt et al. 1993) and mice (NTP 1986a). Increased relative liver weights with associated pathological changes occurred at dose levels greater than 10 mg/kg-d in rats and 250 mg/kg-d in mice. Increases in thyroid (NTP 1986a) and kidney weights (NTP 1986a; Serrone et al. 1987;

TABLE 19–5 Subchronic and Chronic Toxicity Studies of Chlorinated Paraffins

Species, Strain, Sex	Dose	Duration, Route	Effects	NOAEL/LOAEL	Reference
Short-chain chlorinated paraffins					
$C_{10–13}$, 58% Cl_2					
Rat, F344, M/F	313, 625, 1,250, 2,500, 5,000 mg/kg-d	90 d, gavage	Gross: No compound-related deaths or clinical signs of toxicity observed. Body weights decreased in males of 2,500 and 5,000 mg/kg-d groups. Organ Weight Changes: Relative liver weights significantly ($p<0.01$) increased in males and females at 313 mg/kg-d or higher dose groups. Microscopic: No treatment-related lesions noted in livers from males or females. Kidney nephrosis in males and females of 5,000 mg/kg-d dose group. Rats in other dose groups were not examined microscopically.	Liver pathology LOAEL: 313 mg/kg-d Body weight: NOAEL: 1,250 mg/kg-d LOAEL: 2,500 mg/kg-d	NTP 1986a[a]
Mouse, B6C3F1, M/F	125, 250, 500, 1,000, 2,000 mg/kg-d	90 d, gavage	Gross: 26 deaths occurred due to gavage-related trauma. No clinical signs of toxicity apparent, but body weights of males in 1,000 and 2,000 mg/kg-d dose groups lower than controls. Organ Weight Changes: Relative liver weights were significantly ($p<0.01$) increased in males and females in 500 mg/kg-d or higher dose groups. Microscopic: Hepatocyte hypertrophy and focal hepatic necrosis in both males and females.	Liver pathology: NOAEL: 250 mg/kg-d LOAEL: 500 mg/kg-d Body weight: NOAEL: 500 mg/kg-d LOAEL: 1,000 mg/kg-d	NTP 1986a[a]
Rat, F344, M/F	0, 312, 625 mg/kg-d	6 mo, gavage	Gross: Male body weights were significantly lower ($p< 0.01$) than controls in both dose groups Organ Weight Changes: Relative liver and kidney weights were significantly ($p<0.01$) increased in male and female rats dosed at levels 312 mg/kg-d or higher. Microscopic: Hepatocyte hypertrophy and renal	Liver/kidney weights: NOAEL: ND LOAEL: 312 mg/kg-d	NTP 1986a[a]

			nephropathy observed with increased frequency in all exposed animals as compared with controls. No chemical-related changes in relative adrenal glands, thymus, heart, brain, or spleen observed.		
Rat, F344, M/F	0, 312, 625 mg/kg-d	12 mo, gavage	Gross: Male body weights were significantly lower ($p< 0.01$) than controls in both dose groups. Organ Weight Changes: Relative liver and kidney weights were significantly ($p<0.01$) increased in male and female rats dosed at levels 312 mg/kg-d or higher. Microscopic: Hepatocyte hvpertrophy and renal nephropathy observed with increased frequency in all exposed animals as compared with controls. No chemical-related changes in relative adrenal glands, thymus, heart, brain, or spleen observed.	Liver/kidney weights: NOAEL: ND LOAEL: 312 mg/kg-d	NTP 1986a[a]
Rat, F344, M/F	0, 312, 625 mg/kg-d	2 yr, gavage	Gross: Survival significantly ($P<0.001$) lower among dosed males beginning at wk 89; survival of low-dose females significantly lower after wk 92. Decreased activity among exposed rats beginning wk 90; some high-dose females had distended or firm abdomens. At 24 mo, pale skin and eyes were observed in both exposed males and females. Exposed males judged to be emaciated with a high incidence of stained and wet fur in the pelvis/perianal area. High-dose males had sunken or small eyes and abnormal breathing. Mean body weights were reduced compared with controls beginning at wk 17 for males and wk 42 for females. Microscopic: Liver necrosis/hypertrophy observed in male and females beginning at 312 mg/kg-d. Nephropathy was more severe in dosed male rats and the incidence was increased in dosed females. Renal tubular cell hyperplasia was increased in high-dose males. Increased incidence of inflammation and hyperkeratosis of the forestomach in males beginning at 312 mg/kg-d.	Liver/kidney effects: NOAEL: ND LOAEL: 312 mg/kg-d	NTP 1986a[a]

Species, Strain, Sex	Dose	Duration, Route	Effects	NOAEL/LOAEL	Reference
Mouse, B6C3F1, M/F	0, 125, 250 mg/kg-d	2 yr, gavage	Gross: Survival significantly reduced among high-dose females after wk 100. Survival comparable to controls for low-dose females and exposed males. Exposed females had decreased body weights (6–12%) compared with controls after wk 36. Microscopic: Incidence of kidney nephrosis was increased among high-dose females. No other significant nonneoplastic pathological changes were reported.	Kidney effects: Females: NOAEL: 125 mg/kg-d LOAEL: 312 mg/kg-d	NTP 1986a[a]
Rat, F344, M/F	0, 312, 625 mg/kg-d	90 d, gavage	Gross: Male rats in the high-dose group had significantly decreased body weights as compared with controls. Statistically significant increases in relative liver and kidney weights in both males and females of both dose groups. Microscopic: Hepatocyte and follicular cell hvpertrophy in males and females in all dose groups. Protein accumulation in kidneys of males in the high-dose group. Small increase in α2u-globulin protein in the proximal convoluted tubules of males in the 625 mg/kg-d dose group, but accumulation was not restricted to hyaline droplets. Biochemical: Free plasma T4 levels were significantly decreased in male and female rats. Increased activity levels of hepatic β-oxidation of fatty acids and glucuronidation of T_4 and p-nitrophenol in both sexes in both dose groups.	Liver/kidney weight: NOAEL: ND LOAEL: 312 mg/kg-d Liver/thyroid pathology: NOAEL: ND LOAEL: 312 mg/kg-d	Wyatt et al., Zeneca Central Toxicology Laboratory, 1999, unpublished material
Rat, F344, M/F	10, 100, 625 mg/kg-d	90 d, diet	Gross: No overt toxicity observed. Body weight gains slightly reduced, changes in water consumption, slight skin atonia at 625 mg/kg-d. Organ Weight Changes (relative): 10: None in males or females	Liver weight: NOAEL: 10 mg/kg-d LOAEL: 100 mg/kg-d Liver pathology: NOAEL: 10 mg/kg-d	IRDC 1984, as reviewed by Serrone et al. 1987 (438-

			100: Increase in liver weight in males and females 625: Increase in liver, kidneys, and thyroid in males and females Microscopic (dose, mg/kg-d): 10: No effects in males or females 100: Hepatocellular hypertrophy of liver in males and females, chronic nephritis of the kidney and hypertrophy and hyperplasia of the thyroid in males 625: Hepatocellular hypertrophy of liver and hypertrophy and hyperplasia of the thyroid in males and females, chronic nephritis of the kidney in males, renal tubule pigmentation of kidneys in females	LOAEL: 100 mg/kg-d	022/035)
Rat, F344, M/F	10, 100, 625 mg/kg-d	90 d, gavage	Gross: No overt toxicity observed. Body weight gains slightly reduced, changes in water consumption, slight skin atonia at 625 mg/kg-d. Organ Weight Changes (dose, mg/kg-d) (relative): 10: None in males or females 100: Increase in liver weight in males and females 625: Increase in liver, kidneys, and thyroid weights in males and females Microscopic: 10: No effects in males or females 100: Hepatocellular hypertrophy of liver in males and females, chronic nephritis of the kidney and hypertrophy and hyperplasia of the thyroid in males 625: Hepatocellular hypertrophy of liver and hypertrophy and hyperplasia of the thyroid in males only, chronic nephritis of the kidney in males, renal tubule pigmentation of kidneys in females	Liver weight: NOAEL: 10 mg/kg-d LOAEL: 100 mg/kg-d Liver pathology: NOAEL: 10 mg/kg-d LOAEL: 100 mg/kg-d	IRDC 1984, as reviewed by Serrone et al. 1987 (438–022/029)

Species, Strain, Sex	Dose	Duration, Route	Effects	NOAEL/LOAEL	Reference
Medium-chain chlorinated paraffins $C_{14–17}$, 52% Cl_2					
Rat, Sprague-Dawley, M/F	0, 5, 50, 500, 5,000 ppm (0.3, 3, 30, 300 mg/kg-d)[b]	90 d, diet	Gross: No gross lesions were noted at necropsy other than enlarged livers in the high-dose animals; one female in the 5,000 ppm group had an enlarged lung with pulmonary congestion. Organ Weight Changes (relative): 30: Increase in liver weight in females, none in males 300: Increase in liver and kidney weights in male and females Microscopic: 3: Changes in thyroid in females 30: Changes in liver and thyroid in males and females; changes in inner medulla tubules of kidney in females 300: Changes in liver and thyroid in males and females; changes in kidney proximal tubules in males; changes in inner medulla tubules of kidney in females Biochemical: 3: Serum cholesterol increased in females 30: Increased urinary ascorbic acid excretion, decreased hepatic vitamin A level in males and females, serum cholesterol increased in females 300: Elevated hepatic UDP-glucuronosyltransferase activity, increased urinary ascorbic acid excretion, decreeased hepatic vitamin A level in males and	Liver weight: NOAEL: 3 mg/kg-d LOAEL: 30 mg/kg-d Liver pathology: NOAEL: 0.3 mg/kg-d LOAEL: 3 mg/kg-d Liver biochemistry: NOAEL: 0.3 mg/kg-d LOAEL: 3 mg/kg-d	Poon et al. 1995

			females; females: increased aminopyrine N-demethylase activity, N-acetylglucosaminidase activity, serum cholesterol		
Dog, beagle, M/F	0, 10, 30, 100 mg/kg-d	90 d, diet	Gross: No deaths or clinical signs of toxicity noted. No effect was seen on weight gain, hematological parameters, or urinalysis results. Organ Weight Changes (relative): Significant increase ($p< 0.05$) in relative liver weight in male dogs in 100 mg/kg-d dose group Microscopic: Cloudy, pale hepatocytes and proliferation of hepatocyte smooth endoplasmic reticulm in dogs dosed with 30 or 100 mg/kg-d Biochemical: Statistically significant ($p<0.05$) increases in serum alkaline phosphatase activity in male dogs in 100 mg/kg-d group.	Liver weight: NOAEL: 30 mg/kg-d LOAEL: 100 mg/kg-d Liver pathology: NOAEL: 10 mg/kg-d LOAEL: 30 mg/kg-d Liver biochemistry: NOAEL: 30 mg/kg-d LOAEL: 100 mg/kg-d	Birtley et al. 1980
Rat, Wistar, M/F	0, 250, 500, 2,500, 5,000 ppm (15, 30, 150, 300 mg/kg-d)[b]	90 d, diet	Gross: Reduced weight gain as a result of reduced food consumption was observed in male rats at wk 1 onward in 2,500 and 5,000 ppm dose groups and wk 4 onward in 500 ppm dose group. No deaths or clinical abnormalities observed in test animals. Authors report that there was a tendency towards congestion of the kidney with increasing dietary concentration Organ Weight Changes (relative): 15: None 30: Increase in liver weight in females 150: Increase in liver weight in males and females 300: Increase in liver and kidney weights in males and females Microscopic: 15: None 30: Liver: proliferation of the smooth endoplasmic reticulm	Liver weight: NOAEL: 15 mg/kg-d LOAEL: 30 mg/kg-d Liver pathology: NOAEL: 15 mg/kg-d LOAEL: 30 mg/kg-d Liver biochemistry: NOAEL: ND LOAEL: 15 mg/kg-d Other effects: Inadequate dose-response information given for kidney congestion and reported biochemical effects. More information is needed to derive a NOAEL or LOAEL for these effects.	Birtley et al. 1980

Species, Strain, Sex	Dose	Duration, Route	Effects	NOAEL/LOAEL	Reference
			150: Liver: proliferation of the smooth endoplasmic reticulm 300: Liver: proliferation of the smooth endoplasmic reticulm Biochemical: Authors report "a marked decline" in alkaline phosphatase activity in all dose groups; serum glutamic pyruvate transaminase activity also tended to decline except for a slight increase observed in males in 5,000 ppm dose group.		
Rat, F344, M/F	10, 100, 625 mg/kg-d	90 d, diet	Organ Weight Changes (relative): 10: Increase in liver weight in males (not considered biologically significant), none in females 100: Increase in liver and kidney weights in males and females 625: Increase in liver and kidney weights in males and females; increase in thyroid and adrenal gland weights in males Microscopic (dose, mg/kg-d): 10: No changes detected in males or females. 100: No changes detected in liver and kidney of male and females 625: Hepatocellular hypertrophy of liver in males and females; thyroid hyperplasia of the thyroid in males only, chronic nephritis of the kidney in males, renal tubule pigmentation of kidneys in females; no changes detected in adrenal glands in male rats	Liver weight NOAEL: 10 mg/kg-d LOAEL: 100 mg/kg-d Liver pathology: NOAEL: 100 mg/kg-d LOAEL: 625 mg/kg-d	IRDC 1981, as reviewed by Serrone et al. 1987 (438–023/026)

$C_{14–17}$, 40% chlorine					
Rat, F344, M/F	0, 312, 625 mg/kg-d	90 d, gavage	Gross: Statistically significant increases in relative liver and kidney weights in males and females of both dose groups. Microscopic: Hepatocyte and follicular cell hypertrophy in males and females in all dose groups. Protein accumulation in kidneys of males in high-dose group. A small, but statistically significant increase in α2u-globulin protein in proximal convoluted tubules was observed in male rats in high-dose group, but this was not restricted to hyaline droplets. Biochemical: Free plasma T3, T_4. and TSH levels were not significantly affected in either sex at either dose level. Increased activity levels of hepatic β-oxidation of fatty acids and glucuronidation of T_4 and *p*-nitrophenol in both sexes in both dose groups.	Liver/kidney weight: NOAEL: ND LOAEL: 312 mg/kg-d Liver/thyroid pathology: NOAEL: ND LOAEL: 312 mg/kg-d	Wyatt et al. 1993; Zeneca Central Toxicology Laboratory, 1999, unpublished material
Long-chain chlorinated paraffins					
$C_{20–30}$, 43% Cl_2					
Rat, F344, M/F	100, 900, 3,750 mg/kg-d	90 d, gavage	Gross: No significant adverse effects on body weight gain, water/food consumption, haematology, or clinical biochemistry measurements. Macroscopic: 100: No increases in absolute liver or kidney weights in males. Increased liver weight in females. 900: No increases in absolute liver or kidney weights in males. Increased liver weight in females. 3,750: No increases in absolute liver or kidney weights in males. Increased liver weight in females. Microscopic: 100: Males; no effects. Multifocal granulomatous hepatitis, inflammation, and necrosis in livers from females. 900: Males; no effects. Multifocal granulomatous hepatitis, inflammation, and necrosis in livers from females.	Liver weight: NOAEL: ND for females; 3,750 for males Liver pathology: NOAEL: ND for females; 3,750 for males	IRDC 1981, as reviewed by Serrone et al. 1987 (438–005)

Species, Strain, Sex	Dose	Duration, Route	Effects	NOAEL/LOAEL	Reference
			3,750: Nephrosis of the kidney in males. Multifocal granulomatous hepatitis, inflammation, and necrosis in livers and mineralization of the kidney in females.		
Rat, F344, M/F	0, 235, 469, 938, 1,875, 3,750 mg/kg-d	90 d, gavage	Gross: No significant decreases in body weight were observed in exposed male or females as compared with controls. No deaths or clinical signs of toxicity were observed in either males or females orally exposed to chlorinated paraffin Microscopic: A dose-related increase in the incidence of granulomatous inflammation of the liver was observed in females.	Liver: granulomatous inflammation: Male: LOAEL: ND NOAEL: 3,750 mg/kg-d Female: LOAEL: 235 mg/kg-d NOAEL: ND	NTP 1986a[c]
Mouse, B6C3Fl, M/F	0, 469, 938, 1,875, 3,750, 7,500 mg/kg-d	90 d, gavage	Gross: No significant decreases in body weight was observed in exposed male or females as compared with controls. No deaths or clinical signs of toxicity were observed in either males or females orally exposed to chlorinated paraffin Microscopic: No gross lesions or changes tissue histology were detected that could be attributed to oral exposure to chlorinated paraffin	No adverse effects detected at 469 mg/kg-d	NTP 1986a[c]
Rat, F344, M/F	Male: 0, 1,875, 3,750 mg/kg-d Female: 0, 100, 300, 900 mg/kg-d	6 mo, gavage	Gross: No compound-related clinical signs of toxicity. Some clinical chemistry values altered at 1,875 mg/kg-d in male and 100 mg/kg-d in females. Macroscopic: Dose-related and statistically significant increases in relative liver weights observed in treated females at 900 mg/kg-d. Microscopic: Dose-related increase in the incidence of	Liver weight: Females: NOAEL: 300 mg/kg-d LOAEL: 900 mg/kg-d Liver: granulomatous inflammation: Females:	NTP 1986a[c]

			granulomatous inflammation of the liver occurred in treated females. Granulomatous inflammation of the liver confirmed by clinical chemistry and hematology studies.	NOAEL: ND LOAEL: 100 mg/kg-d	
Rat, F344, M/F	Male: 0, 1,875, 3,750 mg/kg-d Female: 0, 100, 300, 900 mg/kg-d	12 mo, gavage	Gross: No compound-related clinical signs of toxicity. Some clinical chemistry values altered at 1,875 mg/kg-d in male and 100 mg/kg-d in females. Significant alterations were observed at dose levels of 3,750 mg/kg-d in dosed males and 300 mg/kg-d in dosed females at 12 mo. Macroscopic: Dose-related and statistically significant increases in relative liver weights observed in treated males and females. Microscopic: Dose-related increase in the incidence of granulomatous inflammation of the liver occurred in treated males and females. Granulomatous inflammation of the liver confirmed by clinical chemistry and hematology studies.	Liver weight: Females: NOAEL: 100 mg/kg-d LOAEL: 300 mg/kg-d Males: NOAEL: 1,875 mg/kg-d LOAEL: 3,750 mg/kg-d Liver: granulomatous inflammation: Females: NOAEL: ND LOAEL: 100 mg/kg-d Males: NOAEL: ND LOAEL: 1,875 mg/kg-d	NTP 1986a[c]
Rat, F344, M/F	Male: 0, 1,875, 3,750 mg/kg-d Female: 0, 100, 300, 900 mg/kg-d	2 yr, gavage	Gross: Mean body weights not affected. No clinical signs of toxicity observed among dosed animals. No significant decreases in survival as compared with controls Microscopic ($p<0.05$): Males: Lymphocytic and granulomatous inflammation of liver; pigmentation of the liver; spleen congestion; granulomatous inflammation of pancreatic and mesenteric lymph nodes; mesenteric and pancreatic lymphoid hyperplasia beginning at 1,875 mg/kg-d. Hepatocellular hyperplasia and granulomatous inflammation of pancreatic and mesenteric lymph nodes beginning at 3,750 mg/kg-d.	Liver: granulomatous inflammation: Females: NOAEL: ND LOAEL: 100 mg/kg-d Males: NOAEL: ND LOAEL: 1,875 mg/kg-d	NTP 1986a[c]

Species, Strain, Sex	Dose	Duration, Route	Effects	NOAEL/LOAEL	Reference
			Females: Lymphocytic and granulomatous inflammation of liver; pigmentation of the liver/kidney; nephropathy; hepatocellular hypertrophy; spleen congestion; granulomatous inflammation of pancreatic and mesenteric lymph nodes; pancreatic lymphoid hyperplasia beginning at 100 mg/kg-d. Lymphoid hyperplasia of the pancreatic lymph node beginning at 300 mg/kg-d; skin hyperkeratosis at 900 mg/kg-d.		
Mouse, B6C3F1, M/F	0, 2,500, 5,000 mg/kg-d	2 yr, gavage	Gross: Mean body weights comparable with controls throughout the study. Survival was altered in females from treated and controls after wk 65 due to utero-ovarian infection. Microscopic: No significant increases in the incidence of nonneoplastic lesions are reported for male or females.	No adverse effects detected at 2,500 mg/kg-d	NTP 1986a[c]
$C_{22–26}$, 70% Cl_2					
Rat, F344, M/F	100, 900, 3,750 mg/kg-d	90 d, diet	Gross: Slight but statistically significant decreases in body-weight gain. Food consumption slightly increased in male rats at all doses. Macroscopic: 100: No increases in relative or absolute organ weights 900: No increases in relative or absolute organ weights 3,750: Increase in relative and absolute liver weight in males; increase in relative liver weight in females Microscopic: 100: No liver, kidney, or thyroid findings in males or females	Liver weight: NOAEL: 900 mg/kg-d LOAEL: 3,750 mg/kg-d Liver pathology: NOAEL: 900 mg/kg-d LOAEL: 3,750 mg/kg-d Liver biochemistry: NOAEL: 900 mg/kg-d LOAEL: 3,750 mg/kg-d	IRDC 1981, as reviewed by Serrone et al. 1987 (438–024/027)

900: No liver, kidney, or thyroid findings in males or females 3,750: Hepatocellular hypertrophy and cytoplasmic vacuolation (fat accumulation) of the liver in both males and females. Chronic nephritis in males. No effects were seen in the thyroid in either sex. Biochemical: Increases in alanine aminotransferase activity observed in male and female rats at 3,750 mg/kg-d. Increased asparatate aminotransferase activity in females at 3,750 mg/kg-d.

[a]Authors note compound was $C_{10–12}$, 60% chlorination.

[b]Chlorinated paraffins incorporated in feed. Daily dose estimated using standard default for rat daily food consumption of 0.015 kg and standard default for rat average body weight of 0.25 kg.

[c]Authors note that compound was $C_{22–26}$, 43% chlorination.

Wyatt et al. 1993) were also observed in male and female rats exposed to short-chain chlorinated paraffins. Changes in organ weight were accompanied by pathological changes in the corresponding organs.

Medium-chain Chlorinated Paraffins

Poon et al. (1995), IRDC (as reviewed by Serrone et al. 1987), and Birtley et al. (1980) evaluated the toxicity of the medium-chain chlorinated paraffin $C_{14–17}$, 52% chlorine, in 90-d subchronic toxicity studies. Statistically significant increases in relative liver weight were observed in both rats (Birtley et al. 1980; Serrone et al. 1987; Poon et al. 1995) and Beagle dogs (Birtley et al. 1980). Histopathological examination showed proliferation of the endoplasmic reticulum of liver hepatocytes in both rats and dogs (Birtley et al. 1980) and hepatocellular hypertrophy (Seronne et al. 1987). Poon et al. (1995) found minimal to mild single-cell necrosis at 300 mg/kg-d (estimated) and other hepatic effects starting at 30 mg/kg-d (estimated). Poon et al. (1995) and Serrone et al. (1987) reported that significant increases in relative kidney and thyroid weights were also observed in rats along with pathological changes in these tissues. Effects on biochemical parameters occurred at dose levels of 3 mg/kg-d (estimated) or greater.

Significant increases in liver and kidney weight were also observed in rats gavaged with $C_{14–17}$, 40% chlorine, for up to 90 d at 312 or 625 mg/kg-d. Increases in liver weight were accompanied by hepatocyte hypertrophy and an increase in liver β-oxidation activity and T_4 glucuronidation. Free plasma T_3, T_4, and TSH levels were not affected at any dose level in either sex. A statistically significant increase in α2u-globulin protein present in the proximal convoluted tubules was also observed in male rats at 625 mg/kg-d. This effect was not due to hyaline droplets formation. Thyroid follicular-cell hypertrophy was identified in all dosed males and females.

Long-chain Chlorinated Paraffins

Multifocal granulomatous hepatitis has been consistently observed in F-344 rats exposed to $C_{20–30}$, 43% chlorine (Serrone et al. 1987), or C_{23}, 43% chlorine (NTP 1986b), for 90 d or longer. These changes were accompanied by an increase in liver weight and necrosis in female rats administered daily doses of $C_{20–30}$, 43% chlorine, by gavage for 90 d at 100, 900, or 3,750 mg/kg-d (Serrone et al. 1987). These effects were not observed in similarly-treated male rats. Kidney toxicity occurred in high-dose males and females characterized by nephrosis and mineralization. Treatment did not produce any clinical signs of

toxicity, any effects on body weight, or on other measures of toxicity (see Table 19–5).

NTP (1986b) found a dose-related increase in the incidence of granulomatous inflammation of the liver in female rats given C_{23}, 43% chlorine, by gavage for 90 d at 235, 469, 938, 1,875, or 3,750 mg/kg-d. These lesions were not observed in similarly-treated male rats. Treatment for 90 d did not produce any clinical signs of toxicity or any effects on body weight. There were no gross lesions or adverse changes in tissue histology observed in male or female B6C3F1 mice exposed to C_{23}, 43% chlorine, for 90 d at dose levels of 469, 938, 1,875, 3,750, or 7,500 mg/kg-d (NTP 1986b). No deaths or clinical signs related to chemical exposure were observed in males or females in any of the dose groups. No changes in body weight were observed in treated males or females.

In the two year study, the incidence of hepatocellular hyperplasia was increased in male rats exposed daily by gavage with 3,750 mg/kg-d and in females gavaged with 300 or 900 mg/kg-d (see Table 19–5). The incidence of granulomatous inflammation and lymphoid hyperplasia of the pancreatic and mesenteric lymph nodes was also increased among treated rats. The incidence of nephropathy of the kidney was significantly elevated in female rats dosed with 300 or 900 mg/kg-d. Brown staining around the mouth occurred in low-and high-dose males after wk 43. Dosed females showed a high incidence of distended abdomens during the latter part of the study. No significant difference in survival was calculated for treated rats as compared with controls after survival was adjusted for gavage-related deaths. No significant increases in the incidence of nonneoplastic lesions were reported for male or female B6C3F1 mice administered C_{23}, 43% chlorine, for up to 2 yr at dose levels of 2,500 or 5,000 mg/kg-d (NTP 1986b). Mean body weights in the high-dose groups were comparable with controls throughout study. Survival was low in all female groups including controls after wk 65 due to a high incidence of utero-ovarian infection.

Statistically significant increases in absolute liver weight and serum abnormalities were detected in F-344 rats subchronically exposed to $C_{22–26}$, 70% chlorine, at 3,750 mg/kg-d for 90 d (Serrone et al. 1987). Pathological examination revealed hepatocellular hypertrophy and cytoplasmic vacuolation in males and females and chronic nephritis in males exposed to 3,750 mg/kg-d. The NOAEL for absolute and relative organ weight increases and pathological findings for both sexes was 900 mg/kg-d.

Immunological

No studies were identified that investigated the immunological effects of chlorinated paraffins following oral exposure.

Neurological

Administration of a single peroral dose of 1.4 μmol/kg of polychlorohexadecane (chain length and percent chlorination not reported) produced a significant decrease (65%) in the V_{max} value for the presynaptic, sodium-dependent uptake of choline in the brain of 10-d-old mice (Eriksson and Nordberg 1986). This suggests that chlorinated paraffin may have an effect on the cholinergic system, but no comment was made about the significance of this effect on behavior or other neurological parameters. It was also found that the binding affinity of [^{3}H]quinuclidinyl benzilate (QNB), amuscarinic cholinergic receptor antagonist, to mouse cerebral cortex P2 fractions from 10-d-old mice was not affected when measured 7 d after exposure.

Reproductive and Developmental Effects

The teratogenic effects of chlorinated paraffins in rodents are summarized in Table 19–6. Serrone et al. (1987) notes that pregnant rabbits were more sensitive to $C_{10–13}$, 58% chlorine, $C_{14–17}$, 52% chlorine, or $C_{22–26}$, 70% chlorine, than pregnant rats based on maternal toxicity, but that none of the four chlorinated paraffins tested had a teratogenic effect on either rat or rabbit fetuses.

There was an increased number of post-implantation losses, resorptions, fetal deaths, and adactyly and/or shortened digits in pregnant dams exposed to $C_{10–13}$, 58% chlorine, at the highest dose level. However, eight of 25 pregnant dams from the high-dose group died following administration. Signs of maternal toxicity were observed in both mid- and high-dose groups. Serrone et al. (1987) reports that the study authors concluded that the digital malformations could not be interpreted as a direct teratogenic effect and was more likely to be a secondary response due to maternal toxicity.

No studies were identified that addressed the effects on reproduction.

Cancer

The National Toxicology Program (NTP) has conducted oral carcinogenicity bioassays in both rats and mice administered $C_{10–12}$, 60% chlorine, and $C_{22–26}$, 43% chlorine, (NTP 1986a, 1986b). Results of these studies are summarized in Table 19–7.

Evidence of carcinogenicity was observed in F-344/N rats given $C_{10–12}$, 60% chlorine, by gavage 5 d/wk for 104 wk. Dose-related and statistically significant increases in the incidences of hepatocellular carcinomas and of hepatic carcinomas plus adenomas combined were observed in both males and females.

Statistically significant increases in the incidence of mononuclear-cell leukemia occurred in male rats as compared with controls. The incidence of tubular-cell adenomas and adenocarcinomas of the kidney were elevated in male rats, but not significantly. Statistically significant increases in the incidence of thyroid follicular-cell carcinomas plus adenomas combined were observed in female rats. A dose-dependent and statistically significant increase in hepatocellular adenomas and hepatocellular adenomas and carcinomas was observed in B6C3F1 mice given $C_{10–12}$, 60% chlorine, by gavage for 2 yr (NTP 1986a). Dose-dependent and statistically significant increases in the incidences of alveolar and bronchiolar carcinomas, and thyroid follicular-cell adenomas and carcinomas occurred in male and female mice, respectively.

No tumor types were found to be significantly increased in male F-344/N rats given $C_{22–26}$, 43% chlorine, by gavage for 5 d/wk for 103 wk. However, the incidence of pheochromocytomas of the adrenal medulla was significantly increased in female rats. A dose-related increase in the incidence of malignant lymphoma occurred in male mice given $C_{22–26}$, 43% chlorine, at 2,500 or 5,000 mg/kg-d, 5 d/wk for 103 wk (NTP 1986b). The incidence of hepatocellular adenomas and carcinomas combined was elevated in female mice, but not significantly. Survival among females was low among treated and control animals due to a high incidence of utero-ovarian infection and may have decreased the potential of the study to detect treatment-related carcinogenicity (NTP 1986b).

The European Union (EU) is currently evaluating the health risks posed by chlorinated paraffins. At technical meetings on October 1–3, 1996, and February 19–21, 1997, it was agreed by specialized experts representing the Member States that $C_{10–13}$ chlorinated paraffins are not genotoxic. However, no agreement could be reached regarding the significance of the tumors reported by NTP (1986a) or their relevance to man. In a June 1997 meeting of the Commission Group of Specialized Experts in the fields of Carcinogenicity, Mutagenicity, and Reprotoxicity, it was concluded that no significance could be placed on the slight excess in lung, pancreas, stomach, Hadrian gland tumors, or leukemias reported in NTP (1986a). The Specialized Experts decided that only the observed tumors of the liver, kidney, and thyroid should be considered significant. It was also agreed that the liver and thyroid tumors could be attributed to peroxisomal proliferation which could cause a hormonal imbalance and that humans would be much less sensitive to peroxisome proliferation than rats and mice. No plausible mechanism for the observed kidney tumors was agreed upon, but it was thought that either α2u-globulin accumulation or chronic nephropathy might be contributing factors. In 1998, the EU Scientific Committee for Toxicity, Ecotoxicity, and the Environment generally agreed with the conclusions of the Specialized Experts with the exception of ruling out the significance of the increased incidence of lung tumors in male mice. However,

TABLE 19–6 Teratogenicity Studies on Chlorinated Paraffins

Species, Strain	Doses (mg/kg-d)	Duration, Route	Effects	Reference
Short-chain chlorinated paraffins				
$C_{10–13}$, 58% Cl_2				
Rat, Charles River	100, 500, 2,000	d 6−19 of gestation, gavage	Dams: Eight of 25 pregnant dams from the high-dose group died following administration. Signs of maternal toxicity were observed in both mid- and high-dose groups. Fetuses: Increased number of post-implantation losses, increased number of early and late resorptions, and a decrease in viable fetuses per dam in the high-dose group. Adactyly and/or shortened digits were observed in the high-dose group. No effects were observed at the lowest dose level. Authors interpretations: Digital malformations observed at a dose that produced significant mortality in treated dams cannot be interpreted as a direct teratogenic effect and are more likely to be a secondary response due to maternal toxicity.	IRDC 1982, as reviewed by Serrone et al. 1987 (438–016)
Rabbit, Dutch Belted	10, 30, 100	d 6−27 of gestation, gavage	Embryotoxicity was seen in both the mid-dose and the high-dose groups. No effect was observed on the occurrence of malformations at any dose level.	IRDC 1982/83, as reviewed by Serrone et al. 1987 (438–031; 037)
Medium-chain chlorinated paraffins				
$C_{14–17}$, 52% Cl_2				
Rat, Charles River	500, 2,000, 5,000	d 6−19 of gestation, gavage	Dams: Maternal toxicity was observed in the high-dose group. Fetuses: There were no biologically or meaningful relevant statistically significant differences in Caesarean section observations or in the incidence of fetus malformations in litters belonging to the treated groups as compared with corresponding controls.	IRDC 1981/83/84, as reviewed by Serrone et al. 1987 (438–017; 034; 047)

Rabbit, Dutch Belted	10, 30, 100	d 6−27 of gestation, gavage	Dams: No maternal toxicity was observed but body weight losses were observed in the high-dose group dams. Fetuses: There were no biologically meaningful differences in the numbers of litters/fetuses with malformations or in the developmental and genetic variations when the treated groups were compared with controls.	IRDC 1982/83, as reviewed by Serrone et al. 1987 (438–020; 032; 036)
Long-chain chlorinated paraffins				
$C_{20–30}$, 43% Cl_2				
Rat, Charles River	500, 2,000, 5,000	d 6−19 of gestation, gavage	Dams: Maternal toxicity observed in the high-dose group. One female died on d 18 of gestation. Fetuses: No differences in the incidence of fetal malformations were observed when treated groups were compared to controls.	IRDC 1981/83, as reviewed by Serrone et al. 1987 (438–015; 033)
Rabbit, Dutch Belted	500, 2,000, 5,000	d 6−27 of gestation, gavage	Two of 12 dams at the high dose and one of the 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 fetuses when compared to controls. The data did not indicate a teratogenic response.	IRDC 1981, as reviewed by Serrone et al. 1987 (438–018; 030)
$C_{22–26}$, 70% Cl_2				
Rat, CD	500, 2,000, 5,000	d 6−19 of gestation, gavage	Dams: No maternal toxicity was observed in any of the pregnant rats that were given chlorinated paraffin. Fetuses: There were no biologically meaningful differences in the incidence of developmental variations and malformations in the treated groups as compared with controls.	IRDC 1983, as reviewed by Serrone et al. 1987 (438–045; 046)
Rabbit, Dutch Belted	100, 300, 1,000	d 6−27 of gestation, gavage	Does: No biologically meaningful differences were observed in maternal appearance, behavior, or body-weight gain. Fetuses: There were no adverse treatment-related differences in Caesarean section observations or in the incidence of fetus malformations in the liters of the treated groups as compared with controls. There was no difference between treated and control fetuses in the occurrence of genetic and developmental variation.	IRDC 1981, as reviewed by Serrone et al. 1987 (438–018; 030)

TABLE 19–7 Carcinogenicity, Studies on Chlorinated Paraffins

Species, Strain, Sex, Number	Dose (mg/kg-d)	Duration, Route	Results			Reference
Short-chain chlorinated paraffins C_{12}, 60% Cl_2						
Rat, F344, M/F, 50/sex/dose	0, 312, 625	104 wk, gavage	Tumor incidence:			NTP 1986a
			Hepatocellular carcinoma		Adenoma+carcinomas	
			Test for trend			
			Males:			
			0	0/50	0/50	
			312	10/50	13/50	
			625	16/48	16/48 p<0.001	
			Females:			
			0	0/50	0/50	
			312	5/50	6/50	
			625	7/50	7/50 p=0.005	
			Other tumor incidences significantly elevated:			
			Males: mononuclear cell leukemia			
			Females: thvroid follicular cell adenomas/carcinomas			
Mouse, B6C3F_1, M/F, 50/sex/dose	0, 125, 250	103 wk, gavage	Tumor incidence:			NTP 1986a
			Hepatocellular adenomas		Adenoma+carcinomas	
			Test for trend			
			Males:			
			0	11/50	20/50	
			125	20/50	34/50	
			250	29/50	38/50 p<0.001	
			Females:			
			0	0/50	3/50	
			125	18/50	22/50	
			215	22/50	28/50 p<0.001	
			Other tumor incidences significantly elevated:			
			Males: alveolar/bronchiolar carcinomas			
			Females: thyroid follicular cell adenomas/carcinomas			

Long-chain chlorinated paraffins				
C_{23}, 43% Cl_2				
Rat, F344, M/F, 50/ sex/dose	Males: 0, 1,875, 3,750 Females: 0, 100, 300, 900	103 wk, gavage	Tumor Incidence: 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, tumor test for trend).	NTP 1986b
Mouse, B6C3F_1, M/F, 50/sex/dose	0, 2,500, 5,000	103 wk, gavage	Tumor incidence: 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 males (p= 0.009, life-table test for trend; p=0.011 tumor test for trend). Tumor trend not significant for hepatocellular carcinomas and adenomas combined (4/50 in controls, 3/49 in low-dose, and 10/50 in high-dose animals). Authors note that toxicity and premature death in females may have decreased the potential of the study to detect carcinogenic effects.	NTP 1986b

it was felt that this reconsideration does not alter the outcome of the risk characterization for man. The Committee also noted that one cannot totally discount the possibility that liver and thyroid tumors could arise in man following exposure to short-chain chlorinated paraffins, but there would be very large differences in carcinogenic sensitivity between animals and humans in the induction of these tumors. The Commission also in agreed with the use of a NOAEL of 100 mg/kg-d for kidney carcinogenicity in male mice (EUSCTEE 1998).

The International Agency for Research on Cancer (IARC) last evaluated the carcinogenicity of chlorinated paraffins in 1989–1990 (IARC 1990). At that time, based on the available data IARC concluded that there was sufficient evidence for the carcinogenicity of the chlorinated paraffin C_{12}, 60% chlorine, in experimental animals and that it was possibly carcinogenic to humans (Group 2B). IARC (1990) concluded that there was limited evidence for the carcinogenicity of C_{23}, 43% chlorine, in experimental animals.

As of September 1999, chlorinated paraffins are not listed in EPA's IRIS (Integrated Risk Information System) database. However, based on the available carcinogenicity of these compounds, EPA decreed in 1994 (EPA 1994) that there was sufficient evidence for adding short-chain chlorinated paraffins to the list of chemicals subject to reporting under section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA). EPA concluded that long-chain chlorinated paraffins should not be classified as potential carcinogens based on the animal data (EPA 1994).

Genotoxicity

The chlorinated paraffins—$C_{10–13}$, 58% chlorine; $C_{14–17}$, 52% chlorine; $C_{20–30}$, 43% chlorine; and $C_{22–26}$, 70% chlorine—did not cause chromosomal or chromatid aberrations in rat bone marrow cells from male F-344 rats administered by gavage at 5 g/kg-d for 5 consecutive days (Serrone et al. 1987).

Administration of $C_{10–13}$, 58% chlorine, by gavage to male Charles River rats at dose levels of 250, 750, or 2,000 mg/kg-d for 5 consecutive days did not result in an increased frequency of dominant lethal mutations in offspring following mating with 20 potentially mated females (see Serrone et al. 1987).

The chlorinated paraffins—$C_{10–13}$, 50% chlorine (Birtley et al. 1980); $C_{10–12}$, 60% chlorine (NTP 1986a); $C_{14–17}$, 52% chlorine (Birtley et al. 1980); $C_{20–30}$, 42% chlorine (Birtley et al. 1980); $C_{23–26}$, 43% chlorine (NTP 1986b); and $C_{10–23}$, 70% chlorine (Meijer et al. 1981)—have been tested in the Ames assay, with or without exogeneous metabolic activation at or near toxic doses. All were found to be negative for mutagenicity.

Hepatocytes taken from male rats exposed to near toxic doses of $C_{10–12}$, 60%

chlorine, of up to 2 g/kg-d were negative for unscheduled DNA synthesis 2 or 12 hr after dosing (Ashby et al. 1990). Moderate hepatocyte proliferation was observed 12, 24, and 36 hr after exposure to dose levels of 1,000 or 2,000 mg/kg-d of $C_{10–12}$, 60% chlorine. Quantitatively greater responses were measured for hepatocytes taken from rats exposed to positive control compounds. Chlorinated paraffins—$C_{10–13}$, 50% chlorine; $C_{20–30}$, 42% chlorine; $C_{14–17}$, 52% chlorine—all with or without a stabilizer, did not induce cell transformation in baby hamster kidney cells in vitro at concentrations of 0.25, 2.5, 25, and 2,500 μg/mL.

$C_{10–12}$, 60% chlorine, inhibited intercellular communication in a rat liver epithelium-derived cell line (IAR 20) in vitro, when assessed 1 and 12 hr after exposure (Warngard et al. 1996).

QUANTITATIVE TOXICITY ASSESSMENT

Noncancer

Dermal Assessment

No dermal toxicity studies of adequate duration (i.e., subchronic or chronic) were found in the literature for deriving a dermal RfD for any chlorinated paraffins.

Inhalation RfC

The subcommittee did not locate any inhalation toxicology studies of adequate duration (i.e., subchronic or chronic) for deriving an inhalation RfC for any of the chlorinated paraffins.

Oral RfD

Chlorinated paraffins, if used as FRs in residential furniture, will most likely be applied as a latex backcoating, possibly in combination with antimony trioxide and other FRs. According to chlorinated paraffin manufacturers, the chlorinated paraffins that are most likely to be used in latex back coating applications are the long-chain chlorinated paraffins ($C_{20–30}$) with high chlorine content (i.e., 70%). This is because of the high flame-retardancy of these chemicals as compared with the medium- or short-chain chlorinated paraffins.

Currently, no chronic toxicity data are available for a long-chain chlorinated paraffin with high chlorine content (i.e., 70%). A subchronic toxicity study is available for $C_{22–26}$, 70% chlorine (Serrone et al. 1987). The subcommittee concluded that this study provides sufficient data for calculating an oral RfD for long-chain, highly chlorinated paraffins (the details of this study were reviewed in the Hazard Identification section under Systemic Effects of Oral Exposure). The critical effect observed in this study was liver toxicity (increases in relative liver weight, hepatocellular hypertrophy, cytoplasmic fat vacuolation, increases in serum alanine aminotransferase and aspartate aminotransferase activities). These effects occurred at a dose level of 3,750 mg/kg-d. The authors also report a slight increase in the incidence of kidney nephritis in males at the 3,750 mg/kg-d dose level. No toxic effects were observed in either male or female rats at the dose level of 900 mg/kg-d or lower. Therefore, in this study a LOAEL of 3,750 mg/kg-d and a NOAEL of 900 mg/kg-d was identified.

Based on the NOAEL for liver and kidney toxicity for $C_{22–26}$, 70% chlorine, in male and female rats, the estimated RfD for long-chain chlorinated paraffins ($C_{20–30}$), 70% chlorine, is 0.3 mg/kg-d (see Table 19–8). To derive the oral RfD, the NOAEL was divided by a composite uncertainty factor (UF) of 3,000 which consists of a factor of 3 to extrapolate from animals to humans (factor UF_A). A factor of 3 instead of 10 was used because the toxicokinetics and dynamics of long-chain chlorinated paraffins are anticipated to be similar in rodents and humans. A factor of 10 was used to account for the possible sensitivity of children and elderly to long-chain chlorinated paraffins (factor UF_H). A factor of 10 was applied to account for less-than-lifetime toxicity data (factor UF_S) and another factor of 10 was applied because the toxicity database for the long-chain chlorinated paraffin $C_{22–26}$, 70% chlorine, is incomplete (UF_D).

The subcommittee has moderate to high confidence that the RfD calculated for $C_{22–26}$, 70% chlorine, is sufficiently protective of human health for several reasons. A NOAEL was available for $C_{22–26}$, 70% chlorine. Dose levels at which toxicity occurred for $C_{22–26}$, 70% chlorine, reported by Serrone et al. (1987) are comparable across studies. In a 2-year study (NTP 1986b), liver and kidney effects occurred in female rats at a dose level of 300 mg/kg-d, but did not occur at 100 mg/kg-d. In addition, the application of two 10-fold uncertainty factors (less-than-lifetime data, insufficient toxicity database) in the oral RfD derivation should be sufficiently protective if a significant critical effect occurs at dose level of less than 900 mg/kg-d. The use of a three-fold uncertainty factor to account for possible differences in sensitivity between rodents and humans is also sufficiently conservative because current mechanistic data suggest that it is not likely that humans are more sensitive than rodents to chlorinated paraffins.

TABLE 19–8 Oral Reference Dose for C22–26, 70% Chlorine

Critical Effect	Species	Effect Level (mg/kg-d)	Uncertainty Factors	RfD (mg/kg-d)	Reference
Liver and kidney toxicity	Rat	NOAEL: 900	UF_A: 3 UF_H: 10 UF_S: 10 UF_D: 10 Total: 3,000	0.3	IRDC 1981, as reviewed by Serrone et al. 1987

NOAEL, no-oberved-adverse-effect level; RfD, reference dose; UF_A, extrapolation from animals to humans; UF_H, intraspecies variation; UF_S, extrapolation from a study of less-than-lifetime in duration; UF_D, inadequate or deficient toxicity database.

Cancer

Short-chain Chlorinated Paraffins

There is adequate evidence for the carcinogenicity of the short-chain chlorinated paraffin C_{12}, 60% chlorine, in rodents (NTP 1986a). Chronic oral administration of C_{12}, 60% chlorine, induced dose-dependent increases in the incidence of hepatocellular carcinomas and adenomas in both F-344 and B6C3F1 mice. The combined incidence of thyroid follicular-cell carcinomas and adenomas was significantly elevated in female mice and rats. The incidence of alveolar and bronchiolar carcinomas was significantly elevated in male mice, and the incidences of tubular-cell adenomas and adenocarcinomas of the kidney and mononuclear-cell leukemia were significantly elevated in male rats.

Tests for the genotoxicity of C_{12}, 60% chlorine, have been consistently negative suggesting that it may be causing cancer in rodents by nongenotoxic mechanisms. For example, liver peroxisome proliferation may be responsible for the liver, thyroid, and kidney tumors observed in the NTP (1986a) bioassay (Bentley et al. 1993; Cattley et al. 1998). Peroxisomal proliferation is associated with hepatocarcinogenesis in rats and mice (Ashby et al. 1990; Bentley et al. 1993; Cattley et al. 1998). Morphological analysis of the livers from rats and mice exposed to $C_{10–13}$, 58% chlorine, has consistently shown a pattern of peroxisomal proliferation, hepatocyte hypertrophy, and the induction of hepatic P450 4Al, fatty acetyl CoA oxidase, and T_4 glucuronidation product levels (Ashby et al. 1990; Wyatt et al. 1993). It is believed that the increase in the incidence of thyroid follicular cell carcinomas and adenomas in females may be the result of increased T_4 glucuronidation in conjunction with peroxisomal proliferation which decreases plasma T_4 levels resulting in the stimulation of pituitary TSH production. In turn, increased TSH production stimulates thyroid

hypertrophy and hyperplasia and the eventual formation of follicular cell carcinoma (Wyatt et al. 1993). Hypertrophy and hyperplasia of the thyroid have been reported to occur in F-344 rats exposed to short-chain chlorinated paraffins for 90 d (Serrone et al. 1987).

At this time, there is no adequate explanation for the formation of kidney tumors observed in male rats. It has been suggested that an unidentified sex-specific protein may stimulate sustained DNA synthesis in the kidney following chronic administration of short-chain chlorinated paraffins (Wyatt et al. 1993). Increased protein accumulation has been observed in dosed males accompanied by nephropathy, manifested by increased incidences of regenerating tubules. Immunocytochemical staining for α2u-globulin in the tubules shows that this protein is present but is not the predominant protein that accumulates, and no hyaline droplets have been observed in male rats treated with high doses of short- or medium-chain chlorinated paraffins for 90 d (Wyatt et al. 1993). No hypothesis has been presented for the possible mechanisms associated with the increased incidence of alveolar and bronchiolar carcinomas in male mice or mononuclear cell leukemia in male rats. The subcommittee does acknowledge that these tumor types, along with kidney tumors in male rats, did not occur across species, and therefore less weight should be given to these findings in the evaluation of the carcinogenicity of $C_{10–13}$, 58% chlorine.

Medium-chain Chlorinated Paraffins

Currently, there are no human or animal data available for evaluating the carcinogenicity of medium-chain chlorinated paraffins.

Long-chain Chlorinated Paraffins

Currently, there are no epidemiological or cancer bioassay data for long-chain chlorinated paraffins ($C_{22–26}$) paraffins with 70% chlorination, which are the type of chlorinated paraffin that are most likely to be used as FRs in residential furniture. Meijer et al. (1981) tested a long-chain chlorinated paraffin of similar chemistry ($C_{10–23}$, 70% chlorine) for mutagenicity in three strains of *S. typhimurium* and found that this compound was negative for mutagenicity at all concentrations tested in two of the three strains. A positive response was observed in one strain at the highest concentration tested, but this may have been a chance occurrence since no dose-response for mutagenicity was observed. The authors also point out that no toxic effects were seen suggesting

that this compound may not penetrate into bacterial cells. No other genotoxicity data are known to be available for long-chain chlorinated paraffins with 70% chlorination.

The subcommittee believes that the best study available for evaluating the carcinogenicity of long-chain chlorinated paraffins with 70% chlorination is the NTP (1986b) rodent carcinogenicity bioassay for the long-chain chlorinated paraffin $C_{22–26}$, 43% chlorine (see Table 19–7). In this bioassay, no tumor types were consistently elevated across species in F-344 rats and B6C3F1 mice administered C_{23}, 43% chlorine, for 103 wk. In mice, there was a dose-related increase in the incidence of malignant lymphoma among males as compared with controls. The incidence of hepatocellular adenomas and carcinomas combined was elevated in female mice in the high-dose group, but the incidence of this tumor category was not significant across dose levels as determined by incidental tumor tests for trend. However, early mortality due to infection was common among females in both the treated and control groups and may have prevented the identification of increased incidences in late-forming tumor-types. In rats, the incidence of pheochromocytomas of the adrenal medulla was increased in females, and no tumor types were found to be significantly increased in F-344 males exposed to chlorinated paraffin as compared with controls. $C_{22–26}$, 43% chlorine, was not genotoxic in the Ames assay with or without exogenous metabolic activation (NTP 1986b) and did not induce chromosomal aberrations in F-344 rats administered toxic doses (Serrone et al. 1987).

Based on the animal and genotoxicity data for $C_{22–26}$, 43% chlorine, the subcommittee concluded that there is limited evidence for its carcinogenicity in rodents. This conclusion is in agreement with that of IARC (1990) and EPA (1994).

Derivation of a Cancer Potency Factor

The subcommittee concluded that the derivation of cancer potency factor (i.e., $0.1/LED_{10}$) for long-chain chlorinated paraffins is not warranted based on the lack of cancer data for long-chain chlorinated paraffins, 70% chlorine, and the limited evidence for the carcinogenicity of C_{23}, 43% chlorine. The subcommittee does acknowledge that there are adequate data for the carcinogenicity for $C_{10–12}$, 60% chlorine, in rodents, but these chlorinated paraffins are not likely to be used as FRs in residential furniture. Therefore, the subcommittee concluded that the derivation of a cancer potency estimate for short-chain chlorinated paraffins was not necessary.

EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

Noncancer

Dermal Exposure

Dermal exposure to chlorinated paraffins was estimated using the dermal exposure scenario described in Chapter 3. This exposure scenario assumes that an adult spends 1/4th of his or her time sitting on furniture upholstery backcoated with chlorinated paraffins and also assumes 1/4th of the upper torso is in contact with the upholstery and clothing presents no barrier. Exposure to other chemicals present in the backcoating was not included in this assessment.

First Iteration

As a first estimate of exposure, it was assumed that skin, clothing, and the upholstery did not impede dermal exposure to chlorinated paraffins present in the backcoating. It was also assumed that there would be sufficient water present from sweat to facilitate dissolution of chlorinated paraffins from the backcoating and absorption through the skin. In this scenario, only the dissolution rate of chlorinated paraffins from the backcoating is assumed to be the limiting factor in absorption by the body. It is assumed that all of the chlorinated paraffins that dissolves is immediately absorbed into the body by the sitting person.

Dermal exposure was estimated using Equation 1 in Chapter 3. For this calculation, the subcommittee estimated an upholstery application rate (S_a) for chlorinated paraffins of 3 mg/cm^2. The extraction rate (μ_w) for chlorinated paraffins was estimated to be 0.025 based on extraction data for hexabromocyclododecane in polyester fiber (McIntyre et al. 1995). The release rate from the fiber for estimating extraction was 0.04/d at 28° C calculated using the equation $2d/2\ \pi R$ (d=film thickness, R=fiber radius) with a correction from fiber to film of a factor of 0.63.

Using these assumptions, an estimated absorbed daily dose of 0.59 mg/kg was calculated for chlorinated paraffins. In the absence of a dermal RfD, the subcommittee believes it is appropriate to use the oral RfD for C_{22-26}, 70% chlorine, as the best estimate of the internal dose from dermal exposure. A hazard index of 1.97 was calculated for this first iteration by dividing the estimated daily dermal dose of 0.59 mg/kg-d by the oral RfD for chlorinated paraffins of 0.3 mg/kg-d. This hazard index of 1.97 indicates that dermal exposures to long-chain chlorinated paraffins at the worst-case levels might be a health

concern. The subcommittee recommends that the dermal absorption of these substances from treated fabric be investigated.

Alternative Iteration

The estimated dermal daily dose for chlorinated paraffins can be calculated using an estimate of the dermal penetration rate for chlorinated paraffins (Chapter 3, Equations 2 and 3). Instead of assuming that all dissolved chlorinated paraffins immediately penetrates the skin and enters systemic circulation, it is assumed that the skin slows the absorption of chlorinated paraffins to a specific amount of chemical absorbed per unit of time. This estimate can be measured experimentally and is referred to as the skin permeability coefficient K_p. However, the dermal penetration constant for chlorinated paraffins has not been measured experimentally. However, K_p can be estimated from a correlation between the octanol-water partition coefficient (K_{ow}) and molecular weight (mass/unit amount of substance) using Equation 2 in Chapter 3 yielding an alternate K_p of 5.77×10^{-5} cm/d.

The water solubility of long-chain chlorinated paraffin, 70% chlorination, was not available. Therefore the alternative exposure estimate could not be calculated. However, it was determined that the calculated dose rate for chlorinated paraffins would only be a concern in this scenario if the water solubility of long-chain chlorinated paraffins exceeded 650 g/liter—which is not possible.

Inhalation Exposure

Particles

Inhalation exposure estimates for chlorinated paraffins were calculated using the exposure scenario described in Chapter 3. This scenario assumes that a person spends 1/4th of his or her lifetime in a 30-m^3 room containing 30 m^2 of chlorinated paraffins-treated fabric and the room is assumed to have a air-change rate of 0.25/hr. It is also assumed that 50% of the chlorinated paraffins present in 25% of the surface area of the treated fabric is released over 15 yr and 1% of released particles are small enough to be inhaled.

Particle exposure was estimated using Equations 4 and 5 in Chapter 3. The subcommittee estimated an upholstery application rate (S_a) for chlorinated paraffins of 3 mg/cm^2. The release rate (μ_r) for chlorinated paraffins from upholstery fabric was estimated to be 2.3×10^{-7}/d (see Chapter 3, Equation 5)

yielding a room airborne particle concentration (C_p) of 1.1 µg/m^3 and a short time-average exposure concentration of 0.28 µg/m^3. The time-averaged exposure concentration for particles was calculated using Equation 6 in Chapter 3.

In the absence of relevant inhalation exposure data, the subcommittee chose to estimate inhalation RfCs from oral RfDs The subcommittee, however, recognizes that it is not an ideal approach and also recognizes that the estimated RfC levels might be considerably different than actual levels (if inhalation data were available). Extrapolating from one route of exposure (oral) to another (inhalation) requires specific knowledge about the uptake kinetics into the body by each exposure route, including potential binding to cellular sites. The subcommittee believes that its extrapolation of oral RfDs to inhalation RfCs is highly conservative; it assumes that all of the inhaled compound is deposited in the respiratory tract and completely absorbed into the blood. The NRC Committee on Toxicology (NRC 1985) has used this approach when inhalation exposure data were insufficient to derive inhalation exposure levels. The subcommittee believes that such an approach is justified for conservatively estimating the toxicological risk from exposure to this FR. The RfC should be used as interim or provisional levels until relevant data become available for the derivation of inhalation RfC.

To calculate a hazard index for the inhalation route, a provisional inhalation RfC of 1.05 mg/m^3 was derived using the oral RfD for $C_{22–26}$, 70% chlorine (see the following section for the derivation of the oral RfD) and Equation 7 in Chapter 3.

Division of the time-average exposure concentration of 0.28 µg/m^3 by the provisional RfC for chlorinated paraffins of 1.05 mg/m^3 yields a hazard index of 2.7×10^{-4}. This suggests that under the subcommittee's worst-case exposure assumptions, Chlorinated paraffins would not be considered to be a toxic risk by the inhalation route of exposure.

Vapors

Volatility data for chlorinated paraffins were not located. Therefore, the subcommittee did not calculate worst-case exposure estimates for this exposure.

Oral Exposure

The assessment of noncancer toxicological risk for oral exposure to chlorinated paraffins is based on the oral exposure scenario described in Chapter 3.

This scenario assumes a child is exposed to chlorinated paraffins by sucking on 50 cm^2 of fabric backcoated with chlorinated paraffins, 1 hr/d for two yr. The subcommittee estimated an upholstery application rate (S_a) for chlorinated paraffins of 3 mg/cm^2. Oral exposure was calculated using Equation 15 in Chapter 3. The extraction rate (μ_w) for chlorinated paraffins was estimated to be 0.025 based on extraction data for hexabromocyclododecane in polyester fiber (McIntyre et al. 1995). The release rate from the fiber for estimating extraction was 0.04/d at 28°C calculated using the equation $2d/2\ \pi R$ (d=film thickness, R=fiber radius) with a correction from fiber to film of a factor of 0.63.

The worst-case average oral daily dose for chlorinated paraffins was estimated to be 0.16 mg/kg-d. Division of the dose estimate by the oral RfD for chlorinated paraffins of 0.3 mg/kg-d gives a hazard index of 0.053. This suggests that under the subcommittee's worst-case exposure assumptions, chlorinated paraffins do not pose a noncancer toxicological risk when incorporated into residential furniture upholstery at the estimated application levels.

Cancer

Dermal Exposure

There are inadequate data for assessing the carcinogenicity of chlorinated paraffins when exposure occurs by the dermal route of exposure.

Inhalation Exposure

There are inadequate data for assessing the carcinogenicity of chlorinated paraffins when exposure occurs by inhalation.

Oral Exposure

EPA has concluded that long-chain chlorinated paraffins should not be classified as potential carcinogens (EPA 1994). This conclusion is based on limited evidence for the carcinogenicity of the long-chain chlorinated paraffin, $C_{22–26}$, 43% chlorine, in rodents and the fact that cancer data are not available for long-chain chlorinated paraffin, 70% chlorine. It is the opinion of the subcommittee that long-chain chlorinated paraffins are not likely to be human carcinogens and derivation of a cancer potency factor for this class of chlorinated paraffins is

not warranted (see Cancer in Quantitative Toxicity Assessment for conclusions regarding short- and medium-chain chlorinated paraffins).

RECOMMENDATIONS FROM OTHER ORGANIZATIONS

The subcommittee is not aware of any exposure limits recommended by the regulatory agencies or other organizations.

DATA GAPS AND RESEARCH NEEDS

Chronic toxicity data are not available for $C_{22–26,}$ 70% chlorine, for any route of exposure. Properly conducted reproductive/developmental studies on chlorinated paraffins are not available. Human dermal absorption data for chlorinated paraffins are not available either. Information on the teachability of long-chain chlorinated paraffins from latex or other types of backcoating following exposure to simulated human secretions (saliva, sweat) is also needed. The volatility of $C_{22–26}$, 70% chlorine, is also not reported in the literature.

Based on a dermal hazard index greater than one, the dermal absorption of chlorinated paraffins from treated fabric should be investigated.

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