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Provisional Peer-Reviewed Toxicity Values for

High Flash Aromatic Naphtha
(CASRNs 64742-95-6 and 88845-25-4)

Superfund Health Risk Technical Support Center
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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 HIGH FLASH AROMATIC NAPHTHA (CASRNs 64742-95-6 and 88845-25-4)

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

High Flash Aromatic Naphtha (HFAN) is a classification of C8−C10 aromatic hydrocarbons identified by ASTM[1] method D-3734. By definition, this chemical class must contain a combined total of 75% trimethylbenzene and ethyltoluene isomers (of which at least 22% is ethyltoluene and at least 15% is trimethylbenzene). HFAN is synonymous with "Light Aromatic Solvent Naphtha" (CASRN of 64742-95-6). Several commercial formulations that fall within this chemical class are discussed in this review, including Aromatol, LX1106-01, Shellsol A, and Solvesso 100. Use of the terms "HFAN" and "light aromatic solvent naphtha" within this document is intended to encompass these and other similar commercial formulations.

No chronic or subchronic RfDs or RfCs or cancer assessment for HFAN are available on IRIS (U.S. EPA, 2008), the Drinking Water Standards and Health Advisory list (U.S. EPA, 2006), or in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997). No documents for HFAN are listed in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991a, 1994a). There are no occupational exposure limits for HFAN listed by the Occupational Safety and Health Administration (OSHA, 2008), the National Institute of Occupational Safety and Health (NIOSH, 2005), or the American Conference of Governmental Industrial Hygienists (ACGIH, 2007). Neither the Agency for Toxic Substances and Disease Registry (ATSDR) nor the International Agency for Research on Cancer (IARC) has published documents on HFAN toxicity or carcinogenicity (ATSDR, 2008; IARC, 2008). The National Toxicology Program (NTP, 2008) has not performed toxicity or carcinogenicity assessments for HFAN and this hydrocarbon fraction is not in the 11th Report on Carcinogens (NTP, 2005). The World Health Organization (WHO, 2008) has not published an Environmental Health Criteria Document for HFAN.

[1]ASTM International, originally known as the American Society for Testing and Materials (ASTM) is a voluntary standards development organization. Online at http://www.astm.org.

To identify toxicological information supporting the derivation of provisional toxicity values for HFAN and to identify studies published since the MADEP (2003), updated literature searches (January 2001−September 2007) of the following databases were performed in September 2007: MEDLINE, TOXLINE, BIOSIS, TSCATS1/2, CCRIS, GENETOX, DART/ETIC, HSDB, and Current Contents (last 6 months) were conducted in September 2007, review. Additional references were located by tree-search from the key studies identified. An additional literature search was conducted in July of 2009 using PUBMED.

REVIEW OF PERTINENT DATA

Human Studies

No studies that specifically address the toxicity of HFAN to humans were located.

Animal Studies

Oral Exposure

Subchronic Studies—Three subchronic oral toxicity studies of HFAN have been conducted by industry (Bio/Dynamics Inc., 1990a,b; Mobil Oil Corporation, 1994) and submitted to United States Environmental Protection Agency (U.S. EPA) under the Toxic Substances Control Act (TSCA). None of these studies appears to have been reviewed by external scientific peers.

In the first of these studies, Bio/Dynamics Inc. (1990a) administered 100% pure LX1106-01 (Solvent Naphtha, Petroleum, Light Aromatic, CASRN 64742-95-6) in corn oil to groups of Sprague-Dawley rats daily via gavage for up to 96 days. The authors did not report the chemical or isomeric composition of the test substance. In the study groups of 10 rats/sex were administered doses of 0 (corn oil only), 500, 750, or 1250 mg/kg-day. The authors noted excessive salivation and anogenital staining in all groups of treated animals, but these effects are not necessarily adverse and are likely associated with the gavage procedure and hydrocarbon elimination. During Week 13 of the study, they reported dose-related decreases in group mean body weights of both males (up to 20%) and females (up to 11%): differences from controls were statistically significant for the 750 and 1000 mg/kg-day groups of both sexes (see Table 1); they reported decreased food consumption in males, but not in females. The authors reported statistically significant changes in organ weights and organ weight to body weight ratios in the heart, liver, and kidney (see Table 1). These changes in heart and kidney weights were relatively small and consistent with decreased body weight in the affected animals; however, the increase in liver weight reflects a compound-related effect on the liver. Histological examination of the liver revealed increased incidence of centrolobular hepatocytic swelling in all treated female groups (see Table 1); however, the authors reported no treatment-related liver lesions in males. While the authors reported nephropathy, including hyaline droplet accumulation in males, it was not dose-related. In high-dose rats, the authors reported statistically significant elevations (approximately 1.5-fold) in some serum liver enzymes: alanine aminotransferase (ALT [SGPT]) in males and females, and alkaline phosphatase (ALP) in males (see Table 1). The authors also reported small (less than 2-fold)—but statistically significant—elevations in total serum protein and albumin in both males and females; the increases in serum albumin were statistically significant at ≥500 mg/kg-day. The biological significance of the serum protein changes is uncertain. In females, the authors also reported occasional small (less than 2-fold), statistically significant changes in levels of other compounds in serum, such as glucose, chloride, and phosphate, but these changes were sporadic and not consistently related to dose. High-dose females showed decreases in hemoglobin and red blood cell count at the end of the study. Based

on these observations, the low dose of 500 mg/kg-day is a LOAEL based on liver changes, including centrilobular hepatocytic swelling. Serum chemistry changes (increases in ALT and ALP) indicating a possible effect on the liver were found only at the high dose.

Mobil Oil Corporation (1994) reported the results of a second subchronic study conducted with rats. The authors did not identify the composition of the light aromatic solvent naphtha used in the study. The report is stamped "company sanitized" and names of the authors, laboratory, and test substances have been removed from the report. In the study, groups of Sprague-Dawley rats (10/sex/group) were given unspecified light aromatic solvent naphtha via gavage (in corn oil) at doses of 0, 30, 125, 500, or 1250 mg/kg-day, 5 days per week, for 13 weeks. The authors evaluated the animals daily, measured body weights weekly, and analyzed serum chemistry during Week 13 and hematology during Weeks 5 and 13 of the study. At study termination, they performed gross necropsies on all animals and weighed major organs (adrenals, brain, epididymides, heart, kidneys, liver, ovaries, prostate, spleen, testes, thymus, and uterus). Based on macroscopic findings, the aorta, kidneys, and liver from all animals and dose groups were processed for microscopic evaluation.

Three animals died or were sacrificed (one high-dose male; one mid-dose female; one high-dose female) due to misintubation (Mobil Oil Corporation, 1994). There were no other deaths prior to terminal sacrifice. At the two highest doses, the authors reported symptoms consistent with toxicity, including salivation, pale reddish-brown oral discharge (no further characterization), and anal staining. Table 2 summarizes the affected variables of interest in the study. Body weight (minus 9% for males and 11% for females) and body-weight gain (minus 22% for males and 27% for females) were statistically significantly reduced in high-dose animals in comparison with controls over the course of the study. Body-weight gain was also significantly reduced in the 30 (8%) and 500 mg/kg-day females (18%)—but not at 125 mg/kg-day. These comparisons persisted throughout the study. The authors reported that terminal body weights of high dose females were statistically significantly decreased when compared to controls.

Table 1. Summary of Significant Terminal Effects in Rats Exposed by Gavage to LX-1106-01 for up to 90 Days[a]

Males (*n* = 10 unless noted otherwise)				
Variable[b]	**Control**	**500 mg/kg-day**	**750 mg/kg-day**	**1250 mg/kg-day**
Body Weight (g)	584.0 ± 91.3 (7)	537.6 ± 57.6 (7)	504.1 ± 31.7 (8)[c]	468.5 ± 40.2 (8)[d]
Clinical Chemistry				
ALT (SGPT) (IU/L)	27 ± 2	25 ± 4	30 ± 5	36 ± 8[c]
ALP (IU/L)	97 ± 16	97 ± 16	92 ± 23	157 ± 50[d]
Total Protein (g/dL)	6.4 ± 0.3	6.7 ± 0.2	6.8 ± 0.4	7.0 ± 0.3[d]
Albumin (g/dL)	4.1 ± 0.2	4.5 ± 0.2[d]	4.7 ± 0.2[d]	5.0 ± 0.2[d]
Organ Weight				
Heart (g)	1.560 ± 0.208 (9)	1.470 ± 0.189	1.361 ± 0.100[c]	1.288 ± 0.185[d]
Kidney/BW ratio	6.51 ± 0.85	7.96 ± 1.00[c]	8.39 ± 0.81[d]	9.14 ± 1.52[d]
Liver (g)	14.953 ± 2.084	15.622 ± 2.268	17.382 ± 2.204	17.437 ± 2.368[c]
Liver/BW ratio	2.75 ± 0.13	3.22 ± 0.27[d]	3.74 ± 0.32[d]	4.14 ± 0.38[d]
Females (*n* = 10 unless noted otherwise)				
	Control	**500 mg/kg-day**	**750 mg/kg-day**	**1000 mg/kg-day**
Body Weight (g)	296.3 ± 23.9 (7)	271.0 ± 6.4 (6)	264.3 ± 9.9 (8)[c]	268.5 ± 24.9 (8)[c]
Hematology				
Hemoglobin (g/dL)	16.0 ± 0.5	16.4 ± 0.7 (9)	16.0 ± 0.6 (9)	15.2 ± 0.6 (9)[c]
RBCs	6.92 ± 0.21	7.02 ± 0.27 (9)	6.96 ± 0.36 (9)	6.54 ± 0.34[c]
Clinical Chemistry				
ALT (SGPT) (IU/L)	24 ± 4	24 ± 3 (9)	26 ± 4 (9)	36 ± 6[d]
Fasting Glucose (µg/dL)	136 ± 12	117 ± 15 (9)[c]	121 ± 17(9)	111 ± 16[d]
Total Protein (g/dL)	6.8 ± 0.3	7.2 ± 0.3 (9)	7.0 ± 0.4 (9)	7.6 ± 0.6[d]
Albumin (g/dL)	4.6 ± 0.4	5.1 ± 0.3 (9)[d]	5.0 ± 0.3 (9)	5.6 ± 0.4[d]
Organ Weights				
Heart/BW ratio	3.44 ± 0.28	3.62 ± 0.29 (9)	3.82 ± 0.20 (9)[d]	3.80 ± 0.21[d]
Kidney/BW ratio	7.44 ± 0.41	8.02 ± 0.75 (9)	8.33 ± 075 (9)[c]	8.86 ± 0.64[d]
Liver (g)	7.706 ± 1.050	8.181 ± 0.749 (9)	8.569 ± 1.069	10.890 ± 1.324[d]
Liver/BW ratio	2.97 ± 0.26	3.31 ± 0.23 (9)[c]	3.61 ± 0.28[d]	4.57 ± 0.33[d]
Histopathology				
Centrolobular Hepatocytic Swelling[e]	0/10	6/10[f]	10/10[g]	9/10[g]

[a]Bio/Dynamics Inc., 1990a
[b]Mean ± standard deviation or incidence, as appropriate
[c]Significantly different from control, $p < 0.05$, Dunnett's or Kruskall-Wallace Test
[d]Significantly different from control, $p < 0.01$, Dunnett's or Kruskall-Wallace Test
[e]No statistical evaluations for this variable were made by the study's authors
[f]Significantly different from control, $p < 0.05$, Fisher's exact test conducted for this review
[g] Significantly different from control, $p < 0.01$, Fisher's exact test conducted for this review

Table 2. Summary of Effects in Rats Exposed by Gavage to Unspecified Light Aromatic Solvent Naphtha (CASRN 64742-95-6) for 13 Weeks[a]

Males (*n* = 10 unless noted otherwise)					
Variable[b]	**Control**	**30 mg/kg-day**	**125 mg/kg-day**	**500 mg/kg-day**	**1250 mg/kg-day**
Body Weight (g)	493 ± 27	499 ± 32	489 ± 31	484 ± 37	448 ± 46 (9)[c]
Body-Wt Gain (g)	230.3 ± 24.6	231.6 ± 24.3	225.2 ± 21.6	217.3 ± 25.7	178.2 ± 37.2 (9)[d]
Clinical Chemistry					
Total Bilirubin (µg/dL)	0.12 ± 0.02	0.12 ± 0.02	0.12 ± 0.02	0.12 ± 0.02	0.15 ± 0.03 (9)[c]
Total Protein (g/dL)	7.0 ± 0.2	7.1 ± 0.2	7.1 ± 0.3	7.4 ± 0.2[d]	7.5 ± 0.3 (9)[d]
Albumin (g/dL)	4.7 ± 0.2	4.9 ± 0.2	4.8 ± 0.2	5.0 ± 0.2	5.4 ± 0.3 (9)[d]
A/G ratio	2.2 ± 0.2	2.2 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	2.6 ± 0.3 (9)[d]
Phosphorus	6.3 ± 0.2	5.8 ± 0.3[d]	6.1 ± 0.2	6.2 ± 0.3	6.7 ± 0.3 (9)[c]
Pathology					
Large Liver[e]	0/10	0/10	0/10	2/10	4/10
Yellow Aorta[e]	0/10	0/10	0/10	8/10[f]	8/10[f]
Hepatocytic Hypertrophy[e]	0/10	0/10	1/10	3/10	5/10[g]
Females (*n* = 10 unless noted otherwise)					
	Control	**30 mg/kg-day**	**125 mg/kg-day**	**500 mg/kg-day**	**1250 mg/kg-day**
Body Weight (g)	318 ± 24	290 ± 19[c]	312.6 ± 21	294.6 ± 14 (9)	283 ± 21 (9)[d]
Body-Wt Gain (g)	129.3 ± 18.3	107.5 ± 15.0[c]	119.5 ± 15.7	105.6 ± 13.6 (9)[d]	94.5 ± 14.8 (9)[d]
Clinical Chemistry					
ALT(IU/L)	30 ± 6	29 ± 4	28 ± 4	35 ± 8 (9)	46 ± 9 (9)[d]
ALP(IU/L)	175 ± 38	184 ± 57	172 ± 40	235 ± 88 (9)	314 ± 73 (9)[d]
Total Protein (g/dL)	6.8 ± 0.3	7.0 ± 0.1	6.9 ± 0.3	7.0 ± 0.2 (9)	7.2 ± 0.3 (9)[d]
Albumin (g/dL)	3.4 ± 0.1	4.0 ± 0.8	3.9 ± 0.7	4.1 ± 0.7 (9)	4.2 ± 0.6 [c]
A/G ratio	2.4 ± 0.3	2.3 ± 0.2	2.5 ± 0.1	2.5 ± 0.2 (9)	2.8 ± 0.5 (9)
Urea Nitrogen (µg/dL)	16.9 ± 2.4	16.2 ± 2.2	15.8 ± 2.4	15.0 ± 1.8 (9)	13.4 ± 3.2 (9)[d]
Creatinine (µg/dL)	0.65 ± 0.05	0.70 ± 0.04	0.68 ± 0.04	0.69 ± 0.04 (9)	0.77 ± 0.06 (9)[d]
Organ Weights					
Adrenal (g)	0.066 ± 0.008	0.072 ± 0.012	0.071 ± 0.009	0.069 ± 0.012 (9)	0.081 ± 0.009 (9)[c]
Adrenal/BW ratio	0.022 ± 0.003	0.026 ± 0.005	0.024 ± 0.004	0.025 ± 1.0.005 (9)	0.030 ± 0.002 (9)[d]
Liver (g)	8.578 ± 0.903	7.890 ± 0.535	8.492 ± 0.595	9.315 ± 1.0.710 (9)	10.625 ± 1.337 (9)[d]
Liver/BW ratio	2.826 ± 0.200	2.833 ± 0.207	2.874 ± 0.114	3.310 ± 0.246 (9)[d]	3.969 ± 0.333 (9)[d]
Kidney/BW ratio	0.695 ±0.040	0.729 ± 0.074	0.706 ± 0.068	0.781 ± 0.054 (9)[c]	0.806 ± 0.048 (9)[d]

Table 2. Summary of Effects in Rats Exposed by Gavage to Unspecified Light Aromatic Solvent Naphtha (CASRN 64742-95-6) for 13 Weeks[a]

Pathology					
Large Liver[e]	1/10	0/10	0/10	3/10	7/10[f]
Yellow Aorta[e]	0/10	0/10	0/10	7/10[f]	9/10[f]
Hepatocytic Hypertrophy[e]	0/10	0/10	1/10	10/10[f]	10/10[f]

[a]Mobil Oil Corporation, 1994
[b]Mean ± standard deviation or incidence, as appropriate
[c]Significantly different from control, $p < 0.05$, Dunnett's Test or Tukey Test
[d]Significantly different from control, $p < 0.01$, Dunnett's Test or Tukey Test
[e]No statistical evaluations for these variables were made by the study's authors
[f]Significantly different from control, $p < 0.01$, Fisher's exact test conducted for this review
[g]Significantly different from control, $p < 0.05$, Fisher's exact test conducted for this review

The authors reported no statistically significant or biologically important hematological effects (Mobil Oil Corporation, 1994). Specifically, changes suggesting anemia (reduced RBC and hemoglobin) observed among high-dose females in the previous study with rats (Bio/Dynamics, 1990a) were not observed in this study at any dose in either sex during Week 5 or terminal evaluations. Table 2 shows the affected clinical chemistry variables at study termination. The affected variables were total protein, albumin, albumin/globulin (A/G) ratio, total bilirubin, and inorganic phosphorus in males and total protein, urea nitrogen, creatinine, alanine aminotransferase (ALT), inorganic phosphorus, and alkaline phosphatase (ALP) in females. These variables appeared to change consistently with dose, were statistically different from controls at the high dose, and, in some cases, were reported by the study authors to be outside the historical control range. Statistically significant and dose-related increases in mean total bilirubin (high-dose males; 1.3 times higher than control value), mean ALT (high-dose females; 1.5 times higher than the control), and mean ALP (high-dose females; 1.8 times higher than the control value) suggest possible liver effects. Significantly increased serum creatinine levels in high-dose females (1.2 times that of the mean control value) indicate possible kidney damage. Total serum protein was significantly elevated relative to controls at 500 and 1250 mg/kg-day. The observed elevations in albumin, serum protein, and decreased urea nitrogen also could indicate dehydration or changes associated with protein and carbohydrate metabolism in parallel with decreased body weight at the higher doses. Recall that the Bio/Dynamics Inc. (1990a) study also reported elevated serum protein and albumin levels.

As shown in Table 2, the authors reported statistically significant increases in the absolute and/or relative weights of the adrenals, kidneys, and livers in females at 1250 mg/kg-day (Mobil Oil Corporation, 1994). At 500 mg/kg-day, the authors also reported statistically significant increases in the relative weights of the liver and kidneys. The reported elevations in absolute weights of adrenals, kidneys, and livers in males were not statistically significant. Relative liver weights were reported to be increased above controls for high-dose males, but these data are not shown in the study report. The predominant findings at gross necropsy were enlarged livers and a yellow coloration of the ascending aorta wall in animals treated with 500 or 1250 mg/kg-day. There were no histological findings in aorta sections and thus, the toxicological relevance of the yellow coloration is unknown. Histopathological examination of the liver revealed dose-related increases in the incidence of hepatocytic hypertrophy in both males and females. Although the authors reported no histological effects in female kidney tissues, male kidney sections had changes that may be consistent with nephropathy typical of male rats (dose-related hyaline droplet deposition, and nondose-related cortical tubular degeneration, consisting primarily of epithelial swelling).

In conclusion, the LOAEL for this study (Mobil Oil Corporation, 1994) is 500 mg/kg-day. Liver effects, including hepatocytic hypertrophy was observed in females at this level. Additional liver effects, including clinical chemistry changes (increased serum bilirubin, ALT and ALP) in addition to increased liver weight and hepatocyte hypertrophy were observed at higher doses.

Bio/Dynamics Inc. (1990b) administered 100% pure LX1106-01 (Solvent Naphtha, Petroleum, Light Aromatic, CASRN 64742-95-6) in gelatin capsules daily to groups of Beagle dogs (four/sex) at doses of 0, 125, 250, or 500 mg/kg-day for up to 90 days. The authors did not report the chemical or the isomeric composition of the test substance. They monitored clinical signs, body weight, and food consumption throughout the study. Hematological and clinical chemistry variables were examined at intervals throughout the study. Ophthalmoscopic

examinations were made prior to study initiation and at the end of the study. All dogs received a gross necropsy, major organs were weighed, and histopathological examinations of all major tissues and organs were made for all animals.

No dogs died or were sacrificed in moribund condition during the study Table 3 summarizes the significant effects observed in this study (Bio/Dynamics Inc., 1990b). Other than watery stools in one mid-dose and two high-dose males, the authors reported no treatment-related clinical signs or treatment-related abnormalities during the ophthalmological examinations. They reported no statistically significant changes in group mean body weights relative to controls, but high-dose dogs lost weight during the study (0.8 and 0.4 kg for males and females, respectively) and the terminal body weights for both males and females were 20% lower than their respective controls. Food consumption was statistically comparable among all groups.

Treatment was associated with anemia that affected males to a greater extent than females (Bio/Dynamics Inc., 1990b). Mean red blood cell (RBC) counts, percent hematocrit, and hemoglobin values were statistically significantly decreased in comparison with controls in high-dose males and females after 6 weeks of exposure. Decreased RBCs also were observed among mid-dose males both at 6 weeks and at study termination. Platelet counts were elevated in high-dose dogs of both sexes, statistically significantly in females. Activated partial thromboplastin time (APPT) was also elevated significantly in females suggesting, along with elevated platelet counts, a treatment-related effect on clotting. There were no treatment-related adverse effects on clinical chemistry variables.

As shown in Table 3, the authors reported significantly elevated kidney/body weight and liver/body weight ratios in the high dose group relative to controls (Bio/Dynamics Inc., 1990b). However, they reported no treatment-related pathological changes indicative of an adverse effect on the liver or kidney. In fact, the authors reported no treatment-related adverse effects for any tissue or organ following gross and microscopic examinations. In conclusion, the study NOAEL is 125 mg/kg-day. The LOAEL for the study is 250 mg/kg-day based on significantly reduced red blood cell levels in males. Reductions in hemoglobin and hematocrit also were observed at the next higher dose.

Table 3. Summary of Significant Terminal Effects in Dogs Exposed Orally Via Gelatin Capsules to LX-1106-01 for up to 90 Days[a]

Males (*n* = 4 unless noted otherwise)				
Variable[b]	**Control**	**125 mg/kg-day**	**250 mg/kg-day**	**500 mg/kg-day**
Body Weight (kg)	10.3 ± 0.4	10.9 ± 0.6	10.0 ± 1.2	8.4 ± 1.4
Hematology				
Terminal RBC (mil/µL)	7.81 ± 0.59	7.32 ± 0.55	6.77 ± 0.15[c]	6.74 ± 0.44[c]
Wk 6 RBC (mil/µL)	7.53 ± 0.67	6.95 ± 0.19	6.51 ± 0.36[c]	6.38 ± 0.39[c]
Wk 6 HGB (g/dL)	17.4 ± 1.7	16.2 ± 0.2	15.6 ± 1.0	15.0 ± 0.6[c]
Wk 6 HCT (%)	50 ± 5	45 ± 2	44 ± 4	42 ± 3[c]
Platelets (100 T/µL)	3.68 ± 0.64	4.06 ± 1.05	4.47 ± 1.18	5.181 ± 0.19
Organ Weights				
Liver/BW ratio	2.60 ± 0.27	2.98 ± 0.40	3.12 ± 0.33	3.63 ± 0.61[c]
Females (*n* = 4 unless noted otherwise)				
	Control	**125 mg/kg-day**	**250 mg/kg-day**	**500 mg/kg-day**
Body Weight (kg)	8.6 ± 0.7	8.3 ± 0.8	8.1 ± 1.1	6.9 ± 0.8
Hematology				
Wk 6 RBC (mil/µL)	7.6 ± 0.41	7.34 ± 0.68	7.20 ± 0.20	6.35 ± 0.25[d]
Wk 6 HGB (g/dL)	18.0 ± 1.1	17.5 ± 1.4	16.7 ± 0.2	14.9 ± 0.9[d]
Wk 6 HCT (%)	50 ± 4	49 ± 5	47 ± 0	41 ± 3 [c]
APPT (sec)	9.5 ± 0.8	9.5 ± 0.4	10.2 ± 0.5	10.7 ± 0.6[c]
Platelets (100 T/µL)	3.42 ± 0.29	3.80 ± 1.17	4.64 ± 0.67	5.41 ± 0.46[d]
Organ Weights				
Kidney/BW ratio	3.84 ± 0.48	4.45 ± 0.57	3.95 ± 0.33	5.06 ± 0.62[c]
Liver/BW ratio	2.86 ± 0.22	3.12 ± 0.64	3.04 ± 0.60	3.95 ± 0.35[c]

[a]Bio/Dynamics Inc., 1990b
[b]Mean ± standard deviation
[c]Significantly different from control, $p < 0.05$, Dunnett's Test
[d]Significantly different from control, $p < 0.01$, Dunnett's Test

Developmental/Reproductive Toxicity Studies—Bio/Dynamics Inc. (1990c) conducted an oral teratology study with LX1106-01 (Solvent Naphtha, Petroleum, Light Aromatic, CASRN 64742-95-6) in rats. Groups of 24 pregnant CD rats were given doses of 0, 125, 625, or 1250 mg/kg-day via gavage (in corn oil) on Days 6-15 of gestation. Maternal signs of toxicity, body weight, and food consumption were monitored throughout gestation. All fetuses were examined externally. Half of the fetuses from each litter were examined in detail for soft tissue malformations, and the other half were examined for skeletal variations and malformations.

No maternal mortality occurred in the control, low-, or mid-dose groups (Bio/Dynamics Inc., 1990c). There was one high-dose dam that died, and the death was considered to be treatment-related. A dose-related increase in the incidence of salivation was noted during the 6−15-day exposure interval for control, low-, mid-, and high-dose dams at

0% (0/24), 25% (6/24), 95.8% (23/24), and 95.8% (23/24), respectively. However, the meaning of this finding is unclear in the absence of other clinical signs. Dams in the high-dose treatment group had a greater incidence of anogenital staining and alopecia. These findings also were observed in the Bio/Dynamics Inc. (1990a) and Mobil Oil Company (1994) subchronic toxicity studies. Mean body weights were comparable among dams in control, low- and mid-dose groups on Days 0, 6, 11, 15, and 20 of gestation. High-dose dams had significantly lower mean body weights with respect to controls on Days 11, 15, and 20. Mean body-weight gain measured on Days 0−6 and 11−20 of gestation were statistically significantly lower than controls among mid- and high-dose dams (-23.3% and -51.2%, respectively). Mid- and high-dose dams also had lower gravid uterine weights, but the difference was only statistically significant at the high dose. Food consumption rates were decreased among mid-and high-dose dams during Days 6−11 but were statistically significant with respect to controls only at the high-dose. In contrast to the reduction seen during exposure, high-dose dams had significantly increased food consumption with respect to controls during the posttreatment period. The study authors speculated that food consumption may have increased to compensate for the prior period of decreased food intake. There were no treatment-related effects on pregnancy rate or gestation. The NOAEL for maternal toxicity is 125 mg/kg-day and the LOAEL is 625 mg/kg-day based on reduced body-weight gain during Days 0−6 and 11−20 of gestation.

No treatment-related embryotoxicity, fetal toxicity, or teratogenic effects were noted at 125 or 625 mg/kg-day (Bio/Dynamics Inc., 1990c). Mean fetal body weight at the high dose (1250 mg/kg-day) was significantly reduced with respect to controls (-11%). There were no treatment-related effects on the number of fetuses with external or visceral malformations or the incidence of litters containing fetuses with malformations. The incidences of skeletal malformations (both on per-fetus and per-litter basis) were comparable among control and treated groups. However, high-dose (1250 mg/kg-day) fetuses had clear signs of delayed skeletal ossification, with increased incidences of incompletely ossified thoracic vertebral centrum, un-ossified thoracic vertebral centrum, incompletely ossified and/or un-ossified sacral vertebral transverse processes, un-ossified sternebrae and rudimentary rib structures of the first lumbar vertebrae. The incidence of total fetal skeletal variations at the high dose was 95.7% (135/141) in comparison with 75.5% of controls (120/159), and this difference was statistically significant. The incidence of litters with at least one fetus having a skeletal ossification variation was 100% for the controls and for each treatment group. Based on these findings, the NOAEL for fetotoxicity is 625 mg/kg-day. The LOAEL for fetotoxicity is 1250 mg/kg-day based on reduced mean fetal body weight and delayed skeletal ossification.

Inhalation Exposure

Subchronic Studies—There are two subchronic inhalation studies that have been conducted with commercial formulations of HFAN (Clark et al., 1989; Douglas et al., 1993).

Clark et al. (1989) reported on studies conducted with a blend of Shell and Exxon products SHELLSOL A® and SOLVESSO 100®. Clark et al. (1989) briefly mention an unpublished study conducted by Shell Research Ltd in 1980. In that study, rats were exposed to vapors of SHELLSOL A® at concentrations of 1800, 3700, or 7400 mg/m^3. Increased liver and kidney weights were observed in the mid-and high-concentration group females, as well as a low-grade anemia in all exposed females. No other details are reported. Given these findings, Clark et al. (1989) undertook a longer-term systemic toxicity study that evaluated exposures to a mixture of Shell and Exxon HFAN products. In their study, groups of 50 male and 50 female Wistar rats were exposed by whole-body inhalation to a 50/50 mixture of SHELLSOL A® and

SOLVESSO 100® at mean measured concentrations of 0, 470, 970, or 1830 mg/m^3, for 6 hours/day, for 5 days/week for, 12 months. In the mixture to which rats were exposed, the following components were identified by gas chromatography (%): nonaromatics (0.46); *o*-xylene (2.27); *n*-propylbenzene (4.05); 1-methyl-3-ethylbenzene (7.14); 1-methyl-4-ethylbenzene (16.60); 1,3,5-trimethylbenzene (9.35); 1-methyl-2-ethylbenzene (7.22); 1,2,4 trimethylbenzene (32.70); 1,2,3-trimethylbenzene (2.76); 1-methyl-3-*n*-propylbenzene and 1,2-diethylbenzene (6.54), and 1-ethyl-3,5-dimethylbenzene (1.77). Test atmospheres were generated by evaporating the test substance with quartz tube into part of the ventilation system then mixing it with chamber air via micrometering pumps to achieve the desired test concentration. Test concentrations were measured by two methods: for 10 minutes every 40 minutes by hydrocarbon analyzer; and for 2 hours (consecutive) each exposure period via gas chromatography with flame ionization detector.

Groups of 10 rats/sex were killed in an interim sacrifice after 6 months of exposure; groups of 25 rats/sex were killed after 12 months of exposure and additional groups of 15/sex were allowed to recover for 4 months after cessation of exposure prior to sacrifice and subsequent examination (Clark et al., 1989). Hematologic variables were measured for 10 males and females from control and high-concentration groups during Weeks 1, 2, 4, 6, 8, 12, 20, 24, 28, and 32 and from all rats and groups at 6 months, 12 months and following the 4-month recovery period. Serum chemistries were similarly evaluated at 6 and 12 months and following the 4-month recovery period. Urinalysis was conducted for 12/sex/group pretest, after 3, 6, 9, and 12 months of exposure, and 3 months after exposure ended. All rats were necropsied, and the liver, kidneys, spleen, brain, heart, and testes were weighed. Histological preparations were made of all major organs and tissues and were evaluated following 12 months of exposure.

There were no treatment-related effects on mortality (Clark et al., 1989). The authors reported increased aggression in males in the high-concentration group; the authors observed that some of these males were more difficult to handle than rats in the other exposure concentration groups.

Over the first 4 weeks of the study, body weight was significantly decreased with respect to controls in males from the high-concentration group and females from the mid-concentration group (-2%). Body weight also was significantly decreased with respect to controls over the first 12 weeks of the study in females from the high-concentration group (-3%). There were no other differences between treatment groups thereafter and no significant or important changes with respect to body weight were attributed to exposure (Clark et al., 1989).

When compared to controls, Clark et al. (1989) reported the following statistically significant hematological changes in the high-concentration groups (%):

Reduced mean red cell volume: females, Week 16 (-2%);
Reduced hematocrit: males, Weeks 20 and 24 (-2 to 4%);
Reduced red cell count: males, Weeks 16, 20, and 24 (-3 to 4%);
Increased mean cell hemoglobin: males, Week 20 (+3%);
Increased mean cell hemoglobin concentration: male, Weeks 24 and 28 (+2%);
Elevated leukocyte counts: males, Weeks 2, 4, 6, 8, and 24 (+10 to 30%) and females, Weeks 6, 24, and 28 (+25%).

At the 6-month interim evaluation, females in all three treatment groups had significantly reduced eosinophil counts (30−55%) with respect to controls (Clark et al., 1989). Though no atypical cells were found in the blood films, this reduction reportedly was apparent in females of the mid- and high-concentration groups at the end of the 4-month recovery period (specific data not reported). The only other finding of significance was a decrease in osmotic fragility among males at the high concentration at 12 months, but the difference relative to controls was small and not biologically important. A significantly increased total lymphocyte count was also reported for males in the high-concentration group (2.7 versus 2.1, control value). However, since no atypical cells were observed in blood films, this observation was not considered to be biologically important. In addition, when lymphocytes were evaluated on a percentage basis, there was no dose-response and little difference between rats in the control (63%) and high-concentration groups (62%).

There were no treatment-related effects on serum chemistry variables at any interim or terminal evaluation (Clark et al., 1989). Aside from organ-weight changes noted below, there were no treatment-related gross pathological changes. Similarly, there were no treatment-related histological changes in any tissue or organ.

High-concentration group males at the 6-month necropsy had significant increases in liver (10 %) and kidney weights (12%) (Clark et al., 1989). These observations persisted at the 12-month necropsy. In females, significantly decreased kidney/body-weight ratios were observed with respect to controls in all treatment groups (2−4% lower when adjusted for initial body weight). Decreased liver weight (12%) also was observed in females of the high-concentration group relative to controls. Clark et al. (1989) noted that decreased liver weight could be attributed to one very low value in the high-exposure group and that the apparent reduction in kidney weight was likely due to "the relatively high kidney weights of two of the control animals."

In summary, there are no biologically significant effects among rats tested at the low and middle concentrations in the Clark et al. (1989) study. The only effects observed at the high concentration (1830 mg/m^3) were transient and sporadic mild changes in hematological variables, increases (males) and decreases (females) in liver and kidney weights and unquantified, minimally qualified "aggression" in males. The increased aggression observed in males is not likely to have toxicological relevance given the lack of treatment-related findings in the neurotoxicity study conducted by Douglas et al. (1993), which is discussed below. Therefore, the NOAEL for this study is 1830 mg/m^3 (highest concentration tested).

Douglas et al. (1993) exposed groups of 20 adult male Charles River COBS CD rats to vapors of HFAN at mean measured concentrations of 0, 101, 432, or 1320 ppm (whole-body exposure; values taken from Table 2 of the study report) 6 hours/day, 5 days/week for 90 days. Assuming a molecular weight of 120 grams/mole (on the basis of the reported composition of the native sample used to generate exposure vapors), these air concentrations are equivalent to 0, 496, 2120, and 6479 mg/m^3. The purpose of the study was to evaluate the potential neurotoxicity of HFAN. The HFAN used in the study conformed to the ASTM standard and contained: 55% trimethylbenzenes, 28% ethyltoluenes, 3.97% *n*-propylbenzene, 2.74% cumene, 3.20% *o*-xylene, and 6.19% ≥ C10. Test atmospheres were generated in the study by passing the liquid test substance through a metered pump into a bead-packed column containing nitrogen that was heated to 200ºC. The tests substance was vaporized as it passed though the column, then passed to the test chamber inlet; vapors were diluted with chamber air to the desired

concentrations. Exposure concentrations were monitored with gas-phase infrared spectroscopy on an hourly basis throughout the study; accuracy was confirmed with vapor standards.

Rats were weighed and clinically evaluated weekly. Neurotoxicity testing (motor activity and functional observational battery) was conducted at 5, 9, and 13 weeks of exposure. Groups of 10 animals per dose were sacrificed at the end of the study and detailed histopathological examination of peripheral and central nervous system tissues was conducted. No other tissues were examined.

Body weight was significantly reduced with respect to controls in the group exposed to the high concentration every week throughout the study (Douglas et al., 1993). At termination, rats from the high-concentration group weighed approximately 12% less than controls. Rats from the group exposed to the 432-ppm concentration had a transient variance from control body weight only at the 4th week of the study and by study end, weighed more than controls. There were no treatment-related clinical signs of toxicity and no differences between HFAN-exposed rats at any concentration with respect to controls, in terms of clinical signs, motor activity, or the functional observational battery of tests. No treatment-related histopathological changes were observed following comprehensive examination of tissues from the peripheral and central nervous systems. The NOAEL for the study is 432 ppm (2120 mg/m^3). The LOAEL is 1320 ppm (6479 mg/m^3) based on reduced body weight.

Nau et al. (1966) conducted a series of subchronic inhalation studies with rats and Rhesus monkeys with a C9−C12 aromatic fraction formulated from a large number of naphtha samples obtained from some members of the American Petroleum Institute. These studies are not considered in this document because the test substance does not meet the current ASTM standard for HFAN (i.e., did not contain the requisite trimethylbenzene and ethyltoluene [C9] components). The sample had 74% alkyl benzenes, of which only 42% was C9, 29% was C10, and 3% was C11 and contained a large fraction of aliphatic hydrocarbons, including 20% paraffins and 6% cyclo-paraffins.

Smith et al. (1999) conducted a series of subchronic inhalation studies with rats and mice with a C9−C16 aromatic fraction of Jet-A. Because the test substances used included a large fraction (approximately 21%) of aliphatic compounds (BDM International, 1998), these studies are not considered in this PPRTV document. Specifically, the aliphatic fraction contained (by volume) 3.2% paraffins, 4.1% monocycloparaffins, 6.5% dicycloparaffins, 6.7% tricycloparaffins, and 1.1% sulfur compounds. The aromatic fraction of the test substance (78.4% of total volume) contained 41.3% alkylbenzenes, 18.6% benzenocycloparafins, 2.9% benzodicycloparaffins, and 15.6% naphthalenes.

Developmental/Reproductive Toxicity Studies—Developmental toxicity and reproduction studies conducted via the inhalation route of exposure are available for HFAN.

McKee et al. (1990) conducted a developmental toxicity study in mice and a three-generation reproduction study in rats. In the developmental toxicity study, pregnant CD-1 mice (30/group) were exposed to mean measured concentrations of 0, 102, 500, or 1514 ppm HFAN vapors 6 hours/day, on Days 6−15 of gestation. Assuming a molecular weight of 120 g/mole (on the basis of the reported composition of the native sample used to generate exposure vapors), these concentrations are equivalent to 0, 501, 2454, and 7431 mg/m^3. Based on the intermediate exposure protocol, these exposure concentrations were adjusted to 0, 125, 613, and 1858 mg/m^3, respectively. (In these adjustments, the reported concentrations were

multiplied by the following ratio: 6 hours/24 hours. See Table 4. Human equivalent concentrations were estimated by multiplying these adjusted concentrations by a dosimetric adjustment, which is the ratio of the animal:human blood:gas partition coefficients for HFAN; in the absence of experimental values, a default value of 1 was used. All concentrations for this discussion are presented as reported concentrations). The HFAN used in the study conformed to current ASTM standards and contained (%): *o*-xylene (2.74); cumene (3.97); *n*-propylbenzene (7.05); 4-ethyltoluene (5.44); 2-ethyltoluene (8.37); 1,3,5-trimethylbenzene (8.37); 1,2,4-trimethylbenzene (40.5); 1,2,3-trimethylbenzene (6.18); ≥C10 (6.19), and unaccounted (1.26). The system used to generate and validate the test atmospheres was identical to the one used by Douglas et al. (1993) described above.

Maternal mortality was observed in the groups exposed to 2454 (2/30) and 7431 mg/m^3 (14/32); two replacement animals were added, increasing the size of the high concentration group (McKee et al., 1990). Clinical signs of toxicity were noted predominantly in the high-concentration exposure group and included abnormal gait, labored breathing, hunched posture, weakness, inadequate grooming, circling behavior, and ataxia. Mean maternal body weight differed significantly from controls in all treatment groups on Day 15 of gestation, the end of the exposure period (39 ± 3.3, 35 ± 7.6, 36 ± 4.9, and 33 ± 6.0 grams for 0, 501, 2454, and 7431 mg/m^3 exposure groups, respectively), but was statistically different from controls on Day 8 of the study (3 days postexposure) only at the highest exposure concentration (47 ± 3.4 for controls, versus 40 ± 8.7 for 7431 mg/m^3). Mean body-weight gain was significantly reduced with respect to controls (both Day 6−15 and Day 0−18 intervals) for dams in the middle and high concentration groups, but not for dams from the low concentration group. Mean maternal body-weight gains for the 0, 501, 2454, and 7431 mg/m^3 treatment groups for Days 0−18 were 23 ± 2.7, 19 ± 8.8, 19 ± 5.6, and 14 ± 6.8 grams, respectively. A similar pattern, but with smaller inter-group differences, was observed for the 6−15 day interval. Statistically significant hematological deviations from control values (reduced mean hematocrit and mean corpuscular volume; data not shown) were observed in high-exposure dams. No adverse clinical signs or dose-related hematological variations were observed among low- or mid-exposure dams. There were no effects on organ weights or pathological changes among any of the HFAN-exposed dams with respect to controls. The LOAEL for maternal toxicity is 501 mg/m^3 (lowest concentration tested), based on reduced body weight during exposure, with increasingly greater toxicity (mortality, hematological effects) at higher exposure concentrations.

Table 4. Inhalation Dose-Response Summary for RfC Derivation

Species/ Method	Sex	Exposure (mg/m^3)	$NOAEL_{HEC}$[a] (mg/m^3)	$LOAEL_{HEC}$[a] (mg/m^3)	Responses at the LOAEL	Reference
Subchronic Toxicity						
Rat/whole-body	M/F	0, 1800, 3700, 7400 mg/m^3 for 13 wks; exposure regimen not reported	None	Uncertain	Low-grade anemia in females	Clark et al., 1989
Rat/whole-body	M/F	0, 470, 970, 1830 mg/m^3 for 12 months (adjusting for 6/24 hr/d and 5/7 d/wk, concentrations are 0, 84, 173 and 327 mg/m^3)	327	None		Clark et al., 1989
Rat/whole-body	M	0, 101, 432, 1320 ppm for 90 days (equivalent to 0, 496, 2120, or 6479 mg/m^3; adjusting for 6/24 hr/d, 5/7 d/wk, concentrations are 0, 89, 379, or 1157 mg/m^3)	379	1157	Reduced body weight (versus controls) throughout the study (12% deficit at termination)	Douglas et al., 1993
Developmental Toxicity						
Mouse/ whole-body	F	0, 102, 500, 1514 ppm for 6/24 hr/d on Days 6-15 gestation (equivalent to 0, 501, 2454, or 7431 mg/m^3; adjusting for 6/24 hr/d, concentrations are 0, 125, 613, 1858 mg/m^3)	Maternal: None Fetal: 125	Maternal: 125 Fetal: 613	Maternal: reduced mean body weight on GD15; reduced body weight and body-weight gain at ≥613; 44% mortality, clinical signs, reduced hematocrit at 1858 mg/m^3 Fetal: reduced mean body weight; increased cleft palate, delayed ossification, and fetal death at 1858 mg/m^3	McKee et al., 1990
Mouse/ whole-body	F	0, 500, 1000−1500, regimen uncertain	Uncertain	Uncertain	Reported increase in total malformations (9% versus 4% controls), but no details are presented and data for the highest dose are not discussed	Ungvary and Tatrai, 1985
Rabbit/ whole-body	F	0, 500, 1000, continuously, Days 7−20 of gestation	500	1000	100% abortion (3/3 rabbits)	Ungvary and Tatrai, 1985
Rat/ whole-body	F	0, 600, 1000, 2000, continuously, Days 7−15 of gestation	None	600	Delayed skeletal development	Ungvary and Tatrai, 1985

Table 4. Inhalation Dose-Response Summary for RfC Derivation

Species/ Method	Sex	Exposure (mg/m^3)	$NOAEL_{HEC}$[a] (mg/m^3)	$LOAEL_{HEC}$[a] (mg/m^3)	Responses at the LOAEL	Reference
Rat/ whole-body	F	0, 600, 1000, 2000, 6 hr/d on Days 7−15 of gestation (adjusting for 6/24 hr/d: 0, 150, 250, 500)	500	None	No effects on fetal body weight or behavior (malformations, etc. were not examined)	Lehotsky et al., 1985
Reproductive Toxicity						
Rat/ whole-body	M/F	0, 506, 2429, 7264, 6 hr/d for three generations (adjusting for 6/24 hr/day: 0, 127, 607, 1816 mg/m^3)	127	607	Decreased pup body weight (mid-and high-exposure groups on Days 14−21 of lactation in F_3 generation: 10% and 24% less than controls, respectively, regardless of sex); also in high-concentration groups on Days 7−21 of lactation in F_1 and F_2. Significant mortality in high-concentration F_2 parental males (85%) and females (90%) during initial exposure week to produce F_3 generation; significant decreases in male fertility, litter size and pup viability in high-concentration F_2 females with unconfirmed mating that received additional exposure between Day 20 of gestation and natural delivery.	McKee et al., 1990

[a]HEC calculated as follows: $NOAEL_{HEC}$ = NOAEL × exposure hours/24 hours × exposure days/7 days × dosimetric adjustment. For nonrespiratory effects, the chemical is treated as a Category 3 gas (U.S. EPA, 1994b) and the dosimetric adjustment is the ratio of the animal:human blood:gas partition coefficients for HFAN (in the absence of experimental values, a default value of 1 was used).

The following statistically significant effects were noted only among high-concentration dams (exposed versus control value): number pregnant/number mated (22/30 versus 26/30), number of litters with viable fetuses (13 versus 24), and mean postimplantation loss per dam (4.3 ± 3.7 versus 0.9 ± 0.9). The mean number of live fetuses per litter also was decreased significantly in the high exposure concentration group (7.9 ± 4.3 versus 10.7 ± 1.8). Although this endpoint was statistically significantly reduced in the low-concentration group (8.7 ± 4.6) as well, the researchers did not consider the change at this concentration to be biologically meaningful because, when compared to controls, there was no change in the mid-concentration group (9.3 ± 3.1). The only treatment-related anomalies in the study were observed among high-concentration fetuses and included an increased incidence of cleft palate (one fetus in one litter among controls versus 14 fetuses in seven litters among high-concentration dams) and delayed skeletal ossification (unossified 5^{th} or 6^{th} sternebrae: 0 controls, 1 fetus in 1 litter at 501, 3 fetuses in 2 litters at 2454 and 25 fetuses in 10 litters at 7431 mg/m^3; reduced skull ossification: 0 controls, 501, or 2454 mg/m^3; 18 fetuses in 6 litters at 7431 mg/m^3). Mean fetal body weight was significantly reduced among mid- and high-concentration treatment groups relative to controls (1.25 ± 0.14, 1.24 ± 0.08, 1.16 ± 0.11, 0.82 ± 0.17 for control, 501, 2454, and 7431 mg/m^3 groups, respectively). Considering these results, 501 mg/m^3 is a NOAEL and 2454 mg/m^3 is a LOAEL for fetal toxicity based on reduced mean fetal body weight), with increasing toxicity (developmental anomalies, fetal death) at higher concentrations.

McKee et al. (1990) exposed Charles River COBS CD rats for three generations to HFAN vapors of generated in the same manner as in the previously described mouse study. Groups of 30 per sex in the parental generation were exposed to mean measured concentrations of 0, 103, 495, or 1480 ppm 6 hours/day, 5 days/week for a total of 12 weeks. Assuming a molecular weight of 120 g/mole (as above), these concentrations are equivalent to 0, 506, 2429, or 7264 mg/m^3. Based on the intermediate exposure protocol, these exposure concentrations were adjusted to 0, 90, 434, and 1297 mg/m^3, respectively. (In these adjustments, the reported concentrations were multiplied by the following ratios: 6hours/24 hours and 5 days/7 days. Human equivalent concentrations were estimated by multiplying these adjusted concentrations by a dosimetric adjustment, which is the ratio of the animal:human blood:gas partition coefficients for HFAN; in the absence of experimental values, a default value of 1 was used. All subsequent concentrations for this discussion of this study are presented as reported concentrations). After mating (2-week period), males were removed and female exposure (changed to 6 hours/day, 7 days/week) continued throughout gestation until birth on Gestational Day 20. Exposure ceased on Day 20 of gestation and throughout the first 5 days postdelivery, then resumed during Days 5−21 of lactation. Parental males and females were sacrificed. Pups were randomly selected from the F_1 generation (30/sex/group) to produce the F_2 generation and then exposed in the same manner as the parental generation. This process was repeated one more time to establish an F_3 generation, with the exceptions that 40/sex/group were selected and that all pups at the F_2 high-concentration were retained due to high mortality.

In the parental generation, signs of toxicity included significantly reduced body-weight gains among both males and females at the mid- (5−7%, both sexes) and high-concentrations (14−16% males; 5−7%, females) (McKee et al., 1990). There were seven females at the high concentration that died or were sacrificed prior to delivery of the first litter. There were no treatment-related effects on indices of mating or fertility.

The only effect on F_1 pups was decreased body weight among the high-concentration group on Days 7−21 of lactation (McKee et al., 1990). The same trend was observed among both F_2 and F_3 generations at the high concentration and also at the middle exposure concentration in the F_3 generation (Days 14−21 of lactation). For example, in the F_3 generation at Day 21, male and female body weights were 10% less than controls in the mid-concentration group and 24% less than controls in the high-concentration groups. There were no effects on mating or fertility indices for either sex in the F_1 or F_3 generations. However, the male fertility index (64.3% versus 89.7% controls), mean litter size at birth (8.7 ± 4.3 versus 12.0 ± 2.0 in controls), and the gestation survival index (number of pups alive at birth/number of pups born: 85.1% versus 97.4% control) were significantly reduced in the F_2 generation at the highest concentration. The authors attributed these observations with regard to fertility and survival in the F_2 to unconfirmed mating in dams (6/24, 8/24, 1/24, and 9/24 from control, low-, mid- and high-exposure concentration groups) that led to additional exposure up to the time of birth[2]. When dams with unconfirmed mating are eliminated from the data pool, the magnitude of these effects is reduced to nonsignificance.

There was significant mortality among high-concentration parental F_2 rats during the first week of exposure to produce the F_3 generation (beyond Postnatal Day 22, 36/40 males and 34/40 females) (McKee et al., 1990). The remaining few survived to produce litters. The only treatment-related effect on F_3 pups was reduced mean body weight, as described above for the other generations. There were no effects on male fertility or any other index of mating or survival.

In summary, HFAN exposure to 7264 mg/m^3 resulted in significant body-weight depression and mortality during periods of exposure in rats, but was not associated with effects on mating, fertility or pup survival indices, except in the F_2 generation (decreased male fertility and subsequent litter size and pup viability) in association with dams that received additional exposure between Day 20 of gestation and natural delivery (McKee et al., 1990). Exposure to 2429 mg/m^3 resulted in significantly decreased body weights among F_2 and F_3 pups on Days 14−21 of lactation. The NOAEL for this study is 506 mg/m^3. The LOAEL is 2429 mg/m^3 for reduced pup body weight in two generations.

Ungvary and Tatrai (1985) conducted a series of developmental toxicity studies via inhalation exposure with a commercial formulation of HFAN known as Aromatol. These studies are poorly reported in English and provide few details. Groups of pregnant mice (115 controls pooled with other studies; 19 mid- and 15 high-concentration mice) were exposed to vapors of Aromatol at concentrations of 0, 500, or 1000−1500 mg/m^3. It is not possible to discern the exact exposure protocol from the report. In the text, authors state that exposures were 24 hours/day continuously or three exposures for 4 hours per day spaced intermittently over Days 6−15 of gestation. However, the table that presents results for a number of chemicals and experimental animals has a footnote stating that exposure was for the latter protocol. The results and consequent effect levels from this study are unclear. The authors report, "Aromatol exerted a moderate teratogenic effect in mice (the incidence of anomalies of the uropoetic apparatus increased)." Details are shown only for the middle dose and are confined to a significantly

[2]In dams with confirmed mating, exposure took place from gestation day (GD) 0–20 and then was discontinued through Lactation Day 5. Mating was not confirmed in 24 of the test animals, including 6 controls, 8 at 506 mg/m^3, 1 at 2429 mg/m^3, and 9 at 7264 mg/m^3. Due to the fact that GD 0 was not determined, exposure of these dams continued through delivery instead of being discontinued on GD 20 prior to natural delivery. When dams with unconfirmed mating were removed from the dataset, there were no differences between controls and exposed rats.

higher percentage of total malformations (9%) with respect to controls (4%). No other details, including the percentage of individual malformations or anomalies are given. It is not possible to reliably determine a NOAEL or LOAEL for this study.

Ungvary and Tatrai (1985) exposed pregnant rabbits (60 pooled controls, 10 low-, and 3 high-concentration) to Aromatol vapors at concentrations of 0, 500, or 1000 mg/m^3 continuously on Days 7−20 of gestation. All rabbits aborted at the high concentration. No effects were observed on maternal weight gain or relative liver weights. There were no deaths and no abortions among rabbits exposed to 500 mg/m^3. In addition, there were no effects on fetal mortality (5% exposed versus 5.2% controls), skeletal growth or the incidence of malformations with respect to controls at 500 mg/m^3 (data not shown in report). The NOAEL for the study appears to be 500 mg/m^3. Exposure to 1000 mg/m^3 was frankly toxic, producing 100% abortion.

Ungvary and Tatrai (1985) exposed groups of rats to Aromatol vapors at concentrations of 0, 600, 1000, or 2000 mg/m^3 continuously on Days 7−15 of gestation. All components of the mixture were found in maternal and fetal blood, as well as in amniotic fluid (determined by gas chromatography). Delayed skeletal development was dose-related, with 8, 17, 15, and 60% of the fetuses affected at 0, 600, 1000, and 2000 mg/m^3, respectively. Fetal body weights were significantly reduced at the two highest concentrations and the percentage of total malformations was reported to be significantly elevated at the highest concentration (4%, 2%, 1%, and <1% for 2000, 1000, 600, and 0 mg/m^3, respectively). The incidence of individual malformations was not presented. Maternal toxicity is only addressed in a statement that "The dose-dependent toxic effect of Aromatol was slight in the mother and moderate in the offspring." Based on this information, there is no NOAEL for the study and the LOAEL is 600 mg/m^3 on the basis of delayed skeletal development.

Lehotsky et al. (1985) conducted a developmental neurobehavioral study to investigate the effects of Aromatol, carbon disulfide, methyl ethyl benzenes, and trimethylbenzenes on developing rats. Groups of pregnant CFY rats were exposed to vapors of Aromatol (whole-body exposure) at concentrations of 0, 600, 1000, or 2000 mg/m^3 for 6 hours per day on Days 7−15 of gestation. There were 10 air-exposed pregnant rats that served as controls for all of the test substances under investigation. Rats were allowed to deliver naturally, numbers of pups per litter were recorded, and then litters were randomly culled to 10 pups each. Pups were weighed as a litter on Day 1 and on the day when eyes and ears opened. Following weaning on Day 21, males and females were separated and 10 per sex were administered a behavioral test battery. The test battery included measures of startle reaction, motor coordination, avoidance behavior, and behavioral patterns.

The authors reported that "Aromatol had no significant effect on any of the monitored parameters, either in dams or in offspring" (Lehotsky et al., 1985). They reported further that the dose-related neurotoxic effects observed in dams and neonates exposed to carbon disulfide (for which data were shown in detail) were not observed for Aromatol. No further details relevant to potential toxicity following exposure to Aromatol are presented in the paper. Based on these results, the NOAEL for this study is 2000 mg/m^3 (highest concentration tested).

Other Studies

Genotoxicity

Reverse mutation assays with *Salmonella typhimurium* were negative with and without metabolic activation in studies conducted with two different commercial preparations of HFAN, including a commercial HFAN known as LX1106-01 (FMC Corp., 1978; Life Science Research Limited, 1988). LX1106-01 induced primary DNA damage in *Escherichia coli* without metabolic activation (Life Science Research Limited, 1990a) and was clastogenic in human lymphocytes in the presence of S9, even at nontoxic concentrations (Life Science Research Limited (1990b).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR HIGH FLASH AROMATIC NAPHTHA

Because the toxicity data based on the three unpublished studies (Bio/Dynamics Inc., 1990a,b; Mobil Oil Corporation, 1994) are not peer-reviewed, no provisional chronic or subchronic RfDs are developed. However, the Appendix of this document contains screening chronic and subchronic RfD values that may be useful in certain instances. Please see Appendix A for details.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR HIGH FLASH AROMATIC NAPHTHA

No human epidemiology studies suitable for deriving subchronic or chronic p-RfCs for HFAN were located. The inhalation database for animals includes subchronic, developmental, reproductive, and neurotoxicity studies of HFAN in rats, mice, and rabbits. To facilitate comparison of the studies, the NOAEL and LOAEL values from each of the studies were adjusted for continuous exposure and then converted to human equivalent concentrations ($NOAEL_{HEC}$ and $LOAEL_{HEC}$) based on the guidance provided in U.S. EPA (1994b); Table 4 provides details of the models used to generate these estimates. Although U.S. EPA (1991b) recommended against adjusting for continuous exposure in developmental toxicity studies, more recently U.S. EPA (2002) argued that such adjustment should be made for developmental toxicants. Thus, the effect levels in the developmental toxicity studies also are adjusted for continuous exposure.

After adjusting for continuous exposure, the human equivalent concentration (HEC) was calculated using the dosimetric adjustment appropriate to the observed effect (U.S. EPA, 1994b). For all of the studies, extrarespiratory effects were observed, so HFAN was treated as a Category 3 gas. As such, a $NOAEL_{HEC}$ or $LOAEL_{HEC}$ is derived by multiplying the duration-adjusted NOAEL or LOAEL by the ratio of blood/gas partition coefficients for animal/human ($[H_{b/g}]_A/[H_{b/g}]_H$). A value of 1 is used for the ratio of the blood/gas partition coefficients if the animal blood/gas partition coefficient is greater than the human blood/gas partition coefficient or if one or more of the blood/gas partition coefficients are not known. Therefore, due to the lack of available blood/gas partition coefficients for HFAN, the human-equivalent effect concentrations ($NOAEL_{HEC}$ and $LOAEL_{HEC}$ values) are equivalent to their duration-adjusted counterparts. Table 4 summarizes effect levels from the available inhalation studies.

Subchronic p-RfC

The only adverse effect reported in inhalation toxicology studies is decreased body weight at the high exposure level ($LOAEL_{HEC}$ = 1157 mg/m^3) in the 3-month rat study (Douglas et al., 1993). No effects were seen in this study at the next lower concentration ($NOAEL_{HEC}$ = 379 mg/m^3). Consistent with these findings, no effect on body weight or any other endpoint examined was found in the 12-month rat study performed at lower exposure levels ($NOAEL_{HEC}$ = 327 mg/m^3) (Clark et al., 1989). Studies of developmental and reproductive toxicity found maternal effects ranging from reduced maternal body weight at the end of exposure (GD15) ($LOAEL_{HEC}$ = 125 mg/m^3) to maternal deaths and overt clinical signs of toxicity (e.g., abnormal gait, ataxia, labored breathing, hunched posture, weakness) at higher concentrations (McKee et al., 1990). Effects on fetuses and pups were observed at concentrations ($LOAEL_{HEC}$ = 600 mg/m^3 or more) that also produced maternal toxicity (McKee et al., 1990). Effects on the developing fetuses included reduced body weight, developmental delay, cleft palate, and fetal death. The latter effects were observed at high concentrations (HEC = 1850 mg/m^3) that produced marked maternal toxicity, including death (McKee et al., 1990). Additional developmental toxicity studies appeared to find similar results in multiple species (Ungvary and Tatrai, 1985), although poor reporting makes these studies difficult to interpret.

The most sensitive endpoint was decreased maternal body weight versus controls ($LOAEL_{HEC}$ = 125 mg/m^3, no NOAEL identified) on Gestation Day 15 (GD15; the end of the exposure period) in mice in the study by McKee et al. (1990). Sufficient data are provided in the report to perform BMD modeling. BMD modeling was performed using the maternal body weight measurements from GD15 (Table 5). Appendix B presents details of BMD modeling for this data set. None of the models in the BMDS were able to provide adequate fit—even after dropping the high dose. These results are also presented in Appendix B.

Table 5. Data Set for Decreased Maternal Body Weight on GD15 in Pregnant Mice Exposed on GD6−15[a]

HEC (mg/m^3)	**0**	**125**	**613**	**1858**
Mean (g)	39	35	36	33
Standard Deviation (g)	3.3	7.6	4.9	6.0
Number of Animals	26	24	25	13

[a]McKee et al., 1990

In the absence of a BMDL for this endpoint, the $LOAEL_{HEC}$ of 125 mg/m^3 for maternal toxicity in mice from the study by McKee et al. (1990) is the appropriate POD from which to derive the p-RfC.

A subchronic p-RfC for HFAN is derived using the $LOAEL_{HEC}$ of 125 mg/m^3 in mice and a composite UF of 100 as follows:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= LOAEL_{HEC} \div UF \\ &= 125 \text{ mg/m}^3 \div 100 \\ &= \textbf{1 or } \mathbf{1 \times 10^0 \text{ mg/m}^3} \end{aligned}$$

The composite UF is based on the following factors:

- An UF of 3 ($10^{0.5}$) is applied for interspecies extrapolation to account for potential pharmacodynamic differences between mice and humans. Converting the mouse data to HECs by the dosimetric equations accounts for pharmacokinetic differences between mice and humans; thus, it was not necessary to use the full UF of 10 for interspecies extrapolation.
- An UF of 10 is used to account for the range of sensitivity within human populations due to the absence of information on the degree to which humans of varying gender, age, health status, or genetic makeup might vary in response to HFAN exposure.
- An UF of 3 ($10^{0.5}$) is applied for using a LOAEL in place of a NOAEL. A NOAEL was not identified. A full UF of 10 was not applied because the observed change at the LOAEL was significant only at the end of exposure on GD15. Body weight gain over the GD6−15 exposure interval or the GD0−18 interval was not significantly decreased.
- A UF of 1 is used for database deficiencies. The database includes a comprehensive 12-month study in rats that found no biologically significant effects at any exposure level, a 3-month neurotoxicity study in rats that identified NOAEL and LOAEL values for reduced body weight, but found no evidence of neurotoxicity at any level, a multigeneration reproduction study in rats that identified NOAEL and LOAEL values at high levels based on pup body weights, an adequate developmental toxicity study in mice that found fetal effects only at high exposure levels that also produced maternal effects, and additional developmental studies in mice, rats, and rabbits that reported fetal effects, but were inadequate studies. An oral developmental toxicity study in rats found results consistent with those of the inhalation mouse study.

Confidence in the key study (McKee et al., (1990) is moderate. The study is a well-reported investigation, but it does not identify a NOAEL for maternal toxicity. It is unclear if the increased sensitivity observed in this study relative to others in the database is due to gestational exposure or use of mice rather than rats. However, confidence is raised by the observation of the same critical effect in nongestational animals that were exposed for 13 weeks, with the LOAEL defined at a higher dose (Douglas et al., 1993). Confidence in the database is high. The database contains the following adequate studies: 12-month toxicity study in rats (Clark et al., 1989), subchronic neurotoxicity study in rats (Douglas et al., 1993), developmental toxicity (mice) (McKee et al., 1990), and a multigeneration reproduction study (rats) (McKee et al., 1990). A neurobehavioral developmental study in rats (Lehotsky et al., 1985) is also available but does not examine traditional developmental endpoints. There is uncertainty in the dose-response for developmental toxicity due to the lack of clear reporting for some of the studies (Ungvary and Tatrai, 1985). Overall, confidence in the subchronic p-RfC is moderate.

Chronic p-RfC

A chronic p-RfC for HFAN is derived using the same POD as for the subchronic p-RfC (mouse $LOAEL_{HEC}$ of 125 mg/m^3) and a composite UF of 1000 as follows:

Chronic p-RfC = $LOAEL_{HEC} \div UF$
= $125\ mg/m^3 \div 1000$
= **0.1 or $1 \times 10^{-1}\ mg/m^3$**

The composite UF of 1000 includes the same areas of uncertainty enumerated above for the subchronic p-RfC, as well as an additional 10-fold UF, as follows:

- A factor of 10 is applied for using data from a less-than-lifetime study to assess potential effects from chronic exposure.

For reasons outlined above for the subchronic p-RfC, confidence in the key study is moderate. Confidence in the database and overall confidence in the chronic p-RfC are reduced to moderate due to additional uncertainty associated with the lack of a lifetime exposure study.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR HFAN

Weight-of-Evidence Descriptor

Studies evaluating the carcinogenic potential of oral or inhalation exposure to HFAN in humans or animals were not identified in the available literature. The limited genotoxicity data are equivocal, with negative reverse mutation assays in *Salmonella* and positive results in *E. coli* and human lymphocytes with regard to DNA damage. Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), *"Inadequate Information is Available to Assess the Carcinogenic Potential"* of HFAN.

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APPENDIX A. DERIVATION OF SUBCHRONIC AND CHRONIC SCREENING ORAL RfD VALUES FOR HIGH FLASH AROMATIC NAPTHA

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for high flash aromatic naphtha (HFAN). However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

The database for HFAN includes three subchronic oral toxicity studies in rats and dogs, as well as an oral teratology study in rats; these studies do not appear to have been subject to independent, scientific peer review. Table A-1 summarizes the NOAEL and LOAEL values from these studies.

Subchronic Screening RfD

A NOAEL for HFAN exposure in the available database is 125 mg/kg-day (Table A-1). On the basis of the subchronic study conducted with dogs (Bio/Dynamics Inc., 1990b), mild anemia, evidenced by a decrease in RBC count (with intermittent—but significant—reductions in hemoglobin and hematocrit) in male dogs exposed to ≥250 mg/kg-day is the most sensitive endpoint associated with subchronic HFAN exposure. The reduction in RBC count was dose-related in males throughout the study, but it was present in females only at mid-study. In dogs, exposure to higher doses (500 mg/kg-day) was associated with mild effects on the liver and kidneys consistent with observations at high doses (900−1250 mg/kg-day) in rats and with a possible clotting deficit in females (increased platelet count and APPT). Among rats, a decrease in RBCs indicative of anemia was noted only in females exposed to 1250 mg/kg-day in the Bio/Dynamics (1990a) study, but not in rats of either sex exposed to up to 893 mg/kg-day (daily average) in the study reported by Mobil Oil Company (1994). It is possible that this discrepancy is attributable to differences in the hydrocarbon fraction to which the animals in the different studies were exposed. The chemical and isomeric composition of the test substance is not reported for either study. HFAN was fetotoxic only at high doses in the presence of maternal toxicity in rats.

Table A-1. Oral Dose-Response Summary for RfD Derivation

Species/ Exposure Method	Sex	Dose (mg/kg-day)	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Reference
Subchronic						
Rat Gavage	M/F	0, 500, 750, 1250 (daily doses)	500	750	11−13% decreased terminal body weight in males and females; mild liver changes at higher dose (increased serum ALT and ALP, as well as increased liver weight and hepatocyte hypertrophy)	Bio/Dynamics Inc., 1990a
Rat Gavage	M/F	0, 30, 125, 500, 1250 (given 5/7 days/wk), adjusted to daily exposures of 0, 21, 89, 357, 893	357	893	Mild effects on the liver, as indicated by clinical chemistry changes (increased serum bilirubin, ALT and ALP) in addition to increased liver weight and hepatocyte hypertrophy	Mobil Oil Corporation, 1994
Dog Capsules	M/F	0, 125, 250, 500 (daily doses)	125	250	Anemia in males and transient anemia in females; possible clotting deficit (increased platelets and APPT) in females at the higher dose	Bio/Dynamics Inc., 1990b
Developmental Toxicity						
Rat Gavage	M/F	0, 125, 625, 1250 (GD 6-15)	Maternal Toxicity: 125	Maternal Toxicity: 625	Decreased mean body-weight gain and gravid uterine weight	Bio/Dynamics Inc., 1990c
			Fetotoxicity: 625	Fetotoxicity: 1250	Decreased mean fetal body weight; increased incidence of total skeletal variations indicative of delayed skeletal ossification	

Sufficient data are available to conduct a benchmark dose (BMD) for the most sensitive endpoint: anemia in dogs. Table A-2 shows the BMD data set for this endpoint.

Table A-2. Data Set for Decreased Terminal Mean RBC Count in Male Dogs[a]

Dose (mg/kg-day)	0	125	250	500
Mean	7.81	7.32	6.77	6.74
Standard Deviation	0.59	0.55	0.15	0.44
Number of Animals	4	4	4	4

[a]Bio/Dynamics Inc., 1990b

Appendix B details the BMD modeling. No continuous-response model provides adequate fit to the data with all doses. However, after dropping the highest dose, a linear model with modeled variance provides adequate fit to the data set and yielded a $BMDL_{1SD}$ (lower confidence limit on the BMD associated with a benchmark response of 1 standard deviation from the control mean response) of 84.8 mg/kg-day, rounded to 85 mg/kg-day. A subchronic screening RfD for HFAN was derived by applying a UF of 300 to the dog $BMDL_{1SD}$ of 85 mg/kg-day as follows:

Subchronic Screening RfD = $BMDL_{1SD} \div UF$
= 85 mg/kg-day ÷ 300
= **0.3 or 3×10^{-1} mg/kg-day**

The composite UF of 300 is composed of the following:

- An UF of 10 is applied for interspecies extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- An UF of 10 for intraspecies differences is used to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A database UF of 3 ($10^{0.5}$) is employed. The toxicological database for oral exposure to HFAN includes adequate subchronic bioassays in two species and an adequate developmental toxicity study in one species (rats). The oral database lacks a multigeneration reproduction study, but one is available via the inhalation route of exposure. A neurotoxicity study has also been conducted by inhalation exposure. Given that the effects observed in the existing inhalation studies appear to be consistent with those observed in the oral studies with regard both to dose and response, it is possible that oral exposure to HFAN would not result in developmental, reproductive or neurotoxic effects at doses lower than those observed to produce mild liver and hematological effects.

Confidence in the principal study is moderate. Although the study was conducted according to rigorous test guidelines and is well reported, the number of animals used is small (4/sex/dose for dogs). The dose-response curve for the most sensitive endpoint (decreased RBC count) is shallow and moderately variable. However, the observation of similar slight and transient hematological effects in inhalation studies increases certainty that the observations in dogs are not anomalous. Confidence in the database also is moderate. There are no human data or mechanistic information to determine whether the critical endpoints observed in animal species are also relevant to humans. In addition, multigeneration and neurotoxicity studies have not been conducted for HFAN via the oral route of exposure. The animal database contains studies on a variety of endpoints that are considered to be of moderate-quality. Collectively, these studies in dogs and rats present a consistent dose-response pattern. There is some uncertainty as to whether the liver and kidneys effects are truly adverse, due to the lack of treatment-related histological findings and only mildly elevated serum chemistry indicators. Overall confidence in the subchronic screening RfD is moderate.

Chronic Screening RfD

The subchronic $BMDL_{1SD}$ of 85 mg/kg-day can be used as the point of departure for calculation of the chronic screening RfD. A composite UF of 3,000 is applied to the $BMDL_{1SD}$ to calculate a chronic screening RfD as follows:

Chronic Screening RfD = $BMDL_{1SD} \div UF$
= 85 mg/kg-day ÷ 3,000
= **0.03 or 3×10^{-2} mg/kg-day**

The composite UF of 3,000 includes the same areas of uncertainty enumerated above for the subchronic screening RfD, as well as an additional 10-fold UF, as follows:

- A factor of 10 is applied for using data from a less-than-lifetime study to assess potential effects from chronic exposure.

For reasons outlined above for the subchronic screening RfD, confidence in the key study supporting this screening value is moderate. Confidence in the database and overall confidence in the chronic screening RfD are lower than for the subchronic screening RfD due to additional uncertainty associated with the lack of chronic exposure studies. Such studies would be valuable in determining whether the mild effects observed in the subchronic studies could result in more significant effects over a lifetime of exposure.

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING

The model-fitting procedure for continuous data (e.g., data presented as means and standard deviations [SDs]) is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model (one-degree polynomial model) to the means is evaluated. If the linear model adequately fits the means ($p \geq 0.1$), then it is selected as the model for BMD derivation. If the linear model does not adequately fit the means, then the more complex models are fit to the data while assuming constant variance. Among the models providing adequate fit to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means is evaluated. If the linear model does not provide adequate fit to the means while the variance model is applied, then the polynomial, power, and Hill models are fit to the data and evaluated while the variance model is applied. Among those providing adequate fit to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected as the best fitting model for BMD derivation. If the test for constant variance is negative and the nonhomogenous variance model does not provide an adequate fit to the variance data, then the data set is considered not to be suitable for BMD modeling.

Oral Screening RfD

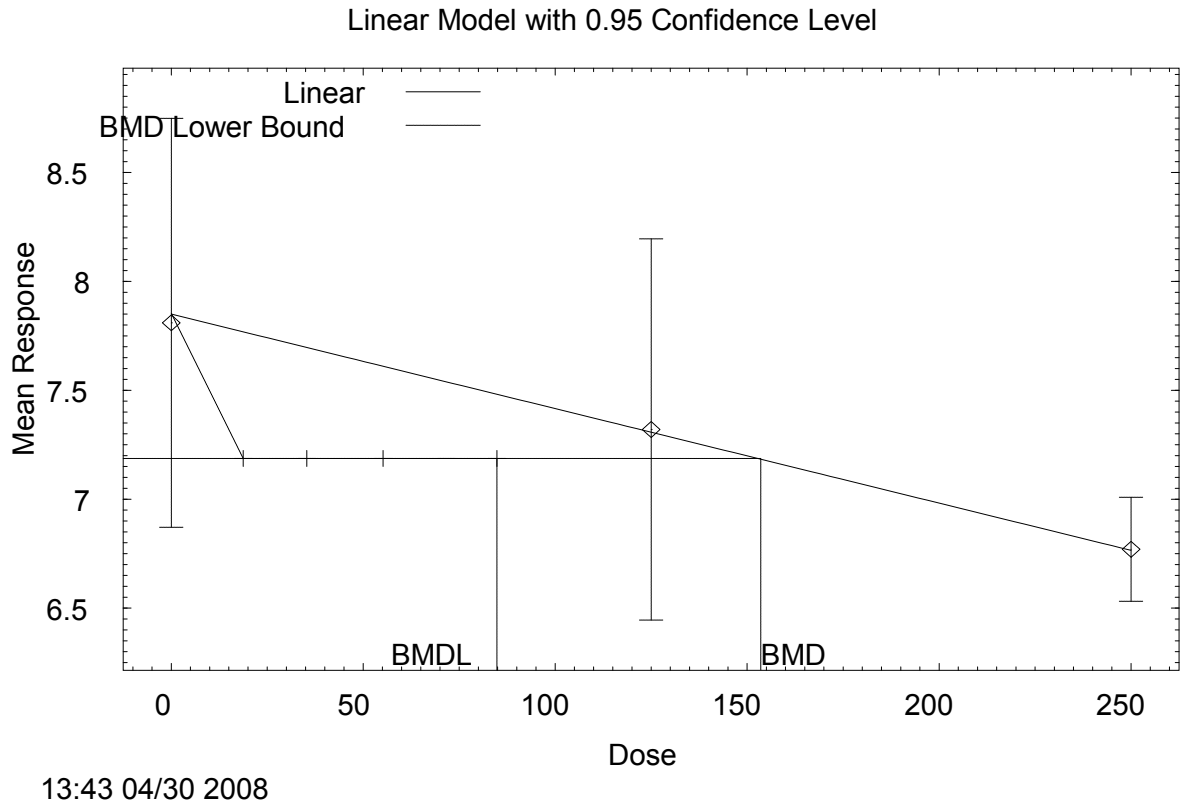
Following the above procedure, continuous-variable models in the EPA Benchmark Dose software (version 1.4.1) were fit to the data in Table A-2 (p. 37) for decreased terminal mean RBC count in male dogs observed in the Bio/Dynamics Inc. (1990b) study. The BMDs and the 95% lower confidence limits (BMDLs) calculated are estimates of the doses associated with a change of 1 SD from the control, as recommended by U.S. EPA (2000).

BMD modeling results for the dataset are shown in Table B-1. None of the models fit the data and provided a BMDL computation when all doses were used. Therefore, models were run again with the highest dose dropped. With the highest dose dropped, the assumption of constant variance was still not supported. However, running the linear model with modeled variance and the highest dose dropped provided adequate fit to both the means and the variance. The best fitting model is illustrated in Figure B-1.

Table B-1. Model Predictions for Decreased Terminal Mean RBCs in Male Dogs					
Model	**Variance *p*-Value[a]**	**Means *p*-Value[a]**	**AIC**	**BMD_{1SD} (mg/kg-day)**	**$BMDL_{1SD}$ (mg/kg-day)**
All dose groups					
Linear (constant variance)[b]	0.0988	0.1528	-3.316	NA	NA
Linear (modeled variance)[b]	0.1302	0.06376	-1.769	NA	NA
Polynomial model (modeled variance)[b, c]	0.1302	0.06376	-1.769	NA	NA
Power model (modeled variance)[d]	0.1302	0.06376	-1.769	NA	NA
Hill model (modeled variance)[d]	0.1302	0.7843	-5.199	128.211	Computation failed
Highest dose dropped					
Linear (constant variance)[b]	0.044	0.905	-3.372	NA	NA
Linear (modeled variance)[b]	**0.2633**	**0.3789**	**-5.607**	**153.549**	**84.813**

[a]Values <0.10 failed to meet conventional goodness-of-fit criteria
[b]Coefficients restricted to be negative
[c]Polydegree = 3 selected, but defaulted back to linear
[d]Power restricted to ≥1

NA = not applicable; model does not fit the data adequately



BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control and are in units of mg/kg-day

Figure B-1. Fit of Linear Model with Nonhomogeneous (Modeled) Variance to Data on Decreased Terminal Mean RBCs in Male Dogs (Bio/Dynamics Inc., 1990b)

Inhalation p-RfC

Following the above procedure, the continuous-variable models in the EPA Benchmark Dose software (version 1.4.1) were fit to the data in Table 5 for decreased mean body weight on gestational Day 15 in maternal mice observed in the McKee et al. (1990) study. The BMDs and the 95% lower confidence limits (BMDLs) calculated are estimates of the concentrations associated with a change of 1 SD from the control, as recommended by U.S. EPA (2000). The assumption of constant variance was not met, but the variance model included in the BMDS provided adequate fit to the variance data. Adequate fit to the means was not obtained with any of the available models, even after dropping the high dose (Table B-2).

Table B-2. Model Predictions for Decreased Maternal Body Weight in Mice on GD15

Model	Variance *p*-Value[a]	Means *p*-Value[a]	AIC	BMD_{1SD} (mg/m^3)	$BMDL_{1SD}$ (mg/m^3)
All dose groups					
Linear (constant variance)[b]	0.0007	0.06015	397.887	NA	NA
Linear (modeled variance)[b]	0.4258	<.0001	399.886	NA	NA
Polynomial model (modeled variance)[b, c]	0.4258	<.0001	399.886	NA	NA
Power model (modeled variance)[d]	0.4258	<.0001	399.886	NA	NA
Hill model (modeled variance)[d]	0.4258	0.02524	386.095	NA	NA
Highest dose dropped					
Linear (constant variance)[b]	0.0002	0.0177	339.240	NA	NA
Linear (modeled variance)[b]	0.5085	<.0001	341.0249	NA	NA
Polynomial model (modeled variance)[b, c]	0.5085	<.0001	341.0249	NA	NA
Power model (modeled variance)[d]	Not appropriate: too few degrees of freedom to test fit				
Hill model (modeled variance)[d]	Not appropriate: too few degrees of freedom to test fit				

[a]Values <0.10 failed to meet conventional goodness-of-fit criteria
[b]Coefficients restricted to be negative
[c]Polydegree = 2 selected, but defaulted back to linear
[d]Power restricted to ≥1

NA = not applicable; model does not fit the data adequately