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Provisional Peer-Reviewed Toxicity Values for

White Mineral Oil

(CASRN 8012-95-1 and 8020-83-5)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Commonly Used Abbreviations

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR WHITE MINERAL OIL (CASRN 8012-95-1 AND 8020-83-5)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. U.S. EPA's Integrated Risk Information System (IRIS).
2. Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3. Other (peer-reviewed) toxicity values, including:
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore,

users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Food-grade and medicinal-grade mineral oils are pure (aromatic-free) mixtures of highly refined paraffinic and naphthenic petroleum hydrocarbons. Mineral oil formulations are often designated by their content (P for paraffinic, N for naphthenic), viscosity (reported in mm^2/sec at 40ºC), and whether the mixture was hydrotreated (H indicating catalytic hydrogenation). Thus, a mixture designated as P15H is a hydrotreated paraffinic mineral oil with a viscosity of 15 mm^2/sec (WHO, 2003). Mineral oils of lower molecular weight (<480) and carbon range are most pertinent to the C9–C32 petroleum fraction. Among the mineral oils that have been studied for toxicity in laboratory animals, the most relevant mixtures are: N10A, N15H, P15H, N70A, N70H, P15H, Marcol 72, Marcol 82, and EZL 600. Paraffinic waxes, which are related mixtures, include many compounds outside the carbon range of interest (e.g., C>32) for this petroleum fraction and, thus, were not considered in this review.

No chronic or subchronic RfDs or RfCs or cancer assessment for mineral oil are available on IRIS (U.S. EPA, 2009), the Drinking Water Standards and Health Advisory list (U.S. EPA, 2006) or in the HEAST (U.S. EPA, 1997). No documents for mineral oil are listed in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA 1991, 1994). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value-time-weighted average (TLV-TWA) of 0.2 mg/m^3 for mineral oil used in metal working and a TLV-TWA of 5 mg/m^3 for pure, highly and severely refined mineral oil; the critical effects are given as lower respiratory tract irritation and pulmonary function (ACGIH, 2007). The National Institute of Occupational Safety and Health (NIOSH) recommended exposure limit (REL) for mineral oil mists is 5 mg/m^3 to protect against respiratory effects (NIOSH, 2008). The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) is also 5 mg/m^3 (OSHA, 2008). Neither ATSDR nor the International Agency for Research on Cancer (IARC) has published documents on mineral oil toxicity or carcinogenicity (ATSDR, 2007; IARC, 2008). The National Toxicology Program (NTP, 2008) has not performed toxicity or carcinogenicity assessments for mineral oil, and this compound is not on the 11^{th} Report on Carcinogens (NTP, 2005). The World Health Organization (WHO, 2003) has published a review of food-grade mineral oils and paraffin

waxes, which was reviewed for pertinent information. In addition, reviews of mineral oil toxicity published by the Massachusetts Department of Environmental Protection (MADEP, 2003) and the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG, 1997) were consulted.

To identify toxicological information pertinent to the derivation of provisional toxicity values for mineral oil, update literature searches (January 2002-August 2009) of the following databases: MEDLINE, TOXLINE, BIOSIS, TSCATS, CCRIS, GENETOX, DART/ETIC, HSDB, and Current Contents were conducted to August, 2009, to identify studies published since the MADEP (2003) review.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure

Oral mineral oil has long been used therapeutically in humans to treat constipation. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHN) suggests a maintenance dose of 1–3 mL/kg-day for oral use of mineral oil to treat constipation in children older than 1 year of age (NASPGHN, 2006); this is roughly equivalent to a dose of 870–2600 mg/kg-day[1]. In their guidelines for treatment of constipation, NASPGHN (2006) reported that long-term studies support the safety and efficacy of mineral oil use; the only study cited, however, was Clark et al. (1987) (reviewed below). The NASPGHN (2006) also noted that, while mineral oil could theoretically interfere with absorption of fat-soluble vitamins, there was no evidence in the literature to support this hypothesis.

Clark et al. (1987) evaluated serum levels of ß-carotene, retinol and α-tocopherol before and after 4 months of mineral oil treatment in 25 children (2–14 years of age, mean age 7.8 years) diagnosed with chronic constipation. Neither the composition nor the physical/chemical parameters of the mineral oil were reported. Mean mineral oil doses administered to the children were 4.0, 2.9, 2.1, and 1.4 mL/kg-day (approximately 3500, 2500, 1800, and 1200 mg/kg-day; with an average dose of 2250 mg/kg-day) for Months 1, 2, 3, and 4, respectively. Treatment was administered between meals to reduce the possibility of interference with vitamin absorption. Serum vitamin levels were measured monthly during treatment. Serum levels of α-tocopherol were not affected by treatment. A significant increase in serum retinol levels (50%, higher than basal levels, $p < 0.01$) was observed at Month 3 only; at other time points, retinol levels were higher with treatment, but not significantly different from basal levels. Serum levels of ß-carotene fell 30% after 1 month of treatment and remained lower (36–54%) throughout the treatment period, although the difference was statistically distinguishable from controls ($p < 0.05$) only during Months 1–3 and not during Month 4. In

[1]Dose conversions have been undertaken and presented throughout this section of the document to characterize the equivalency between mg/kg-day and mL/kg-day for the reader using the following calculations. The specific gravity of white mineral oil is 0.83–0.905; HSDB (2007). Using the midpoint of the range (0.87) and the density of water (1000 mg/mL), a dose of 1 mL/kg-day is calculated to deliver 870 mg/kg-day (1 mL/kg-day × 0.87 × 1000 mg/mL), and a dose of 3 mL/kg-day is calculated to deliver 2600 mg/kg-day (3 mL/kg-day × 0.87 × 1000 mg/mL).

their discussion, the authors cited an earlier study of 19 children treated with mineral oil for up to 6 years with no effect on prothrombin time or serum retinol or α-tocopherol levels (Ballantine et al., 1986, as cited in Clark et al., 1987), although true baseline (pretreatment) measurements were not included in the study. In other studies cited by the authors, fecal carotene excretion was markedly increased in five adults treated with mineral oil for 5 months (Mahle and Patton, 1947, as cited in Clark et al., 1987), and visual dark adaptation (a measure of retinol deficiency) was not affected in 28 patients (age not specified) treated with 5 mL/kg-day (about 4350 mg/kg-day) mineral oil for 131 days (Isaacs et al., 1940, as cited in Clark et al., 1987).

Speridião et al. (2003) evaluated anthropometric parameters in 25 children (ages 2–12 years) treated with mineral oil and increased dietary fiber (for chronic constipation) for up to 90 days. Chronic constipation is associated with anorexia, so anthropometric parameters, together with food intake diaries, were used to assess improvement in nutritional status associated with treatment. The composition and physical/chemical parameters of the mineral oil were not reported. The median mineral oil dose was 1.0 mL/kg-day (about 870 mg/kg-day). In 16 patients who completed the treatment, height, weight, and midarm muscle area were unchanged, while triceps skinfold thickness and midarm circumference were significantly increased. No other effects of mineral oil treatment were discussed.

In a prospective study comparing mineral oil with lactulose (a synthetic disaccharide compound used in the treatment of constipation) in the treatment of chronic constipation, Urganci et al. (2005) treated 20 children (2–12 years old, average age, 3.8 years) with mineral oil for 8 weeks in conjunction with instructions for behavioral modification and increased fiber intake. No information was provided on the composition or physical/chemical parameters of the mineral oil. The mineral oil dose was initiated at 1 mL/kg-day and modified by the patients' parents to achieve improvement in the symptoms; the mean effective dose was 1.88 mL/kg-day (about 1600 mg/kg-day). Mineral oil treatment was judged to be superior to lactulose based on compliance and symptom control. Compliance with mineral oil treatment was very high (95% during Weeks 1–4 and 90% during the final 4 weeks), affected only by taste aversion in 1/20 and watery stools in 2/20 patients. The authors reported that families considered any side effects minor and acceptable.

Gal-Ezer and Shaoul (2006) presented a case report of a 17-year old girl whose doctor had prescribed treatment with 25 mL mineral oil twice daily for chronic constipation. The mineral oil composition and physical/chemical parameters were not given. Without her doctor's input, the patient had increased the dose to 400 mL daily (348,000 mg/kg-day) and continued this treatment for at least 5 months before her follow-up visit. A physical examination at the time of follow-up revealed no abnormalities. Serum levels of fat-soluble vitamins (A and E), as well as calcium, phosphorus, alkaline phosphatase (ALP) (as measures of vitamin D status) and prothrombin time (as a measure of vitamin K status) were measured as a precaution. All levels were within normal limits.

Inhalation Exposure

Studies of inhalation exposure to mineral oil are limited to analyses of the effects of mineral oil mists. These studies are typically of workers exposed to mineral oil aerosols generated from metalworking operations. It is unlikely that environmental releases of petroleum hydrocarbons will result in the formation of aerosols of hydrocarbons in the C9–C32 range. Thus, studies of mineral oil mists were not included in this review.

Lipoid pneumonia can occur when mineral oil is aspirated into the lungs during oral therapeutic use (NASPGHN, 2006); however, this route of exposure is not likely to occur under environmental exposure conditions.

Animal Studies

Oral Exposure

Subchronic Studies—In a subchronic feeding study, Baldwin et al. (1992) administered two food grade white oils to F344 rats for 90 days at dietary concentrations of 0, 10, 100, 500, 5000, 10,000, or 20,000 ppm. The test materials were oleum-treated white oil (OTWO) and hydro-treated white oil (HTWO); both of which were derived from naphthenic crudes. OTWO had a specific gravity of 0.874 at 15ºC and a viscosity of 26 mm^2/sec at 40ºC; HTWO had a specific gravity of 0.878 at 15ºC and a viscosity of 69 mm^2/sec at 40ºC. Neither the average molecular weight nor the carbon range of the materials was reported. The oils were dissolved in "DISTOL"-grade hexane for diet preparation; this solvent was also incorporated into the control diet (fed to groups of 20 rats/sex). Only two experiments were conducted; the first used only the three highest concentrations and groups of 10 male and 10 female rats per concentration, while the second used the entire range reported above and 10 female rats per concentration. The rats were given the diet ad libitum for 13 weeks; ranges of intakes were estimated by the authors and are reported below in Table 1.

Table 1. Estimated Dose Ranges for White Oil Intake[a]

Test Material	Dietary concentration (ppm)	Experiment 1		Experiment 2
		Male Dose Range (mg/kg-day)	Female Dose Range (mg/kg-day)	Female Dose Range (mg/kg-day)
OTWO	10	-	-	0.65–1.2
	100	-	-	6.5–12.2
	500	-	-	33.5–58.2
	5000	245–455	298–482	337–594
	10,000	490–852	595–979	661–1163
	20,000	1039–1812	1214–1920	1336–2321
HTWO	10	-	-	0.66–1.2
	100	-	-	6.4–11.5
	500	-	-	32.5–57.6
	5000	244–441	294–481	320–576
	10,000	506–894	592–975	664–1213
	20,000	1009–1744	1216–1927	1327–2225

[a]Baldwin et al., 1992

Clinical observations were made daily, while body weight and food intake were recorded weekly (Baldwin et al., 1992). Experiment 1 included hematology (packed cell volume, erythrocyte count [RBC], total leukocyte count [WBC], platelet count, hemoglobin concentration [Hb], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], and erythrocyte and platelet volume distribution width) and clinical chemistry analyses (glucose, total protein, blood urea nitrogen [BUN], calcium, phosphate, electrolytes, total cholesterol, triglycerides, total bilirubin, creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma glutamyl transferase [GGT], and lactate dehydrogenase [LDH]) on blood samples collected at sacrifice.

Necropsy procedures differed between the two experiments (Baldwin et al., 1992). In the first experiment, all animals were examined grossly, and brain, heart, liver, kidneys, spleen, and testes were weighed. Histopathology examinations were made on a comprehensive list of tissues (not specified) from control and 20,000-ppm animals, as well as on the lung, liver, kidneys, spleen, and mesenteric lymph nodes of 5000- and 10,000-ppm animals. Tissue analysis for hydrocarbons was performed on 5 animals in the control and 20,000-ppm groups; it is not clear whether these animals were from the initial group of 10 or were maintained as a satellite group. In the second experiment, 5 rats from the 500- and 10,000-ppm groups were sacrificed after 25 days, and all other animals were sacrificed after 13 weeks. Liver and spleen were weighed, and these organs, together with the mesenteric lymph nodes, were subjected to microscopic examination.

All rats survived the treatment, and there were no clinical signs of toxicity (Baldwin et al., 1992). A statistically significant increase (data and magnitude not reported; $p \leq 0.05$ compared with controls) in food intake was noted during Weeks 3–6 in males exposed to 20,000-ppm OTWO; there were no other effects on food intake. The authors did not discuss results of body weight measurements nor were data on this endpoint provided. Increases in the numbers of leukocytes and granulocytes (data not given) were noted in high-dose (20,000 ppm) rats of both sexes and with both test materials; in addition, females given this concentration of OTWO were reported to have hypochromic microcytic anemia (data not shown; characterized by the study authors as "slight"). Statistically significant changes in several clinical chemistry parameters were observed in female rats exposed to ≥5000 ppm of both oils, with more pronounced effects occurring with exposure to OTWO than with HTWO. A few changes were observed in males, but they were far more limited. The observed changes in females (increased bilirubin, ALT, and AST, and >4-fold increased GGT) are suggestive of a potential cholestatic effect in the liver, while the changes observed in males are of uncertain significance. Table 2 shows the statistically significant clinical chemistry changes in both sexes; these data were collected during Experiment 1, as clinical chemistry was not evaluated during Experiment 2.

Table 2. Selected Clinical Chemistry Changes in Rats Fed Mineral Oils in the Diet for 90 Days[a]

Parameter	Control	OTWO (ppm)			HTWO (ppm)		
		5000	10,000	20,000	5000	10,000	20,000
Males							
ALP (IU/L)	386	353	350[b]	334[c]	373	375	366
Triglycerides (mmol/L)	1.29	1.05	0.77[c]	0.84[c]	1.12	1.12	0.74[c]
ß Globulin (g/L)	19	21	21	22[b]	21	20	21
Females							
Bilirubin (µmol/L)	3.50	3.40	3.80	4.30[b]	3.40	3.70	3.70
ALT (IU/L)	59.00	82.60	99.30[c]	96.70[c]	91.30[b]	84.00	92.20[b]
AST (IU/L)	120.00	148.00	175.00	180.00[b]	164.00	152.00	160.00
GGT (IU/L	0.40	0.60	1.80[b]	2.10[b]	0.20	0.40	0.80
Cholesterol (mmol/L)	2.31	2.08[b]	2.15	2.11	2.24	2.32	2.04[c]
Triglycerides (mmol/L)	0.74	0.57	0.35[c]	0.34[c]	0.57	0.56	0.44[c]
Albumin (g/L)	58.00	52.00[c]	51.00[c]	47.00[c]	54.00	53.00[a]	53.00[b]
ß Globulin (g/L)	18.00	24.00[c]	25.00[c]	28.00[c]	21.00[b]	21.00[a]	23.00[c]
A:G	1.37	1.08[c]	1.07[c]	0.94[c]	1.22	1.17[a]	1.15[c]
Glucose (mmol/L)	2.60	2.90[b]	2.80	3.00[c]	2.70	2.70	2.70

[a]Baldwin et al., 1992; data from Experiment 1
[b]Significantly different from control, $p \leq 0.05$
[c]$p \leq 0.01$

Significant ($p \leq 0.05$) increases in absolute liver and spleen weight were observed in male rats treated with ≥10,000-ppm OTWO and in female rats treated with ≥5000 ppm of either oil (although liver weights were not increased at these concentrations in Experiment 2) (Baldwin et al., 1992). Liver-weight increases ranged up to 34% higher than controls in female rats, while spleen weights were increased by up to 80% or more. In addition, absolute kidney weights were significantly increased (8%) in female rats exposed to ≥10,000-ppm OTWO but not in those exposed to HTWO. Neither body weight data nor organ weights adjusted for body weight were reported, so it is difficult to interpret the importance of the reported changes in absolute organ weights. The authors reported enlarged mesenteric lymph nodes in females at all dose levels and in males fed ≥5000-ppm OTWO, but weights were not reported. Table 3 shows the statistically significant organ weight changes. Analysis of tissues for hydrocarbon residues indicated that tissue levels were ~4- to 5-fold higher in females than in males, regardless of the test material. The concentrations of total hydrocarbon residues in the liver and mesenteric lymph nodes of female rats averaged 11.5 and 6.55 mg/g (respectively) for OTWO and 9.2 and 4.22 (respectively) for HTWO. In contrast, the concentrations in the liver and mesenteric lymph nodes of male rats averaged 2.36 and 1.76 mg/g (respectively) for OTWO and 1.76 and <1.0 (respectively) for HTWO. Hydrocarbon residues were not detected in control animal tissues.

Table 3. Selected Changes in Mean Absolute Organ Weight (g) in Rats Fed Mineral Oils for 90 Days[a]

Parameter	Control	OTWO (ppm)			HTWO (ppm)		
		5000	10,000	20,000	5000	10,000	20,000
Males							
Liver, Experiment 1	11.36	11.60	12.42[b]	12.23[b]	12.04	11.86	11.29
Spleen, Experiment 1	0.68	0.74	0.80[b]	0.83[b]	0.77[c]	0.72	0.74
Females							
Liver, Experiment 1	6.19	7.60[b]	8.21[b]	8.79[b]	6.70[c]	7.09[b]	7.10[b]
Liver, Experiment 2	6.11	7.42[b]	8.19[b]	7.84[b]	6.43	6.75	6.62
Spleen, Experiment 1	0.44	0.72[b]	0.81[b]	0.89[b]	0.52[b]	0.53[b]	0.63[b]
Spleen, Experiment 2	0.45	0.64[b]	0.77[b]	0.81[b]	0.48	0.52[c]	0.55[b]
Kidney, Experiment 1	1.26	1.31	1.36[b]	1.35[b]	1.25	1.28	1.26

[a]Baldwin et al., 1992
[b]$p \leq 0.01$
[c]Significantly different from control, $p \leq 0.05$

The authors reported all of the histopathology findings qualitatively; no incidences were reported (Baldwin et al., 1992). Histopathological findings included macrophage aggregates and syncytia in the mesenteric lymph nodes of all groups, including controls, with greater numbers in the treated rats. The lymph nodes of treated rats also contained granulomatous foci at dietary concentrations of ≥5000 ppm in males and females exposed to HTWO and in males exposed to OTWO; these findings were observed at concentrations as low as 100 ppm in females exposed to OTWO. Microgranulomas and granulomas were observed in the livers of treated rats; the lesions ranged from clusters of macrophages, lymphocytes, epithelioid cells, and fibroblasts to granulomas with areas of necrosis and hepatocellular degeneration and inflammation in the surrounding parenchyma. Accompanying changes included slight-to-moderate Kupffer cell hypertrophy, vacuolation, and pigmentation. These hepatic lesions were observed at concentrations of ≥10,000 ppm in males exposed to OTWO (no lesions were observed in males exposed to HTWO) and in females at concentrations ≥100-ppm OTWO or ≥500-ppm HTWO. In the spleen, chronic capsular splenitis was observed in males exposed to ≥5000 ppm of either oil and in females exposed to 20,000-ppm OTWO; however, the authors expressed uncertainty as to the relationship of this effect to treatment. Extramedullary hemopoiesis was observed in the spleens of females exposed to ≥5000 ppm of either oil.

This study identifies a LOAEL of 100 ppm (6.5–12.2 mg/kg-day) for OTWO based on liver granulomas in female rats, with a NOAEL of 10 ppm (0.65–1.2 mg/kg-day) (Baldwin et al., 1992). The LOAEL for HTWO is 500 ppm (32.5–57.6 mg/kg-day), also based on liver granulomas in female rats; the NOAEL is 100 ppm (6.4–11.5 mg/kg-day). Although the authors noted increased incidences of macrophage aggregates and syncytia in the lymph nodes of all treated rats, these changes are not biologically significant. In an assessment of the lymph node lesions reported in several studies of mineral oils and waxes, Carlton et al. (2001) concluded that the lymph node changes (variously termed microgranulomas, histiocytosis, and reticuloendothelial-cell hyperplasia) did not appear to have biological significance in the rat, as these changes have been observed in control F344 populations and have not been linked to adverse effects. Fleming et al. (1998) characterized these changes as focal accumulations of vacuolated macrophages, with no evidence of inflammation or cell damage. Further,

WHO (2003) noted that, in long-term studies of higher molecular weight mineral oils, these lymph node changes did not progress to more severe effects; thus, WHO (2003) considered the lesions to be markers of exposure rather than markers of effect.

Smith et al. (1995) published the results of a subchronic toxicity study of four white mineral oils in beagle dogs and Long-Evans rats that was conducted in 1977 but had not previously been published. The properties of the mineral oils (Marcol 72, Marcol 82, EZL 550, and EZL 600) are shown in Table 4; average molecular weight was not reported. The oils were all derived from paraffinic crude oil; no other information on their composition was reported. Groups of 4 dogs/sex/dose were fed the test materials in the diet at concentrations of 0, 300, or 1500 ppm for 13 weeks. Daily observations for clinical toxicity were made, and food intake was measured daily. Body weights were recorded weekly at the time of physical examination and palpation for masses. Ophthalmoscopic examinations were administered before and at the conclusion of exposure. Hematology (Hb, Hct, RBC, erythrocyte morphology, total and differential WBC count, and clotting time), clinical chemistry (ALT, ALP, BUN, creatinine, glucose, total protein, albumin, globulin, and albumin/globulin ratio) and urinalysis (gross appearance, protein, glucose, pH, specific gravity, ketones, bilirubin, and occult blood) were evaluated after 1 month and at the end of exposure; in addition, serum levels of vitamins A and D_3 were measured in control and high-dose dogs at study termination. Upon sacrifice, all animals were necropsied and organ weights (adrenals, brain, kidneys, liver, ovaries/testes, pituitary, and thyroid) determined. Major organs (not specified) of control and high-dose animals were evaluated for histopathology, along with identified target organs in intermediate dose groups.

Table 4. Properties of Test Materials[a]

Property	Marcol 72	Marcol 82	EZL 550	EZL 600
Purification process	Acid treatment	Hydrogenation	Hydrogenation	Hydrogenation
Viscosity @ 40ºC (centistokes)	12.3	13.8	65.9	31.6
Density at 15ºC (g/m^3)	0.838	0.842	0.864	0.854
Average carbon distribution	C14–C38	C16–C34	C23–C44	C20–C36

[a]Smith et al., 1995

The authors indicated a mild laxative effect of all of the test materials, with occasional diarrhea and mucoidal and mucohemorrhagic discharge (Smith et al., 1995). In addition, the frequency of vomiting was reported to be increased relative to controls in the treated dogs. Data on the frequencies of these observations were not reported, nor were the doses at which the incidences of these effects were increased over controls. No treatment-related effects on body weight or food consumption were reported. Based on dietary intake and body weight measurements, the authors estimated doses of 10 and 50 mg/kg-day in male dogs and 10 and 52 mg/kg-day in female dogs. The authors reported that there were no treatment-related effects on hematology, clinical chemistry, urine parameters, or serum levels of vitamins A or D_3. Among these evaluations, the only data reported were erythrocyte and leukocyte counts, which confirmed the lack of a clear effect on these endpoints. Similarly, there were no effects of treatment on gross necropsy findings, organ weights or histopathology findings in any organ evaluated. Data shown in the report included only relative liver and gonad weight, which were

not affected by treatment. Examination of the liver, mesenteric lymph nodes, gastrointestinal tract, and kidneys for oil deposition did not reveal any significant deposition.

It is not possible to clearly assign effect levels from the data in beagles. While the authors reported mild laxative effects and increased frequency of vomiting in the treated animals, these effects were also reported in control animals and the change relative to controls is unclear, given the lack of data on incidence or frequency. No other effects were observed in the treated beagles.

In the rat study, groups of 20 rats/sex/dose were fed the test materials at the same dietary concentrations (0, 300, or 1500 ppm) for 13 weeks (Smith et al., 1995). Toxicological parameters evaluated were the same as for dogs with a few differences. Food intake was measured weekly in rats. Hematology analysis included reticulocyte count and prothrombin time and was performed on one-half of the rats at 1 month; hematology, clinical chemistry (including AST) and urinalysis were also evaluated on all rats at study termination. Serum levels of vitamins were not assessed. Finally, in rats, the liver, mesenteric lymph nodes and spleen of control and high-dose animals exposed to Marcol 72, Marcol 82, and EZL 550 were re-examined in 1990 in response to another study that identified effects in these organs in F344 rats (Baldwin et al., 1992).

According to the authors, treatment did not affect survival, physical appearance, behavior, clinical signs, ophthalmology, body weight or food consumption in rats; data on these endpoints were not reported (Smith et al., 1995). Using food intake and body weight measurements, the authors estimated average doses of 21 and 108 mg/kg-day in males and 25 and 125 mg/kg-day in females. There was a significant ($p \leq 0.05$) increase (48% over controls) in total leukocyte count in female rats treated with the high dose of EZL 550 and decreases (7%) in total erythrocyte counts in female rats treated with both doses of EZL 600. Review of the data on clotting time indicated changes (both increases and decreases) that did not show an obvious pattern; these changes were not considered biologically significant by the researchers. The authors indicated that there were no treatment-related differences in any organ weights or histopathological findings (data not shown). Special staining of the liver, mesenteric lymph nodes, gastrointestinal tract, and kidney for oil deposition did not indicate significant deposition. In addition, the histopathology re-evaluation of the liver, mesenteric lymph nodes and spleen confirmed the lack of findings in these organs.

This study identified a freestanding NOAEL in Long-Evans rats of 108 or 125 mg/kg-day (in males and females, respectively) for each of the test materials. The limited hematology findings are not considered biologically significant in the absence of toxicological correlates.

In an effort to evaluate strain differences in responses to orally-administered mineral oils, Firriolo et al. (1995) conducted subchronic studies of a low viscosity mineral oil (P15H; specific gravity of 0.851 at 15ºC and viscosity of 14.80 mm^2/sec at 40ºC) in female F344 and CRL:CD rats. No other information on the composition of the mixtures was reported. Dietary concentrations of 0, 0.2, and 2.0% by weight (w/w) were estimated by the authors to result in mean doses of 0, 161, and 1582 mg/kg-day in F344 rats and 0, 158, and 1624 mg/kg-day in CRL:CD rats. Groups of 10 female rats were fed the diets ad libitum for 92 days. Additional groups of 10 female F344 rats were sacrificed after 30 and 61 days of treatment at 0 or

2.0% P15H. Daily examination for clinical signs and mortality was performed, and body weight and food consumption were recorded weekly. Upon sacrifice, blood was collected for hematology (Hct, Hb, RBC, total and differential WBC count, platelet count, MCV, MCHC, and reticulocyte count) and clinical chemistry (albumin, BUN, calcium, creatinine, electrolytes, glucose, phosphorus, ALT, AST, ALP, GGT, total protein, total bilirubin, cholesterol, and triglycerides) analyses. All animals were necropsied, and the heart, kidneys, liver, ovaries, spleen, and mesenteric lymph nodes were weighed. Histopathology evaluation was restricted to the liver, mesenteric lymph nodes and any gross lesions but included all treatment groups. Hydrocarbon content of the liver, kidneys, spleen, and mesenteric lymph nodes was analyzed.

All rats survived to scheduled sacrifice, and there were no treatment-related effects on clinical signs, body weight or food intake in either strain (Firriolo et al., 1995). Hematology and clinical chemistry parameters were comparable to controls in CRL:CD rats. In contrast, F344 rats showed signs of leukocytosis (specifically, an increase in neutrophils as a percent of total leukocyte count) beginning at Day 30, with a statistically significant elevation of leukocyte count at Day 61 and evidence of a dose-response relationship after 92 days. After 92 days, neutrophils as a percent of total WBC were increased 71% ($p \leq 0.05$) over controls in rats exposed to 2% P15H; the increase was not statistically significant in the low-dose group. A few clinical chemistry parameters were also affected in F344 rats; GGT levels were increased over controls at both concentrations (69 and 35% for the 0.2 and 2.0% groups, respectively, $p \leq 0.05$), and triglycerides were significantly decreased in the 2.0% group (29%, $p \leq 0.05$). Other transient changes in clinical chemistry parameters were observed at 30 days but not at 61 or 92 days. The authors reported that the clinical chemistry changes were not toxicologically significant due to the small magnitude of change, lack of dose-response relationship and consistency with historical control ranges.

Absolute and relative liver weights were significantly increased at all sacrifice times in F344 rats exposed to 2% P15H (20 and 30% above controls for absolute and relative weight, respectively) and in the 0.2% group at study termination (10% increase in both parameters) (Firriolo et al., 1995). In addition, absolute and relative weights of mesenteric lymph nodes were significantly increased at all scheduled sacrifices in F344 rats in the 2% group (up to 3.7- to 3.8-fold higher than controls). Data were presented graphically. There were no treatment-related changes in organ weights in CRL:CD rats. Analysis of mineral hydrocarbon content in liver and mesenteric lymph nodes indicated greater deposition in F344 rats than in CRL:CD rats at the same exposure concentration, especially in the liver (2- to 3-fold higher). Levels of mineral hydrocarbons in the liver averaged 5586 and 8237 μg/g in F-344 rats exposed to 0.2 and 2% (respectively), compared with 1694 and 4069 μg/g in CRL:CD rats exposed to the same concentrations. In the mesenteric lymph nodes, levels of mineral hydrocarbons were similar in the two strains of rat (1204 and 1543 μg/g in F-344 rats exposed to 0.2 and 2%, respectively, compared with 886 and 1408 μg/g in CRL:CD rats).

Histologic changes in the liver, consisting of microgranulomas, were noted at study termination in the F344 rats exposed to 0.2% P15H and at Days 61 and 93 in the F344 rats exposed to 2% (Firriolo et al., 1995). The incidence of microgranulomas at study termination was 45 and 95% in the 0.2 and 2% exposure groups, respectively; incidence in the controls was not reported. In CRL:CD rats, an increase in minimal multifocal chronic inflammation (incidence not reported) was observed at study termination in the 2% group; no microgranulomas

were observed in any rats of this strain. Histiocytosis of the mesenteric lymph nodes was noted at Day 30 in the 2% group of F344 rats. This effect progressed to discrete microgranuloma formation over the course of the study. All F344 rats sacrificed on Day 61 had microgranulomas in the mesenteric lymph nodes, and the incidence at study termination was 80 and 90% in the 0.2% and 2% exposure groups. This lesion was not observed in CRL:CD rats at either concentration. This study identified a LOAEL of 161 mg/kg-day in F344 rats based on microgranuloma formation in the liver (no NOAEL can be identified) and a LOAEL of 1624 mg/kg-day and NOAEL of 158 mg/kg-day in CRL:CD rats, based on an increase in multifocal chronic inflammation of the liver. As noted above, histiocytosis of the lymph nodes is not considered adverse (Fleming et al., 1998; Carlton et al., 2001; WHO, 2003).

Smith et al. (1996) administered seven highly refined white mineral oils in the diet to F344 rats in two separate studies (six mineral oil samples [N10A, N15H, P15H, N70A, N70H, P100H] in Study 1 and one [P70H] in Study 2). Purity of the test materials was not reported. Table 5 shows the composition of the mineral oils and the study design. The basic study design involved groups of 20/sex/dose given doses of 20-, 200-, 2000- or 20,000-ppm mineral oils for 90 days and then sacrificed, with a separate group of five/sex at the high dose evaluated for accumulation of hydrocarbons in tissues. In the first study, an additional 10/sex/dose were treated for 90 days and then followed for 28 untreated days. Daily observations were made for clinical signs of toxicity, while body weights and food consumption were recorded twice weekly. Ophthalmological examinations were conducted on control- and high-dose animals before study commencement and at the end of the exposure period. At necropsy, hematology (MCV, RBC, total and differential WBC count, platelet count, reticulocyte count, hematocrit [Hct], Hb, and prothrombin time) and serum chemistry (albumin, albumin/globulin ratio, total bilirubin, creatinine, electrolytes, ALT, AST, ALP, GGT, glucose, total protein, urea, and vitamin E [Study 1 only]) were assessed. Selected organs (adrenals, brain, cecum, heart, kidneys, liver, ovaries/testes, spleen, and thymus, as well as mesenteric lymph nodes in the tissue group of the first study) were weighed. Comprehensive histopathology examinations were made on the control- and high-dose groups, as well as microscopic examination of the lung, liver, kidneys, mesenteric lymph nodes, spleen, and small intestine of all other groups.

Table 5. Test Material Descriptions and Study Number[a]

Sample	Crude Type	Average MW	Carbon Range	Study
N10A	Naphthenic	320	15–30	1
N15H	Naphthenic	330	17–30	1
P15H	Paraffinic	350	18–30	1
N70A	Naphthenic	410	21–35	1
N70H	Naphthenic	420	22–37	1
P70H	Paraffinic	485	27–43	2
P100H	Paraffinic	510	28–45	1

[a]Smith et al., 1996

There were no treatment-related effects on clinical signs, body weight, or ophthalmology (Smith et al., 1996). The authors reported that occasional statistically significant differences in body weight did not reach 10% change from control and were neither dose-related nor consistent over time (data not shown). Food consumption was increased in the highest-dose group; this was attributed to compensation for the caloric loss resulting from substitution of mineral oils for food. Based on food consumption and body weights, the authors estimated daily intakes of test material to be 1.7, 17, 173, and 1815 mg/kg-day in males and 2.0, 19, 190, and 1951 mg/kg-day in females. Decreased erythrocyte counts (reduced by 2 to 4%, $p \leq 0.05$), Hb, and Hct (data not shown) were noted in female rats given ≥2000-ppm N10A or P15H or 20,000-ppm N15H, N70A, or N70H. Significant ($p \leq 0.05$) increases in total leukocyte counts (20–25%, usually neutrophils and monocytes) were recorded in females treated with the 20,000-ppm N10A, N15H, or P15H. Increases in leukocyte counts remained after the recovery period in females treated with 20,000-ppm N15H or P15H and were increased (for the first time) in females treated with P100H and allowed to recover. Increases in total leukocyte counts (+17 to 20%) were also observed in males treated with 20,000-ppm N15H or P15H. No other hematological effects were noted in the animals treated with mineral oils.

No treatment-related effects on clinical chemistry were reported in male rats (Smith et al., 1996). In females treated with 20,000-ppm N10A, N15H, P15H, P70H, or P100H, there were treatment-related increases in ALT, AST, and GGT. Increases in ALT and AST were generally small (10–20%), while 1.75–3 fold increases (relative to control) in GGT were seen with N10A, N15H, and P15H. The authors reported that other statistically significant clinical chemistry changes (on ALP, serum glucose, albumin, and albumin/globulin ratio and total protein) were smaller in magnitude and not dose-related (data not shown but discussed in text). Measurement of vitamin E levels in the first study showed that treatment with N10A, N15H, or P15H reduced vitamin E to 30% (in males) and 45% (in females) of control values, while the effects of N70A, N70H, and P100H were not as pronounced (40–50% of controls in females and 50–70% of controls in males).

Few data on organ weights were provided in the publication (Smith et al., 1996). The text indicated that dose-related increases in absolute and relative liver weights were observed in rats treated with ≥2000-ppm N10A, N15H, P15H, or N70A, with greater increases observed in females than in males. In females, significant ($p \leq 0.05$) increases in relative liver weight were also observed at 200 ppm of N15H, P15H, and N70A (data presented graphically). Increases in liver weight persisted in the recovery groups, although the magnitude of difference was usually less in these groups than in similarly-dosed animals evaluated at termination of exposure. In females treated with 20,000-ppm N10A, N15H, or P15H, absolute and relative weights of mesenteric lymph nodes were increased ($p \leq 0.05$) more than 2.5-fold over control values; these increases also persisted in the recovery groups, while increases appeared for the first time in the recovery groups treated with N70A or N70H. The authors indicated that there were similar changes in male rats but that the magnitude of change was smaller. Increases in absolute and relative spleen weight were observed in rats of both sexes treated with 20,000-ppm N10A, N15H, P15H, N70A, N70H, or P70H; the increases were larger in females (+5 to 15% based on data presented graphically) than in males (data not given) and remained after the recovery period in females only. Relative spleen weight was also increased in females at 2000-ppm P15H (data presented graphically). Small increases in absolute and relative kidney weights (4–10% greater than controls) were reported in males and females treated with 20,000-ppm N10A, N15H, or

P15H and in females treated with 20,000-ppm N70H. After the recovery period, there were no statistically significant differences from controls in kidney weight.

Histopathology evaluation did not indicate any effects of treatment with P70H or P100H (Smith et al., 1996). Treatment-related histopathological changes in the liver, consisting of granulomas and/or microgranulomas, were observed in female rats given 20,000 ppm of N10A, N15H, N70A, or N70H, as well as in the recovery group females given 20,000 ppm of P15H (but not in the main study group exposed to this mixture). Granulomas were described as focal collections of macrophages surrounded by inflammatory cells, occasional necrotic cells, and variable fibrosis, while microgranulomas were small collections of macrophages (three to five) with a few lymphocytes at the periphery. Granulomas and microgranulomas were observed most frequently in the portal area and caudal lobe. The incidence of these effects was not reported; rather, the authors reported mean severity score (see Table 6). After recovery, the severity of the granulomas/microgranulomas was somewhat reduced, but the incidence of effects was unchanged or increased. Focal collections of macrophages were also reported in the mesenteric lymph nodes (usually cortical region) in male and female rats treated with N10A, N15H, P15H, N70A, or N70H. The effects were described as histiocytosis, and a combined incidence/severity score was assigned to each treatment group (Table 6). The incidence of minimal-to-mild histiocytosis in control rats was 31–37%. Some attenuation of the histiocytosis was observed in the female recovery group treated with N10A, N15H, or P15H, while increases in effect were observed in recovery group males and females treated with N70A or N70H.

Effects of the mineral oils were inversely related to average molecular weight (Smith et al., 1996). The only significant effects reported for the two higher molecular weight oils (P70H and P100H) were 10 to 13% increases in ALT and AST, and increases in absolute and relative spleen weight (<10% increase in relative spleen weight based on data shown graphically). No other effects were observed with these test materials; thus, the highest dose tested (1815 mg/kg-day in males and 1951 mg/kg-day in females) is a freestanding NOAEL for these materials.

For the lower molecular weight oils, the high dose (1951 mg/kg-day) is a LOAEL in F344 rats based on granulomas and/or microgranulomas in the livers of female rats. As discussed above, the lesions observed in the mesenteric lymph nodes (microgranulomas or histiocytosis), although more frequent in all treated animals than in controls, are not considered adverse, but rather a marker of exposure (Fleming et al., 1998; Carlton et al., 2001; WHO, 2003). The NOAEL is 190 mg/kg-day.

Table 6. Mean Severity Scores for Histopathological Changes in Liver and Mesenteric Lymph Nodes[a]

		Males	Females	
	Dose (ppm)	Mesenteric Lymph Nodes[b]	Liver[c]	Mesenteric Lymph Nodes[b]
Control (Study 1)	0	7	0	27
Control-recovery (1)	0	31	3	37
Control (Study 2)	0	10	5	0
Control-recovery (2)	0	ND	ND	ND
N10A	20	5	0	45
	200	10	0	125[d]
	2000	170[d]	0	230[d]
	20,000	225[d]	115[d]	310[d]
N10-recovery	20,000	240[d]	80[d]	210[d]
N15H	20	20[d]	0	10
	200	55[d]	0	110[d]
	2000	125[d]	5	225[d]
	20,000	130[d]	120[d]	235[d]
N15H-recovery	20,000	140[d]	40[d]	110[d]
P15H	20	10	0	35
	200	45[d]	5	122[d]
	2000	120[d]	10	230[d]
	20,000	145[d]	30	189[d]
P15H-recovery	20,000	160[d]	80[d]	160[d]
N70A	20	10	0	35
	200	5	15	85[d]
	2000	75[d]	0	170[d]
	20,000	100[d]	15[d]	160[d]
N70A-recovery	20,000	250[d]	50[d]	200[d]
N70H	20	5	0	40
	200	5	0	85[d]
	2000	55[d]	0	95[d]
	20,000	25[d]	20[d]	65[d]
N70H-recovery	20,000	150[d]	80[d]	150[d]
P70H	20	10	0	5
	200	0	0	40
	2000	0	30	40
	20,000	0	0	0
P70H-recovery	20,000	ND	ND	ND
P100H	20	0	0	40
	200	0	0	30
	2000	5	0	15
	20,000	0	0	25
P100H-recovery	20,000	40	0	50

[a]Smith et al., 1996
[b]Mean severity score (1–4 for minimal-marked) multiplied by 100
[c]Mean severity score (1or 2 for microgranulomas and 3 or 4 for granulomas) multiplied by 100
[d]Statistically significant difference from controls ($p \leq 0.05$)

ND = no data.

In a recent study, Scotter et al. (2003) administered three white mineral oils (N15H, N70H, and P70H) to female F344 rats for 28 or 90 days at dietary concentrations of 0% or 2%. Groups of 12 animals per treatment time were used for controls and for each mineral oil. Daily examinations for signs of toxicity, as well as detailed weekly examinations were conducted. Body weights were measured twice weekly, and food intake was estimated for the intervening periods. Excreta (fecal and urinary) were collected from groups of four animals designated for tissue analysis of hydrocarbon content. At necropsy after either 28 or 90 days, blood samples were collected from the groups of four used for tissue analysis. All animals were necropsied, and organ weights (brain, heart, kidneys, liver, spleen, and mesenteric lymph nodes) were recorded. In groups of eight animals/dose/time designated for histopathology examination, mesenteric lymph nodes were also weighed; small intestine and muscle samples from the four animals designated for tissue analysis were weighed. In the histopathology groups, microscopic examinations of the brain, heart, kidneys, liver, mesenteric, and cervical lymph nodes, small intestine, and spleen were performed.

Exposure to the three mineral oils was associated with significantly higher food intake when compared with controls. Average intakes of the test materials were estimated by the authors to be 2518, 2650, and 2608 mg/kg-day in the 28-day study and 2049, 1994, and 2116 mg/kg-day in the 90-day study for N15H, N70H and P70H, respectively (Scotter et al., 2003). Treatment did not result in clinical signs of toxicity. The mean body weight was significantly increased over controls (+5%) in rats treated for 28 days with N15H; no other effects on body weight were observed. In the 28-day study, increases in absolute and relative liver weight, as well as an increase in the absolute weight of mesenteric lymph nodes, were noted in rats treated with N15H. In the 90-day study, treatment with N15H resulted in significant ($p \leq 0.0001$) increases in absolute[2] and relative liver weight (19 and 21% higher than controls for absolute and relative weight, respectively), proximal and distal mesenteric lymph node (2- to 6-fold higher) and spleen (27 and 31% higher) weights. Treatment with N70H resulted in significant ($p \leq 0.05$) increases in absolute and relative lymph node weight and absolute and relative spleen weight. Relative proximal and distal lymph node weight increases were 67 and 20% above controls, while relative spleen weight was increased by 12%. Absolute organ weights were not reported for this treatment group. No organ weight changes were observed with P70H treatment for 90 days.

Analysis of mineral hydrocarbon content in tissues showed detectable levels of the three mineral oils in the distal small intestine (0.72–2.87% w/w), proximal small intestine (0.01–0.14%), heart (0.08–0.37%), and kidney (0.98–2.62%). In addition, mineral hydrocarbons were detected in the distal and proximal mesenteric lymph nodes of animals exposed to N15H (0.21%) and N70H (0.03%) oils, respectively (Scotter et al., 2003).

Statistically significant increases in the incidences of histopathology findings were observed in animals treated with N15H and N70H, as shown in Table 7 (Scotter et al., 2003). Histiocytosis of the proximal lymph nodes was present after 28 days of treatment with N15H ($p \leq 0.01$); no other histopathology was evident at this sacrifice (Scotter et al., 2003). Histiocytosis of the proximal lymph nodes was also observed after 90 days of treatment with

[2]The text of the paper (Scotter et al., 2003) reported that absolute liver weight was significantly increased, but the table indicated that the difference was not statistically significant. A *t*-test conducted for this review indicated that the difference was significant ($p < 0.0001$).

N15H and N70H ($p \leq 0.001$). Individual cell necrosis was observed within the foci of histiocytosis in 5/8 rats treated with N15H ($p \leq 0.05$). Treatment with N15H for 90 days also resulted in increased incidences of total liver granulomas (minimal-to-mild severity) ($p \leq 0.001$) and macrophage accumulation and/or vacuolation in the *lamina propria* of the small intestine ($p \leq 0.001$). Calcification of the kidney medulla was observed at an increased incidence in rats treated with N70H ($p \leq 0.05$).

Table 7. Incidence of Significant Histopathological Findings in Female Rats Treated with Mineral Oils for 28 or 90 Days[a]

	Control	2% N15H	2% N70H
28-day Sacrifice			
Histiocytosis of proximal mesenteric lymph nodes	0/8	6/8[b]	0/8
90-day Sacrifice			
Histiocytosis of proximal mesenteric lymph nodes	0/8	8/8[c]	8/8[c]
Individual cell necrosis within foci of histiocytosis	0/8	5/8[d]	1/8
Calcification of kidney medulla	2/8	6/8	7/8[d]
Liver granuloma - minimal	0/8	6/8	2/8
- mild	0/8	1/8	0/8
- total	0/8	7/8[c]	2/8
Small intestine: macrophage vacuolation in lamina propria	0/8	7/8[c]	0/8

[a]Scotter et al., 2003
[b]$p \leq 0.01$
[c]$p \leq 0.001$
[d]Significantly different from control, $p \leq 0.05$

There were no statistically significant increases in the incidence of microscopic findings in rats treated with 2% P70H for 28 or 90 days (Scotter et al., 2003). Histiocytosis of the proximal mesenteric lymph nodes was present in 2/8 rats treated with P70H for 90 days, but this incidence was not statistically different from controls.

This study identified a LOAEL of 2049 mg/kg-day for N15H based on liver granulomas, individual cell necrosis in foci of histiocytosis of the mesenteric lymph nodes, macrophage vacuolation in the lamina propria of the small intestine, and possible inflammation of the cardiac mitral valve; no NOAEL can be identified. For N70H, a LOAEL of 1994 mg/kg-day based on increased incidence of calcification of the kidney medulla is identified. This effect was noted in a table in the publication but not discussed in the text of the report. In another subchronic study of N70H (Smith et al., 1996), this effect was not observed after exposure of the same strain and sex of rat for 90 days at the same dose. However, there are no other subchronic studies and no long-term studies of N70H to inform the question of kidney effects; thus, the dose in this study is identified as a LOAEL. No effects were observed with P70H treatment; thus, the single dose tested (2116 mg/kg-day) is a freestanding NOAEL.

Chronic Studies—Shoda et al. (1997) conducted a chronic study of liquid paraffin (average molecular weight of 475, average carbon number 25, 35:65 ratio of naphthenic to paraffinic hydrocarbons) administered in the diet to F344 rats. Groups of 50/sex/dose rats were given the test materials at dietary concentrations of 0, 2.5, or 5% ad libitum for 104 weeks. The animals were observed daily for mortality and clinical signs of toxicity; body weights were measured weekly for the first 8 weeks and then monthly thereafter. Food consumption was measured monthly and used to calculate intake of test materials. At sacrifice after 104 weeks,

blood was collected for hematology (WBC, RBC, Hb, Hct, and platelet count), and the animals were necropsied. Weights of the brain, submaxillary gland, lungs, heart, liver, spleen, adrenals, kidneys, and testes were recorded. Major organs (not specified) and any tumor masses were subjected to microscopic examination.

Treatment with the liquid paraffin did not affect survival or clinical signs of toxicity (Shoda et al., 1997). Statistically significant increases in body weight (<5% change from control) were observed throughout most of the study in the treated animals, and there were corresponding increases in food consumption. Using food intake and body weight data, the authors calculated average daily doses of 0, 962.2, and 1941.9 mg/kg-day for males and 0, 1135, and 2291.5 mg/kg-day for females. Although the authors did not report hematology data, the text indicated that there were no treatment-related findings. Significant increases in absolute liver (8% higher than control, $p < 0.05$) and kidney weights (10–15% higher for left and right, $p < 0.01$) were noted in high-dose males. In high-dose females, the absolute and relative weights of submaxillary glands were significantly ($p < 0.05$) decreased (6 and 11% below controls, respectively).

The incidence and severity of granulomatous inflammation of the mesenteric lymph nodes were both increased in a dose-related manner in treated animals (see Table 8) (Shoda et al., 1997). Other nonneoplastic lesions (including microgranuloma of the liver, bile duct proliferation, myocardial fibrosis, and chronic nephropathy) were observed but were not considered treatment-related. There were no statistically significant differences in the incidences of any tumor types. This study identified a freestanding NOAEL of 1941.9 mg/kg-day in males and 2291.5 mg/kg-day in females. As noted earlier in the discussion of Baldwin et al. (1992), granulomas of the mesenteric lymph nodes are not considered adverse (Fleming et al., 1998; Carlton et al., 2001; WHO, 2003).

Table 8. Incidence of Granulomatous Inflammation of Mesenteric Lymph Nodes by Severity Score[a]

	None	1 (slight)	2 (mild)	3 (moderate)	Mean Score[b]
Males[c]					
0	13/50	20/50	13/50	4/50	1.16
2.5%	5/50	3/50	15/50	27/50	2.28
5.0%	9/50	2/50	10/50	29/50	2.18
Females[c]					
0	9/48	17/48	22/48	0/48	1.27
2.5%	4/50	1/50	14/50	31/50	2.44
5.0%	6/49	0/49	14/49	29/49	2.34

[a]Shoda et al., 1997
[b]Sum of severity scores divided by number of animals
[c]Significant trend for increased severity with dose ($p < 0.001$, Jonckheere-Terpstra test performed for this review)

Another chronic study was conducted in F344 rats fed high molecular weight white mineral oils (P70H and P100H) in the diet for 2 years (Trimmer et al., 2004). The study, conducted in three phases, used doses of 0, 60, 120, 240, and 1200 mg/kg-day. In the carcinogenicity phase, 50 rats/sex/dose were treated for 24 months and sacrificed; in the chronic toxicity phase, 10 rats/sex/dose were treated for 12 months and sacrificed. A third phase

examined the reversibility of effects; 20 rats/sex/dose were treated for 12 months and then given the control diet for the following 12 months prior to sacrifice. Satellite groups of 5 female rats/dose were sacrificed at 3, 6, 12, 18, and 24 months for evaluation of hydrocarbon content of tissues (liver, kidneys, mesenteric lymph nodes, and spleen).

All animals were examined weekly for toxicity and were palpated for masses at that time; daily observations for signs of toxicity were also made (Trimmer et al., 2004). Body weights and food consumption were recorded weekly for 13 weeks and monthly thereafter. Quarterly ophthalmology examinations were performed. Blood was collected at 3, 6, 9, 12, 15, 18, 21, and 24 months for comprehensive hematology and serum chemistry evaluations; urine was collected at 3, 6, 12, 18, and 24 months for evaluation of urine chemistry. All rats other than the satellite groups used for tissue content analysis were necropsied. Weights of heart, kidneys, liver, spleen, ovaries, testes, brain, adrenals, and mesenteric lymph nodes were recorded. Control and high-dose animals in the carcinogenicity and chronic phases were subjected to comprehensive histopathological examinations, and the lungs, liver, kidneys, mesenteric lymph nodes, and spleen were examined in intermediate-dose groups. In the recovery-phase animals, tissues identified as target organs in the chronic phase were examined microscopically: liver and mesenteric lymph nodes for P70H and no organs for P100H.

Survival of the high-dose females exposed to P100H was significantly ($p \leq 0.05$) lower than controls (data presented graphically) but was within the normal 24-month survival range for F344 rats (Trimmer et al., 2004). No treatment-related effects on survival or clinical signs were noted. High-dose animals of both sexes (for both test materials) had significantly higher food consumption and body weights than controls; increased food intake was attributed to compensation for reduced calorie intake due to substitution with mineral oil. Statistically significant differences in hematology and clinical chemistry parameters occurred without consistent change from control or correlation with other parameters. The study authors characterized the observed changes as inconsequential or not biologically significant (Trimmer et al., 2004). The absolute and relative weights of mesenteric lymph nodes were significantly ($p \leq 0.01$) increased in females treated for 24 months with P70H (all doses) and with the highest dose of P100H, as well as in males treated with the 1200-mg/kg-day P70H. In the recovery groups, there were no dose-related differences from controls in lymph node weights. There were statistically significant increases in spleen weight (up to 48%, observed at low dose of P100H) in some treatment groups, but the change did not exhibit a dose-response relationship. Analysis of tissues for mineral hydrocarbons showed consistently detectable levels in the liver but not in other organs; hepatic levels reverted to near background levels in recovery group animals assessed after 12 months on the control diet.

Histiocytosis of the mesenteric lymph nodes was observed at similar frequencies (at or near 100%) in both treated and control groups after both 12 and 24 months of treatment (Trimmer et al., 2004). The mean severity score for the effect was reportedly higher (mild rather than minimal) in treated than in control rats. A statistically significant increase in the severity score occurred in rats (both sexes) exposed to 1200-mg/kg-day P70H after 24 months and in females exposed to all doses of P100H for 24 months. An increase in the incidence of cystic degeneration (focal dilated vascular spaces accompanied by eosinophilic debris or necrotic hepatocytes) and angiectasis (focal dilatation of the sinusoidal spaces) in the liver was observed in male rats; the combined incidence of these effects was statistically significantly ($p \leq 0.05$)

different from controls at all doses of P70H and at the high dose of P100H only. However, the authors did not consider this effect to be biologically significant due to its common occurrence in untreated F344 rats. The historical control incidence of the effect was not reported. In addition, the incidence and severity of liver portal vacuoles was increased in males and females treated with ≥120-mg/kg-day P70H or P100H and in males exposed to all doses of P70H; however, the authors characterized these as markers of exposure and not toxicity. No granulomas or microgranulomas were observed in the livers of animals treated with either mineral oil.

There were no treatment-related increases in the incidence of neoplasia (Trimmer et al., 2004). The incidence of adenoma of the pars distalis was statistically different from controls in females exposed to 1200-mg/kg-day P100H, but the authors reported that it was within the historical control range for F344 rats. This study identifies a freestanding NOAEL of 1200 mg/kg-day for both P70H and P100H.

Other Studies

Other Routes

MADEP (2003) observed that emerging data suggested an association between exposure to petroleum distillates and autoimmune diseases. The human study (Lacey et al., 1999) cited as support for this finding was of inhalation exposure to hydrocarbon mixtures containing 10–30% aromatic content and, thus, is not adequate to suggest an association with the aliphatic content of the mixtures. The animal studies of this association (Shaheen et al., 1999; Richards et al., 1999, 2001) were injection studies of pristane (2,6,10,14-tetramethylpentadecane, $C_{19}H_{40}$, a branched aliphatic component of mineral oil). The update literature search did not identify any studies of autoimmune endpoints associated with oral or inhalation exposure to mineral oils. The relevance of the findings of the injection studies of pristane to effects of oral or inhalation exposure to mineral oils is uncertain given likely differences in the toxicokinetics after injection exposure.

Toxicokinetics

The toxicokinetics of medium- and low-viscosity mineral oils were reviewed by WHO (2003). Many of the studies on absorption, distribution and excretion were aimed at identifying differences in toxicokinetics between F344 rats, which are particularly sensitive to the effects of mineral oils, and Sprague-Dawley rats, which are not sensitive. These unpublished toxicokinetics studies using [1–14C]-1-eicosanylcyclohexane as a tracer suggest that mineral oil is absorbed to some extent across the gastrointestinal tract and that the primary route of excretion is fecal (up to 94% of administered radioactivity after 96 hours), with urinary elimination accounting for <10% of administered dose (as reviewed by WHO, 2003). The studies confirmed that F344 rats absorb more mineral oil and excrete it at a slower rate than Sprague-Dawley rats. This finding is consistent with the results of tissue analyses for hydrocarbons during the toxicity study by Firriolo et al. (1995), which indicated that, at equal doses, there was greater deposition of hydrocarbons in liver, lymph nodes and other tissues of F344 rats than in other rat strains.

Immunotoxicity

An unpublished study performed by ImmunoTox was described by WHO (2003); a preliminary report of this study, with few details included, was provided to U.S. EPA under Toxic Substance Control Act Section 8(e) (Equiva Services, 2000). The study description included herein is drawn from information provided by WHO (2003), because the microfiche

(Equiva Services, 2000) contained only preliminary results. The study, conducted in two phases, exposed groups of eight (per strain) female F344 and Sprague-Dawley rats to P15 mineral oil in the diet at concentrations of 0, 0.02, or 2.0% (F344) or 0, 1.0, or 2.0% (Sprague-Dawley). In the first phase, exposure continued for 90 days; in the second phase, exposure continued for 120 days followed by a 30-day recovery period. Body weights and food consumption were measured for the first 90 days of each study. Immune response to sheep erythrocyte sensitization was assessed as IgM response in a modified hemolytic plaque assay on the day of sacrifice (Day 91) in Phase I. In Phase II, IgM antibody titers after dinitrophenol-human serum albumin challenge were measured on Day 91, and the response observed was used to determine whether to continue the study. The latter immune sensitization was repeated on Days 115 and 121, and IgG was measured. A final sensitization with sheep erythrocytes occurred on Day 147 followed by sacrifice on Day 151 for IgM determination in the spleen. Upon sacrifice, brain, liver, spleen, and lymph node weights were recorded, and liver, mesenteric lymph nodes (with adipose tissue) and spleen (Sprague-Dawley only) were examined histopathologically.

Body weights and food consumption rates were not affected by treatment. Absolute and relative liver weights were significantly (*p*-value not reported) increased over control values in Sprague-Dawley rats at both dose levels and to the same general degree; no data were reported by WHO (2003). In F344 rats, statistically significant, dose-related increases in absolute and relative liver weights were observed after 90 days; relative liver weight remained increased after 120 days treatment and 30 days recovery. Spleen and mesenteric lymph node weights of F344 rats were increased at the high dose in both phases. Histopathology after 90 days exposure revealed granulomatous inflammation of the mesenteric lymph nodes in all control and treated F344 rats (6/8, 8/8, and 8/8 for control, low-, and high-dose, respectively), with increased severity at the high dose. F344 rats exposed for 90 days also exhibited granulomatous inflammation of the liver (0/8, 1/8, 7/8). Inflammation of both lymph nodes and liver persisted in the animals exposed for 120 days followed by 30 days recovery. In Sprague-Dawley rats, minimal granulomatous inflammation of the mesenteric lymph nodes occurred in nearly all treated animals (1/16, 15/16, and 15/16 for control, low-, and high dose, respectively); Phase II animals of this strain were sacrificed after 90 days due to the lack of IgM response.

Immunotoxicity testing showed no effect on spleen IgM response in Sprague-Dawley rats (as reviewed by WHO, 2003). In contrast, a dose-dependent reduction in antibody-forming cell response (when expressed per 10^6 spleen cells) was observed in F344 rats; the decrease was statistically significant at the high dose. Because the number of spleen cells was increased at the high dose, no difference from controls was recorded when the results were reported on the basis of total spleen activity. The immunologic effects persisted in the F344 group exposed for 120 days followed by a 30-day recovery period.

Neither WHO (2003) nor Equiva Services (2000) provided dose estimates associated with the dietary concentrations of P15H administered in this study. Based on information from other studies using P15H and these strains of rats (Firriolo et al., 1995; Smith et al., 1996), the doses are estimated to be in the range of 200 and 2000 mg/kg-day (0.2% and 2.0%). This study suggests that immunologic effects and granulomatous inflammation of the liver are observed only at the higher concentration; however, effect levels cannot be determined from this study due to the lack of data.

Relevance of Animal Pathology to Humans

Fleming et al. (1998) compared the morphology of granulomas identified in the lymph nodes, spleen, liver, and bone marrow of long-term human mineral oil users with those observed in the lymph nodes and liver of F344 rats treated with mineral oils and waxes. Lipogranulomas observed on autopsy of human mineral oil users were described as collections of oil or lipid droplets, frequently found in macrophages and forming both micro and macrovesicles. Occasionally, multinucleated giant cells were present, as well as lymphocytes and plasma cells in varying amounts. The aggregation of these cells was termed a lipogranuloma. The authors noted that scarring fibrosis occurred rarely. In contrast to the lipogranulomas in humans, liver lesions in F344 rats were characterized as follicular epithelioid granulomas. These were collections of epithelioid macrophages (enlarged macrophages with eosinophilic cytoplasm, indistinct cell borders and vesicular eccentric nuclei, resembling epithelial cells) with frequent multinucleated cells, lymphocytes and fibrosis. The authors concluded that there were no morphological similarities between the lipogranulomas observed in humans and the liver lesions developed in F344 rats, in that the rat lesions were epithelioid, with extensive inflammation and some necrosis, while the human lesions were histiocytic collections with minimal inflammation. The authors postulated that the different morphology reflected the relative balance between T helper 1 and T helper 2 responses to mineral oil and the different cytokines generated by these lymphocytes. With respect to the lymph node lesions, Fleming et al. (1998) characterized these as focal accumulations of vacuolated macrophages, with no evidence of inflammation or cell damage.

A panel of experts convened to examine the question of whether the lymph node and hepatic lesions in F344 rats were relevant to humans drew a similar conclusion to that of Fleming et al. (1998). Publishing the results of a pathology workshop on this issue at the Fraunhofer Institute of Toxicology and Aerosol Research in Germany, Carlton et al. (2001) concluded that the lesions in F344 rats differed morphologically from those in humans and that the lipogranulomas observed in the liver, spleen, and lymph nodes of humans were "incidental and inconsequential." With respect to the F344 rat, lymph node granulomas were considered to have little or no biological significance, while the liver granulomas, which include inflammatory and occasionally necrotic components, represented an adverse effect of mineral oil exposure in that strain of rat (Carlton et al., 2001).

Genotoxicity

No information regarding the genotoxicity of white mineral oils was located.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR MINERAL OIL

Mineral oils of lower molecular weight (<480) and carbon range are most pertinent to the C9-C32 fraction. These include N10A, N15H, P15H, N70A, and N70H, tested by Smith et al. (1996); Marcol 72, Marcol 82, and EZL 600, tested by Smith et al. (1995); P15H tested by Firriolo et al. (1995); and N15H and N70H tested by Scotter et al. (2003). In contrast, the carbon range of higher molecular weight mineral oils (EZL 550 tested by Smith et al. 1995, and P70H and P100H tested by Smith et al., 1996, Scotter et al., 2003, and Trimmer et al., 2004) includes a

significant proportion of compounds outside the C9–C32 range. Similarly, the liquid paraffin tested by Shoda et al. (1997) had physical properties (viscosity, molecular weight and ratio of naphthenic:paraffinic hydrocarbons) similar to P70H and, thus, is not considered relevant to the C9–C32 fraction. Baldwin et al. (1992) provided no information on the mineral oils tested (OTWO and HTWO) other than viscosity and specific gravity. Thus, it is difficult to determine whether the data are relevant to the C9–C32 fraction or not, so they are not included in the assessment. The data considered relevant to the derivation of provisional oral toxicity values for mineral oil as a surrogate for the C9–C32 fraction are from studies using the lower molecular weight/lower carbon range mineral oils listed above. Overviews of the pertinent animal studies are given in Table 9. Studies of mineral oil effects based on treatment-related exposures in humans (Clark et al., 1987; Gal-Ezer and Shaoul, 2006; NASPGHN, 2006 Speridião et al., 2003; Urganci et al., 2005) are also given in Table 9.

The animal database of mineral oil studies relevant to the C9-C32 fraction includes only subchronic toxicity studies. As Table 9 shows, the effects observed in most of the animal studies and at the lowest doses were liver granulomas in F344 rats. Available information indicates that these lesions occur in F344 but not other rat strains (Firriolo et al., 1995; Smith et al., 1995), possibly because the F344 rat tends to absorb and retain mineral oil constituents to a greater degree than other rat strains (as reviewed in WHO, 2003). While liver granulomas have been noted upon autopsy of human mineral oil users, these lesions appear to differ morphologically from those observed in F344 rats (Fleming et al., 1998; Carlton et al., 2001) and to be of little toxicological consequence in humans (Carlton et al., 2001). However, the available data are not adequate to determine conclusively whether or not the lesions observed in F344 rats are relevant to humans. No data exist to characterize the doses of mineral oil received by the humans in whom lesions were observed nor the durations of use. Consequently, it is not possible to determine whether the inflammatory lesions observed in the rats could occur in humans at higher doses or over a longer duration of exposure. Further, while there are data reviewed by WHO (2003) showing clear differences in the toxicokinetics of mineral oil in F344 rats compared with Sprague-Dawley rats, there are no data to suggest whether the F344 or the Sprague-Dawley strain of rat is a better model for mineral oil absorption, distribution, metabolism, excretion, and toxicological response in humans.

Table 9. Summary of Oral Noncancer Dose-Response Information for Mineral Oils Pertinent to the C9–C32 Aliphatic Fraction[a]

Mixture or Compound	Species and Sex	Dose (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Mineral oil	Human >1 year of age (m/f)	870–2600	Daily maintenance dose	870–2600	NA	NA	Laxative effects. Side effects noted include foreign-body reaction in intestinal mucosa. Maintenance dose for treatment of constipation. Human therapeutic experience.	NASPGHN, 2006
Mineral oil	Human children 2–14 years old (m/f)	2250 (weighted average)	Daily treatment, decreasing doses, for 4 months	2250	NA	NA	Laxative effects; decrease in serum ß-carotene levels. Endpoints included only serum levels of retinol, ß-carotene, and α-tocopherol.	Clark et al., 1987
Mineral oil	Human children 2–12 years old (m/f)	870	Daily for 90 days	870	NA	NA	Laxative effects; slight improvement in anthropometric measures. Endpoints included only anthropometric measures.	Speridião et al., 2003
Mineral oil	Human children 2–12 years old (m/f)	1600	Daily for 8 weeks	1600	NA	NA	Laxative effects; watery stools. Endpoints included only symptom control and compliance with treatment.	Urganci et al., 2005
Mineral oil	Human female = 17 years old (f)	348,000	Daily for 5 months	348,000	NA	NA	No effects on physical exam. Serum levels of fat-soluble vitamins (A and E), calcium, phosphorus, alkaline phosphatase (as measures of vitamin D status), and prothrombin time (as a measure of vitamin K status) were within normal limits.	Gal-Ezer and Shaoul, 2006

Table 9. Summary of Oral Noncancer Dose-Response Information for Mineral Oils Pertinent to the C9–C32 Aliphatic Fraction[a]

Mixture or Compound	Species and Sex	Dose (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Marcol 72 (C14-C38), Marcol 82 (C16-C34), EZL 600 (C20-C36)	Long-Evans Rats (m/f)	0, 21, 108 (m) and 0, 25, 125 (f)	Diet for 13 weeks	108 (m) 125 (f)	NA	NA	----	Smith et al., 1995
N10A (C15-C30), N15H (C17-C30), P15H (C18-C30), N70A (C21-C35), N70H (C22-C37)	F344 rats (m/f)	0, 1.7, 17, 173, 1815 (m) and 0, 2.0, 19, 190, 1951 (f)	Diet for 90 days	190	1951 (f)	Liver granulomas and micro-granulomas in females	No granulomas or microgranulomas were observed in males. Histiocytosis in mesenteric lymph nodes not considered adverse.	Smith et al., 1996
P15H (C18-C30)	F344 (f)	0, 161, 1582	Diet for 92 days	NA	161	Micro-granulomas of liver.	Incidence of microgranulomas increased with both dose and time.	Firriolo et al., 1995
P15H (C18-C30)	Crl:CD (f)	0, 158, 1624	Diet for 92 days	158	1624	Multifocal chronic inflammation of liver	----	Firriolo et al., 1995

Table 9. Summary of Oral Noncancer Dose-Response Information for Mineral Oils Pertinent to the C9–C32 Aliphatic Fraction[a]

Mixture or Compound	Species and Sex	Dose (mg/kg-day)	Exposure Regimen	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
N15H (C17-C30), N70H (C22-C37)	F344 (f)	0, 2049 (N15H), 1994 (N70H)	Diet for 90 days	NA	2049 (N15H) 1994 (N70H)	Liver granuloma; individual cell necrosis in foci of lymph node histiocytosis, macrophage vacuolation of small intestine (N15H only); calcification of kidney medulla (N70H)	----	Scotter et al., 2003

[a]Dose conversions have been undertaken and presented in this Table to characterize doses in mg/kg-day (instead of mL/kg-day) so the reader can compare across studies using the following calculations. The specific gravity of white mineral oil is 0.83–0.905; HSDB (2007). Using the midpoint of the range (0.87) and the density of water (1000 mg/mL), a dose of 1 mL/kg-day is calculated to deliver 870 mg/kg-day (1 mL/kg-day × 0.87 × 1000 mg/mL), and a dose of 3 mL/kg-day is calculated to deliver 2600 mg/kg-day (3 mL/kg-day × 0.87 × 1000 mg/mL).

In addition to animal studies of various mineral oils, available information on the potential toxicity of hydrocarbons in this fraction includes human therapeutic experience with oral mineral oil treatment for chronic constipation. Current recommendations for maintenance doses of mineral oil to treat chronic constipation in children (>1 year of age) are 1–3 mL/kg-day, or 870–2600 mg/kg-day (NASPGHN, 2006). Based on the few studies of mineral oil treatment in humans (Clark et al., 1987; Gal-Ezer and Shaoul, 2006; Speridião et al., 2003; Urganci et al., 2005), side effects are few and minor. While none of the references specified a recommended duration of treatment, one study cited by Clark et al. (1987) involved treatment for up to 6 years. Given the uncertainty in the relevance of the liver lesions observed in F344 rats and the substantial clinical experience behind the human therapeutic dose range, the provisional oral toxicity values for mineral oil were estimated using the lower end of the human therapeutic dose range as the point of departure (POD). The lower end of the therapeutic range (1 mL/kg-day, or 870 mg/kg-day) was regarded as a NOAEL, as the laxative effects were therapeutic and side effects were few. Since the longest duration of treatment cited in the available studies was less than 7 years, the exposure duration associated with the POD was assumed to be subchronic (U.S. EPA, 2002).

A composite UF of 30 was applied to the subchronic NOAEL (870 mg/kg-day) to derive a subchronic p-RfD. The **subchronic p-RfD** for mineral oil is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 870 \text{ mg/kg-day} \div 30 \\ &= \textbf{30 or } \mathbf{3 \times 10^{1}} \textbf{ mg/kg-day} \end{aligned}$$

The composite UF of 30 was composed of the following:

- An UF of 3 ($10^{0.5}$) for intraspecies differences was used. The POD represents the lower end of the therapeutic range and, thus, should provide some protection for potentially sensitive individuals. In addition, the therapeutic range of doses is recommended for children as young as 1 year of age, a population that may be more sensitive than adults. Although these factors argue for a lower intraspecies UF, an UF of 1 was not considered, because there are no data with which to identify potentially sensitive subpopulations. While Gal-Ezer and Shaoul (2006) observed no effects in an individual exposed to 348,000 mg/kg-day for 5 months, this was a case report of only one person. More sensitive individuals may have other responses to such an exposure. In addition, it is possible that individuals (adults or children) who experience adverse responses to mineral oil treatment for constipation switch to readily available alternative treatments, such that the available data on health effects of mineral oil use could be skewed toward individuals who are *less sensitive*. Further, there is evidence that certain strains of rat (F344) are more sensitive to potentially adverse effects of mineral oil exposure than other strains due to toxicokinetic differences. There is no information to address whether there are subpopulations of humans in whom the disposition of mineral oil is similar to that of the F344 rat.
- A database UF of 10 was applied. There is a lack of data on developmental and reproductive toxicity. Absence of any of these studies contributes to database uncertainty. Further, despite the extensive human clinical experience with

mineral oil use, there are few data evaluating potential subclinical effects of mineral oil exposure and no epidemiological data on effects of mineral oil use. The few human studies of mineral oil exposure (Clark et al., 1987; Speridião et al., 2003; Urganci et al., 2005; Gal-Ezer and Shaoul, 2006) have evaluated limited endpoints in small numbers of individuals. The possible association between mineral oil constituents and autoimmune disorders, suggested by injection studies in rodents, merits further investigation and contributes to the database uncertainty. In addition, there remains uncertainty as to the potential relevance of the rat liver granulomas to effects in humans, as potential immunological effects in humans have not been examined. These uncertainties, coupled with the lack of data on developmental and reproductive toxicity, warrant the use of a 10-fold UF for database deficiencies.

To derive the chronic p-RfD, an additional 10-fold UF for exposure duration was applied to the POD, resulting in a total UF of 300. None of the available human studies of mineral oil provided any information on chronic exposure to mineral oil. The **chronic p-RfD** for mineral oil is derived as follows:

Chronic p-RfD = NOAEL ÷ UF
= 870 mg/kg-day ÷ 300
= **3 or 3 × 10^0 mg/kg-day**

Confidence in the POD, derived from the therapeutic dose range (NASPGHN, 2006) is medium. While the clinical experience with mineral oil is strong, few rigorous studies of long-term mineral oil use were available to support the recommendations, and no clear parameters for treatment duration were identified. Confidence in the database is low. There are inadequate data on the relevance of the animal data to toxicity in humans, and there are no data on reproductive or developmental toxicity of mineral oils. Low confidence in the subchronic and chronic RfDs follows.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR MINERAL OIL

Available data on inhalation of mineral oil are limited to mineral oil mists generated during machining operations; these data are not relevant to environmental releases, which are unlikely to generate aerosol formation. As a result, provisional inhalation toxicity values were not derived.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR MINERAL OIL

Weight-of-Evidence Classification

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess the Carcinogenic Potential of Mineral Oils*." Despite the long history of therapeutic mineral oil use in humans, there are no epidemiological studies examining cancer incidence in humans exposed to mineral oils over prolonged periods of time. In addition, there are no chronic studies of low and medium molecular weight mineral oils in animals. Treatment-related increases in tumors have not been observed in any of the subchronic studies, although detection of carcinogenicity in such studies is unlikely. In one chronic rat dietary study of higher molecular weight mineral oil (Trimmer et al., 2004), the only statistically significant difference in tumor incidence was an increased incidence of adenoma of the pars distalis in female rats exposed to 1200-mg/kg-day P100H; however, the incidence at this dose was within the historical control incidence for F344 rats in NTP studies. In a second chronic rat dietary study of higher molecular weight mineral oil (Shoda et al., 1997), there were no treatment-related increases in the incidence of any tumor type. There are no chronic bioassays of mineral oils in any species other than the rat. Genotoxicity data for mineral oils are not available.

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