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Provisional Peer-Reviewed Toxicity Values for

Fluorobenzene
(CASRN 462-06-6)

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Questions regarding the contents of this document 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).

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
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 reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
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
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR FLUOROBENZENE (CASRN 462-06-6)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency'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) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in 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 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 EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six 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 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Fluorobenzene is an intermediate in the production of pharmaceuticals, pesticides, and other organic compounds. The empirical formula for fluorobenzene is C_6H_5F (see Figure 1). A table of chemicophysical properties is provided below (see Table 1). In this document, "statistically significant" denotes a *p*-value of <0.05.

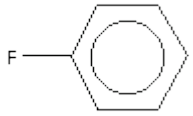


Figure 1. Fluorobenzene Structure

Table 1. Chemico-physical Properties Table (Fluorobenzene)[a]

Property (unit)	Value
Boiling point (ºC at 760 mm Hg)	84.73
Melting point (ºC)	−40
Density (g/cm^3)	1.024
Vapor pressure (Pa at 20ºC)	8000
pH (unitless)	Not available
Solubility in water (g/100 mL at 20ºC)	0.15
Relative vapor density (air = 1)	Not available
Molecular weight (g/mol)	96.10
Flash point (°C)	−15
Octanol/water partition coefficient (unitless)	2.27

[a]Values from DuPont Co. (2003).

No reference dose (RfD), reference concentration (RfC), or cancer assessment for fluorobenzene is included in the EPA IRIS database (U.S. EPA, 2010b) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). No RfD or RfC values are reported in HEAST (U.S. EPA, 2010a). The CARA list (U.S. EPA, 1994) does not include a Health and Environmental Effects Profile (HEEP) for fluorobenzene. The toxicity of fluorobenzene has not been reviewed by ATSDR (2008) or the World Health Organization (WHO, 2010). CalEPA (2008, 2009a) has not derived toxicity values for exposure to fluorobenzene. The American Conference of Governmental Industrial Hygienists (ACGIH, 2010), the National Institute of Occupational Safety and Health (NIOSH, 2005), and the Occupational Safety and Health Administration (OSHA, 2010) have not derived exposure limits.

The HEAST (U.S. EPA, 2010a) has not reported an EPA (1986) cancer weight-of-evidence (WOE) classification for fluorobenzene. Fluorobenzene has not been evaluated under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). The International Agency for Research on Cancer (IARC, 2010) has not reviewed the carcinogenic potential of fluorobenzene. Fluorobenzene is not included in the *11th Report on Carcinogens* (NTP, 2005). CalEPA (2008, 2009a,b,c) has not prepared a quantitative estimate of carcinogenic potential for fluorobenzene.

Literature searches were conducted on sources published from 1900 through March 1, 2010, for studies relevant to the derivation of provisional toxicity values for fluorobenzene, CAS No. 462-06-6. Searches were conducted using EPA's Health and Environmental Research Online (HERO) evergreen database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET

(Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); WHO; and Worldwide Science. The following databases outside of HERO were searched for risk assessment values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for fluorobenzene and includes all potentially relevant repeated short-term, subchronic-duration, and chronic-duration studies. NOAELs, LOAELs, and BMDL/BMCLs are provided in HED/HEC units for comparison except that oral noncancer values are not converted to HEDs and are identified in parentheses as (Adjusted) rather than HED/HECs. Principal studies (PS) are identified in bold.

Table 2. Summary of Potentially Relevant Data for Fluorobenzene (CASRN 462-06-6)

Notes[a]	Category	Number of Male/Female, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b,c]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
Human								
				None				
Animal								
				1. Oral (mg/kg-day)[b]				
	Subchronic			None				
	Chronic			None				
	Developmental			None				
	Reproductive			None				
	Carcinogenic			None				
				2. Inhalation (mg/m^3)[b]				
PS, NPR	**Subacute**	**5/5 Sprague-Dawley rat, inhalation (nose only), 6 hours/day, 7 days a week, 28 days**	**92.5, 375, and 1560**	**Clinical signs: hunched posture and piloerection in medium- and high-dose groups that increased over time. Medium- and high-dose group males showed increased relative liver weight, which was also seen in the high-dose females; relative kidney weights were increased in high-dose males; histopathological effects were observed in the liver and kidneys of high dose males.**	**92.5**	**8.9**	**375**	**Safepharm Labs, Ltd. (1993)**
	Subchronic			None				
	Chronic			None				
	Developmental			None				
	Reproductive			None				
	Carcinogenic			None				

[a]Notes: IRIS = Utilized by IRIS, date of last update; PS = principal study; NPR = not peer reviewed.
[b]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to human equivalent doses (HEDs in mg/kg-day) or human equivalent concentrations (HECs in mg/m^3) units. Noncancer oral data are only adjusted for continuous exposure.
[c]Following EPA guidance for Category 3 gases (U.S. EPA, 2009), concentrations were converted to adjust for continuous exposure by using the following equation: $Conc_{ADJ}$ = Concentrations in mg/L × 1000 L/m^3 × (Hours per Day × Days Dosed ÷ Total Days). Concentrations were calculated for an extrarespiratory effect for a Category 3 gas. Because the Blood Air Partition Coefficient lambda for humans is unknown, a default value of 1.0 is used for this ratio.
$Conc_{HEC}$ = $Conc_{ADJ}$ × Blood Air Partition Coefficient of 1.

HUMAN STUDIES

Oral Exposures

No studies investigating the effects of subchronic- or chronic-duration oral exposure to fluorobenzene in humans were identified.

Inhalation Exposures

No quantitative data were located regarding the toxicity of fluorobenzene to humans following subchronic- or chronic-duration inhalation exposure.

Other Exposures

No subchronic or long-term studies investigating the effects of occupational exposure to fluorobenzene in humans were identified.

ANIMAL STUDIES

Oral Exposures

No subchronic-duration, chronic-duration, reproduction, or developmental studies regarding the effects of oral exposure to fluorobenzene could be located.

Inhalation Exposures

The effects of inhalation exposure of animals to fluorobenzene have been evaluated in a subacute (Safepharm Labs, Ltd., 1993) toxicity study. No subchronic-duration, chronic-duration, reproductive, or developmental inhalation studies could be identified.

Subacute Studies

The study by Safepharm Labs, Ltd. (1993) is selected as the principal study for deriving the screening subchronic p-RfC. In an unpublished, Good Laboratory Practice (GLP)-certified, subacute inhalation toxicity study, Safepharm Labs, Ltd. (1993) exposed groups of 10 Sprague-Dawley rats (5 per gender) per dose to concentrations of 0.4, 1.5, and 6.0 mg/L fluorobenzene (purity not reported) for 6 hours/day, 7 days a week, for 28 days. The study authors exposed a control group of five animals per sex to air only. The test substance was kept in glass flasks that were held in water baths at 20°C. Compressed air was passed through a water trap and respiratory quality filters before entering the system. The main air supply went through a tangential channel at the top of each exposure chamber. Some of this air was bubbled through the test substance before reaching the exposure chamber, which had a volume of approximately 30 L. Temperature and relative humidity were measured daily, and oxygen levels were measured weekly. Concentration of the test substance was measured daily. Mean atmospheric concentrations of fluorobenzene were calculated as 0, 0.37, 1.50, and 6.24 mg/L for the 0-, 0.4-, 1.5-, and 6.0-mg/L-dose groups, respectively. The corresponding exposure concentrations adjusted for continuous exposure in Sprague-Dawley rats are 0, 92.5, 375, and 1560 mg/m^3. During exposure, rats were individually restrained by a polycarbonate tube, and only the nose was exposed to the test atmosphere. Animals were gradually acclimatized to the restraint procedure, and during the study period, they were rotated to account for any variation within the chambers. Rats were monitored throughout each exposure period for changes in appearance, respiration, and behavior.

Clinical observations were noted before each exposure period and after removal from the test chambers. Body weight was measured at Days 0, 7, 14, 21, and 28; food consumption was measured weekly; and water consumption was initially inspected and then measured daily from

Day 15 onward. Home cage, open field, and neurotoxicity functional observations were completed the day before initial dosing and then on Days 13 and 14 for females and Days 27 and 28 for males. Hematology and blood chemistry were analyzed prior to necropsy on Day 29; no fasting occurred before samples were taken. Urine samples following 2 weeks postdosing were also collected over a period of approximately 16 hours while rats were kept in metabolism cages. Animals were fasted, with water provided. Hematology measurements and calculations were performed, including hematocrit, hemoglobin, erythrocyte count, total leukocyte count, differential leukocyte count, platelet count, mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration. Blood chemistry calculations or measurements were done for blood urea, total protein, albumin, albumin/globulin ratio, sodium, potassium, chloride, calcium, inorganic phosphorus, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glucose, and total bilirubin. In urine, researchers measured volume, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, reducing substances, and blood, as well as microscopic examination of sediment. At the study's end, all animals were necropsied; organ weights and relative organ weights were calculated for adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, and testes (including epididymides). Samples of approximately 35 tissues were collected, including adrenals, aorta, bone and bone marrow, brain, cecum, kidneys, larynx, liver, lungs, lymph nodes, mammary gland, muscle, nasal cavity, esophagus, ovaries, pancreas, pituitary, prostate, rectum, salivary glands, sciatic nerve, seminal vesicles, skin, spinal cord, spleen, stomach, testes with epididymides, thymus, thyroid/parathyroid, trachea, urinary bladder, and uterus. All preserved tissues from control and high-dose groups were stained and prepared for microscopic examinations. Lungs, gross lesions, liver, and kidneys from the other dose groups were examined as well. Samples of the sternum bone and the teeth were taken from each rat and pooled to analyze for fluoride.

Data were analyzed to yield group means and standard deviations, where necessary. Absolute and relative organ weights and hematological and blood chemistry parameters were analyzed using one-way analysis of variance incorporating the F-max test for homogeneity variance. Data with heterogeneous variance were tested using the Kruskal-Wallis analysis of variance and Mann-Whitney *U*-test.

There was no mortality during the study. Red/brown staining of the exterior body and wetness of the fur were seen in all groups. The study authors concluded that these observations were a result of restraint. Hunched posture and piloerection were seen at the 375- and 1560-mg/m^3 doses. Incidence increased with progression of the study, and by Day 24, all animals exposed to a concentration of 1560 mg/m^3 showed these behaviors. Animals exposed to 375 mg/m^3 showed these signs from Day 21 and continuing through the study. Rats did not show any significant signs of neurotoxicity. There were no significant adverse effects indicated by body weight, food or water consumption, hematology, blood chemistry, or urine composition. Necropsies revealed no treatment-related macroscopic abnormalities. The males exposed to 375 and 1560 mg/m^3 (medium and high exposures) experienced significant ($p < 0.01$) increases in absolute (126−129%) and relative (115−125%) liver weights; relative liver weight was also elevated (113%) in the high-dose female group (see Tables B.1 and B.2). Relative kidney weight was also significantly increased in the high-dose male group. There were no effects detected in the low-dose group. The results of the histopathology examination of tissues from the control and high-dose animals showed irregularities in the high-dose males consisting of hepatocyte enlargement in the centrilobular liver and abnormal quantities of eosinophilic material in the

renal proximal tubular epithelium as well as groups of basophilic/dilated tubules (see Table B.3). Other adaptive kidney changes were reported, including hydrocarbon nephropathy in males in all dose groups. Eosinophilic droplets were seen in the tubular epithelium of the kidneys of male rats at the medium and high doses. This was noted as a treatment-related effect, typical of hydrocarbon administration. There were no treatment-related respiratory effects found. Additionally, a substantial increase in fluoride was measured in teeth and sternum samples from all groups (see Table B.4).

Authors established a NOAEL of 0.37-mg/L ($NOAEL_{ADJ}$ of 92.5-mg/m^3) fluorobenzene, based on the lack of treatment-related adverse effects at this dose level. A $LOAEL_{ADJ}$ of 375 mg/m^3 is identified based on increased liver weight (absolute and relative) in male rats, which is supported by an increase in incidence of centrilobular hepatocyte enlargement at the higher dose. Although an increase in relative kidney weight, supported by histopathology changes, was observed in treated animals, the effects were only significant in the high-dose group (1560 mg/m^3), making the liver a more sensitive indicator of exposure. This study is GLP certified, and the procedures were based on guideline recommendations Method B8, Annex V of the European Economic Community (EEC) Commission Directive 84/449/EEC, and Organisation for European Economic Co-operation (OECD) Guideline 412 (OECD, 1997). Despite the lack of peer review and the shortness in exposure duration, the quality of the study supports its use in the derivation of a screening subchronic p-RfC.

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Genotoxicity	Conducted Ames test on *Salmonella typhimurium* strains TA98, TA1538, TA1537, TA100, and TA1535 with and without rat liver metabolic activation.	Authors reported no positive results in any strain with or without metabolic activation.	Negative for mutagenicity.	Shimizu et al. (1983)
Genotoxicity	Conducted preincubationally modified Ames test using *S. typhimurium* strains TA97, TA98, TA100, and TA1535 with and without rat and hamster liver metabolic activation.	Test results indicated a positive response. Activation and strain unknown.	Positive for mutagenicity.	Zeiger and Margolin (2000)
Genotoxicity	Performed in vivo micronucleus assay in mice. Procedure was based on the recommendations for OECD Guideline 474 (OECD, 1997), but precise study methods were unavailable.	Results were negative. OECD Guideline 474 (OECD, 1997) defines negative as meaning there was no significant increase in the ratio of normochromatic to polychromatic erythrocytes.	These results suggest no genotoxicity of fluorobenzene.	DuPont Co. (2003)

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Table 3 presents summary of short-term studies. The genotoxicity of fluorobenzene has been tested in multiple studies. In a published study, Shimizu et al. (1983) investigated the mutagenic effects of fluorobenzene on *Salmonella typhimurium*. The study authors conducted an Ames test using S9 rat liver fraction in strains TA98, TA1538, and TA1537 to evaluate potential frameshift mutations, and in strains TA100 and TA1535 to evaluate potential mutation by base-pair substitution and incubation for 3 days. The authors observed no change in the number of revertant colonies and concluded that fluorobenzene is not genotoxic with or without metabolic activation.

In a National Toxicology Program-sponsored, published study, Zeiger and Margolin (2000) performed an in vitro bacterial reverse mutation assay investigating the genetic toxicity of fluorobenzene on *S. typhimurium* strains. The authors conducted a modified Ames test, using a preincubation procedure with and without rat and hamster liver metabolic activation in strains TA97 and TA98 to evaluate potential frameshift mutations and in strains TA100 and TA1535 to evaluate potential mutation by base-pair substitution and incubation for 3 days. The authors reported that fluorobenzene was mutagenic; however, the strains and activation resulting in the positive response were not specified.

Cytotest Cell Research Gmbh & Co. (1991) conducted a micronucleus assay investigating the genotoxicity of fluorobenzene in mice. Though the original report and data of Cytotest Cell Research Gmbh & Co. (1991) is reported in German, an acceptable review of the study has been conducted by DuPont Co. (2003), and information from DuPont Co. (2003) is presented for the purposes of this review. The authors conducted an OECD (1997) 474 mouse micronucleus assay by dosing NMRI male and female mice with fluorobenzene (99.7% pure) in corn oil (unreported dose and method of administration) and measuring the ratio of normochromatic to polychromatic erythrocytes (NCEs and PCEs, respectively). The results were reported to be negative, indicating no significant increase in the number of micronucleated PCEs was found in test subjects as compared to controls.

The genotoxicity of fluorobenzene has been tested using in vitro test systems (Cytotest Cell Research Gmbh & Co., 1991; Zeiger and Margolin, 2000; Shimizu et al., 1983). With these few reported studies, the literature on the mutagenicity of fluorobenzene is equivocal. Further investigations are needed before a conclusive understanding of the mutagenic potential of fluorobenzene can be reached.

DERIVATION OF PROVISIONAL VALUES

Table 4 below presents a summary of noncancer reference values. Table 5 presents a summary of cancer values. The toxicity values are converted to HEC/HED units, with the exception of noncancer oral values, which are converted to adjusted daily doses (ADJ). The conversion process is described in the footnotes. IRIS data are indicated in the tables, if applicable.

Table 4. Summary of Reference Values for Fluorobenzene (CASRN 462-06-6)[a]

Toxicity Type (Units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF	Principal Study
Subchronic p-RfD (mg/kg-day)	None	None	None	None	None	None	None
Chronic p-RfD (mg/kg-day)	None	None	None	None	None	None	None
Screening Subchronic p-RfC (mg/m^3)	Sprague-Dawley rat/male	Centrilobular hepatocyte enlargement	3.0×10^{-2}	BMC	8.9	300	Safepharm Labs, Ltd. (1993)
Screening Chronic p-RfC (mg/m^3)	Sprague-Dawley rat/male	None	None	None	None	None	None

[a]Following the methods in the *Risk Assessment Guidance for Superfund Volume I* (U.S. EPA, 2009) concentrations were converted to adjust for continuous exposure and HEC by using the following equations:
$Conc_{ADJ}$ = Concentrations in mg/L × 1000 L/m^3 × (Hours per Day × Days Dosed ÷ Total Days);
$Conc_{HEC}$ = $Conc_{ADJ}$ × Blood Air Partition Coefficient of 1; concentrations were calculated for an extrarespiratory effect for a Category 3 gas. Because the Blood Air Partition Coefficient lambda for humans is unknown, a default value of 1.0 is used for this ratio.

Table 5. Summary of Cancer Values for Fluorobenzene (CASRN 462-06-6)[a]

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None	None	None	None
p-IUR	None	None	None	None

[a]Following the methods in the *Risk Assessment Guidance for Superfund Volume I* (U.S. EPA, 2009) concentrations were converted to adjust for continuous exposure and HEC by using the following equations:
$Conc_{ADJ}$ = Concentrations in mg/L × 1000 L/m^3 × (Hours per Day × Days Dosed ÷ Total Days);
$Conc_{HEC}$ = $Conc_{ADJ}$ × Blood Air Partition Coefficient of 1; concentrations were calculated for an extrarespiratory effect for a Category 3 gas. Because the Blood Air Partition Coefficient lambda for humans is unknown, a default value of 1.0 is used for this ratio.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

No appropriate human or animal studies examining the effects of oral subchronic-duration exposure could be located. Therefore, derivation of a subchronic p-RfD is precluded.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

No human or animal studies examining the effects of oral chronic-duration exposure could be located. Therefore, derivation of a chronic p-RfD is precluded.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Table 6 presents a summary of inhalation studies identified.

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

No subchronic p-RfC can be derived for the following reason: A nonpeer-reviewed study is selected as the principal study. However, a screening value is provided in Appendix A.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

No human or animal inhalation studies examining the effects of chronic exposure could be located. Because the study used to derive the subchronic p-RfC is a subacute study, it cannot be used to derive a chronic provisional value. Therefore, derivation of a chronic p-RfC is precluded.

Table 6. Summary of Relevant Inhalation Toxicity Studies for Fluorobenzene

Reference	Number of Male/Female, Species	Exposure (mg/m^3)	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/m^3)	$LOAEL_{ADJ}$[a] (mg/m^3)	Critical Endpoint
Safepharm Labs, Ltd. (1993)	5/5 Sprague-Dawley rats	92.5, 375, and 1560	6 hours/day, 7 days a week, 28 days (nose only)	92.5[a]	375[a]	Centrilobular hepatocyte enlargement

[a]Following the methods in the *Risk Assessment Guidance for Superfund Volume I* (U.S. EPA, 2009) concentrations were converted to adjust for continuous exposure and HEC by using the following equations:
$Conc_{ADJ}$ = Concentrations in mg/L × 1000 L/m^3 × (Hours per Day × Days Dosed/Total Days);
$Conc_{HEC}$ = $Conc_{ADJ}$ × Blood Air Partition Coefficient of 1; concentrations were calculated for an extrarespiratory effect for a Category 3 gas. Because the Blood Air Partition Coefficient lambda for humans is unknown, a default value of 1.0 is used for this ratio.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 7 identifies the cancer WOE descriptor for fluorobenzene.

Table 7. Cancer WOE Descriptor for Fluorobenzene

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to humans"	N/A	N/A	No human cancer studies are available.
"Likely to be carcinogenic to humans"	N/A	N/A	No strong animal cancer data are available.
"Suggestive evidence of carcinogenic potential"	N/A	N/A	The evidence from human and animal studies is not sufficient to be suggestive of carcinogenicity.
"Inadequate information to assess carcinogenic potential"	**X**	**Both**	**Inadequate information is available to assess carcinogenic potential. The mutagenicity studies are equivocal, and in vivo studies have not been of sufficient duration to evaluate carcinogenicity.**
"Not likely to be carcinogenic to humans"	N/A	N/A	No strong evidence of noncarcinogenicity in humans is available.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

No human or animal studies examining the carcinogenicity of fluorobenzene following oral exposure have been located. Therefore, derivation of a p-OSF is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No human or animal studies examining the carcinogenicity of fluorobenzene following inhalation exposure have been located. Therefore, derivation of a p-IUR is precluded.

APPENDIX A. PROVISIONAL SCREENING VALUES

DERIVATION OF SCREENING PROVISIONAL INHALATION REFERENCE CONCENTRATIONS

Derivation of Screening Subchronic Provisional RfC (Subchronic p-RfC)

For the reasons noted in the main document, it is inappropriate to derive a provisional subchronic p-RfC for fluorobenzene. However, information is available that, 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 a supplement and develops a screening value. Appendices receive the same level of internal and external scientific peer review as the main document to ensure their appropriateness within the limitations detailed in the main document. Users of the screening toxicity values in a supplement to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of a supplemental 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 study by Safepharm Labs, Ltd. (1993) is selected as the principal study for the derivation of a screening subchronic p-RfC. The study is unpublished but is reviewed in DuPont's (2003) *Robust Summary for Fluorobenzene,* which is publicly available as part of EPA's Chemical Right-to-Know Program. The study is GLP compliant, but does not reach the exposure duration that current EPA and OECD guidelines recommend for an inhalation study.

The critical endpoint, resulting in the benchmark concentration lower bound 95% confidence interval (BMCL), is centrilobular hepatocyte enlargement in male Sprague-Dawley rats. Other endpoints considered for modeling include an increase in kidney weight, eosinophilic droplets in the tubular epithelium of the kidney, and by the enlargement in the liver of male rats exposed to 375 mg/m^3 or more of fluorobenzene, and is specifically mentioned by the study authors as being an "observed effect of concern." There are no other studies of an appropriate duration to support the findings of the Safepharm Labs, Ltd. (1993) study. Chlorobenzene, a similar but more studied chemical than fluorobenzene, has been shown in subchronic- and chronic-duration inhalation rodent studies to cause an increase in liver and kidney weights (ASTDR, 1990). Available data from chlorobenzene support identifying the liver and kidneys as target organs for toxicity in rodents. The significant liver and kidney changes observed in the study by Safepharm Labs, Ltd. (1993) (centrilobular hepatocyte enlargement, relative liver weight, eosinophilic droplets in the kidney, and relative kidney weight) were considered as candidates for determination of a point of departure (POD) and were modeled using EPA's BMDS (version 2.1) (2008). The summary of the modeling results for all endpoints considered is presented in Table C.1. The results from the modeling of the centrilobular hepatocyte enlargement data represent the lowest and most appropriate BMCL, and, thus, POD for developing a screening p-RfC.

The characteristics of fluorobenzene indicate that it is a Category 3 gas and, thus, has effects peripheral to the respiratory system (U.S. EPA, 2009). Because Category 3 gases cause extrarespiratory effects, the concentrations in the study were converted to adjusted doses (to

account for continuous exposure) and then to HEC concentrations utilizing a default blood:air partition coefficient of 1 because the actual value is unknown.

To determine the POD for derivation of the screening subchronic p-RfC, benchmark dose (BMD) modeling of the centrilobular hepatocyte enlargement data has been conducted using EPA's BMDS (version 2.1) (2008). As recommended by EPA (2008), a 10% risk above the control mean has been used as the benchmark response (BMR) level.

The following dosimetric adjustments were made for inhalation exposure in adjusting for continuous exposure and then human equivalent concentrations:

Continuous exposure conversion:

$$\begin{aligned} \mathbf{Conc_{ADJ}} &= \mathbf{Concentration \times (Hours\ per\ Day \times Days\ Dosed \div Total\ Days)} \\ &= 0.37\ mg/L \times 1000\ L/m^3 \times (6\ h \div 24\ h\ in\ a\ day) \times \\ &\quad (28\ Days\ Dosed \div 28\ Total\ Days) \\ &= 370\ mg/m^3 \times 0.25 \\ &= \mathbf{92.5\ mg/m^3} \end{aligned}$$

HEC conversion:

$$\begin{aligned} \mathbf{Conc_{HEC}} &= \mathbf{Conc_{ADJ} \times Blood\ Air\ Partition\ Coefficient} \\ &= 92.5\ mg/m^3 \times 1 \\ &= \mathbf{92.5\ mg/m^3} \end{aligned}$$

Table A.1 presents the model input data for the incidence of hepatocyte enlargement in male rats exposed to fluorobenzene by inhalation for 28 days.

Table A.1. Concentration-Response Data for Fluorobenzene-Induced Hepatocyte Enlargement in Male Rats Exposed by Inhalation for 28 Days[a]

Conc (mg/L)	$Conc_{ADJ}$ (mg/m^3)[b]	$Conc_{HEC}$ (mg/m^3)[b]	Subjects in Dose Group	Incidence
0	0	0	5	0
0.37	92.5	92.5	5	2
1.50	375	375	5	3
6.25	1560	1560	5	4

[a]Safepharm Labs, Ltd. (1993).
[b]Following the methods in the *Risk Assessment Guidance for Superfund Volume I* (U.S. EPA, 2009) concentrations were converted to adjust for continuous exposure and HEC by using the following equations: $Conc_{ADJ}$ = Concentrations in mg/L × 1000 L/m^3 × (Hours per Day ÷ 24 hours) × (Days Dosed ÷ Total Days); $Conc_{HEC}$ = $Conc_{ADJ}$ × Blood Air Partition Coefficient of 1; concentrations were calculated for an extrarespiratory effect for a Category 3 gas. Because the Blood Air Partition Coefficient lambda for humans is unknown, a default value of 1.0 is used for this ratio.

Table A.2 shows the modeling results. Adequate model fit is obtained for hepatocyte enlargement incidence data using the Log-Logistic model. The modeling results for hepatocyte enlargement yield a BMC_{10} of 24.6 mg/m^3 and a $BMCL_{10}$ of 8.9 mg/m^3.

Table A.2. Model Predictions for Hepatocyte Enlargement in Male Rats Exposed by Inhalation for 28 Days[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC[b] for Fitted Model	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)	Conclusions
Gamma	0.29	25.229	74.177	33.904	Hit bound (power = 1)
Weibull	0.29	25.229	74.173	33.904	Hit bound (power = 1)
Log-Probit	0.21	25.855	117.737	40.369	Hit bound (slope = 1)
Log-Logistic	0.91	20.962	24.563	8.871	Lowest AIC Lowest BMCL Hit bound (slope = 1)
Multistage	0.29	25.229	74.173	33.904	Maximum order beta = 0 $\beta 2 = 0$ $\beta 3 = 0$
Logistic	0.23	26.580	198.917	100.387	
Probit	0.23	26.588	201.270	113.902	
Quantal Linear	0.29	25.229	74.173	33.904	

[a]Safepharm Labs Ltd., 1993.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration.

The screening subchronic p-RfC is based on the $BMCL_{10}$ of 8.9 mg/m^3 (lowest $BMCL_{10}$ for a range of 9–114) derived from male rats exposed to fluorobenzene for 28 days (Safepharm Labs Ltd., 1993). The screening subchronic p-RfC for fluorobenzene, based on the $BMCL_{10}$, is derived as follows:

$$\textbf{Screening Subchronic p-RfC} = \textbf{BMCL}_{\textbf{1SD}} \div \textbf{UF}_{\textbf{C}}$$
$$= 8.9 \text{ mg/m}^3 \div 300$$
$$= \textbf{0.03 mg/m}^{\textbf{3}} \textbf{ or } \textbf{3} \times \textbf{10}^{\textbf{-2}} \textbf{ mg/m}^{\textbf{3}}$$

Table A.3 summarizes the uncertainty factors (UFs) for the screening subchronic p-RfC for fluorobenzene.

Table A.3. Uncertainty Factors for Screening Subchronic p-RfC for Fluorobenzene

UF	Value	Justification	Notes
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of a UF_A, because the toxicokinetic portion ($10^{0.5}$) has been addressed in dosimetric conversions.	
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies, and there are no indications of any other studies that may be relevant for the database UF.	
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.	
UF_L	1	A UF_L of 1 is applied because the POD was developed using a BMCL.	
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was utilized as the critical study.	A UF_S greater than 1 is not necessary when using subacute study to support a subchronic value.
UF_C	300		

APPENDIX B. DATA TABLES

Table B.1. Body and Organ Weights in Sprague-Dawley Rats Exposed to Inhaled Fluorobenzene for 28 Days[a]

Exposure Group (Human Equivalent Concentration, mg/m^3)				
Parameter	**0 mg/L (0)[b]**	**0.37 mg/L (92.5)[b]**	**1.50 mg/L (375)[b]**	**6.25 mg/L (1560)[b]**
Male				
Sample size	5	5	5	5
Final body weight[c]	312 ± 17	333 ± 26	339 ± 32	320 ± 36
Adrenal gland[c]	0.0334 ± 0.0080	0.0404 ± 0.0128	0.0419 ± 0.0073	0.0403 ± 0.0114
Brain[c]	1.9417 ± 0.0698	1.9462 ± 0.0771	1.9964 ± 0.0517	1.8847 ± 0.1086
Heart[c]	1.2317 ± 0.1486	1.3466 ± 0.1667	1.3366 ± 0.1477	1.2651 ± 0.1712
Kidneys[c]	2.1192 ± 0.1284	2.3213 ± 0.2689	2.4787 ± 0.2937	2.4747 ± 0.3402
Liver[c]	11.2929 ± 1.1165	12.5349 ± 1.3711	14.263 ± 1.8717[d]	14.5066 ± 1.3553[d]
Lungs[c]	1.5063 ± 0.0570	1.5511 ± 0.0848	1.5056 ± 0.1607	1.4079 ± 0.1811
Pituitary[c]	0.0090 ± 0.0015	0.0133 ± 0.0015[d]	0.0137 ± 0.0026[d]	0.0092 ± 0.0017
Spleen[c]	0.6470 ± 0.0766	0.6445 ± 0.1095	0.7208 ± 0.0796	0.6687 ± 0.1256
Gonads[c]	4.0022 ± 0.2316	4.1775 ± 0.2197	4.1332 ± 0.2833	4.1712 ± 0.2978
Female				
Sample size	5	5	5	5
Final body weight[c]	226 ± 16	237 ± 28	225 ± 23	229 ± 9
Adrenal gland[c]	0.0444 ± 0.0041	0.0609 ± 0.0053[e]	0.0495 ± 0.0123	0.0500 ± 0.0115
Brain[c]	1.7808 ± 0.0678	1.9142 ± 0.0760[e]	1.8002 ± 0.1076	1.8139 ± 00.413
Heart[c]	0.9744 ± 0.0939	0.9638 ± 0.1150	0.8672 ± 0.1020	0.9125 ± 0.0684
Kidneys[c]	1.6653 ± 0.0930	1.7663 ± 0.1963	1.7167 ± 0.1970	1.7858 ± 0.2181
Liver[c]	8.5148 ± 0.6904	8.7789 ± 1.0033	8.5537 ± 0.9723	9.3969 ± 0.3052
Lungs[c]	1.3077 ± 0.1136	1.2636 ± 0.1375	1.2444 ± 0.1017	1.2238 ± 0.0702
Pituitary[c]	0.0144 ± 0.0040	0.0122 ± 0.0034	0.0118 ± 0.0032	0.0123 ± 0.0029
Gonads[c]	0.3413 ± 0.0798	0.3618 ± 0.1134	0.5902 ± 0.0399	0.5237 ± 0.0494

[a]Safepharm Labs, Ltd. (1993).
[b]Following the methods in the *Risk Assessment Guidance for Superfund Volume I* (U.S. EPA, 2009) concentrations were converted to adjust for continuous exposure and HEC by using the following equations: $Conc_{ADJ}$ = Concentrations in mg/L × 1000 L/m^3 × (Hours per Day × Days Dosed ÷ Total Days); $Conc_{HEC}$ = $Conc_{ADJ}$ × Blood Air Partition Coefficient of 1; concentrations were calculated for an extrarespiratory effect for a Category 3 gas. Because the Blood Air Partition Coefficient lambda for humans is unknown, a default value of 1.0 is used for this ratio.
[c]Mean ± SD.
[d]Significantly different from control group at the $p < 0.01$ level by one-way analysis of variance performed by the researchers.
[e]Significantly different from control group at the $p < 0.05$ level by one-way analysis of variance performed by the researchers.

Table B.2. Relative Organ Weights (Percentage of Body Weight) in Sprague-Dawley Rats Exposed to Inhaled Fluorobenzene for 28 Days[a]

Exposure Group (Human Equivalent Concentration, mg/m^3)				
Parameter	**0 mg/L (0)[b]**	**0.37 mg/L (92.5)[b]**	**1.50 mg/L (375)[b]**	**6.25 mg/L (1560)[b]**
Male				
Sample size	5	5	5	5
Adrenal gland[c]	0.0109 ± 0.0027	0.0121 ± 0.0031	0.0127 ± 0.0027	0.0127 ± 0.0029
Brain[c]	0.6374 ± 0.0534	0.5984 ± 0.0282	0.6035 ± 0.0466	0.6021 ± 0.0556
Heart[c]	0.4058 ± 0.0712	0.4113 ± 0.0656	0.4133 ± 0.0789	0.4026 ± 0.0454
Kidneys[c]	0.6994 ± 0.0493	0.7032 ± 0.0306	0.7446 ± 0.0458	0.7842 ± 0.0494[d]
Liver[c]	3.6883 ± 0.1919	3.7994 ± 0.1782	4.2361 ± 0.1889[e]	4.6111 ± 0.1877[e]
Lungs[c]	0.4934 ± 0.0235	0.4721 ± 0.0295	0.4532 ± 0.0373[f]	0.4462 ± 0.0231[f]
Pituitary[c]	0.0029 ± 0.0005	0.0040 ± 0.0004[d]	0.0041 ± 0.0004[e]	0.0029 ± 0.0005
Spleen[c]	0.2112 ± 0.0175	0.1955 ± 0.0287	0.2169 ± 0.0170	0.2109 ± 0.0196
Gonads[c]	1.3114 ± 0.0932	1.2719 ± 0.0852	1.2469 ± 0.0737	1.3447 ± 0.2584
Female				
Sample size	5	5	5	5
Adrenal gland[c]	0.0206 ± 0.0016	0.0257 ± 0.0026[f]	0.0218 ± 0.0031	0.0220 ± 0.0043
Brain[c]	0.7899 ± 0.0374	0.8299 ± 0.0868	0.8073 ± 0.0769	0.8061 ± 0.0392
Heart[c]	0.4308 ± 0.0222	0.4153 ± 0.0394	0.3867 ± 0.0281[f]	0.4048 ± 0.0312
Kidneys[c]	0.7385 ± 0.0425	0.7603 ± 0.0446	0.7663 ± 0.0669	0.7932 ± 0.1066
Liver[c]	3.7672 ± 0.1119	3.7745 ± 0.1368	3.8111 ± 0.2072	4.2625 ± 0.3416[d]
Lungs[c]	0.5784 ± 0.0213	0.5473 ± 0.0473	0.5576 ± 0.0420	0.5434 ± 0.0464
Pituitary[c]	0.0066 ± 0.0020	0.0053 ± 0.0013	0.0054 ± 0.0018	0.0054 ± 0.0012
Spleen[c]	0.2398 ± 0.0324	0.2401 ± 0.0329	0.2643 ± 0.0243	0.2318 ± 0.0149
Gonads[c]	0.0322 ± 0.0054	0.0469 ± 0.0058	0.0565 ± 0.0052	0.0567 ± 0.0080

[a]Safepharm Labs, Ltd. (1993).
[b]Following the methods in the *Risk Assessment Guidance for Superfund Volume I* (U.S. EPA, 2009) concentrations were converted to adjust for continuous exposure and HEC by using the following equations: $Conc_{ADJ}$ = Concentrations in mg/L × 1000 L/m^3 × (Hours per Day × Days Dosed ÷ Total Days); $Conc_{HEC}$ = $Conc_{ADJ}$ × Blood Air Partition Coefficient of 1; Concentrations were calculated for an extrarespiratory effect for a Category 3 gas. Because the Blood Air Partition Coefficient lambda for humans is unknown, a default value of 1.0 is used for this ratio.
[c]Mean ± SD.
[d]Significantly different from control group at the $p < 0.01$ level by one-way analysis of variance performed by the researchers.
[e]Significantly different from control group at the $p < 0.001$ level by one-way analysis of variance performed by the researchers.
[f]Significantly different from control group at the $p < 0.05$ level by one-way analysis of variance performed by the researchers.

Table B.3. Incidences of Histopathological Findings in Kidneys and Livers of Sprague-Dawley Rats Exposed to Inhaled Fluorobenzene for 28 Days[a]

Exposure Group (Human Equivalent Concentration, mg/m^3)				
Parameter	**0 mg/L (0)[b]**	**0.37 mg/L (92.5)[b]**	**1.50 mg/L (375)[b]**	**6.25 mg/L (1560)[b]**
Male Rats				
Kidney				
Groups of basophilic/dilated tubules[c]	0/5	0/5	2/5	2/5
Eosinophilic droplets proximal tubular epithelium[c]	0/5	0/5	3/5	4/5[d]
Liver				
Scattered mononuclear cell foci[c]	5/5	5/5	5/5	5/5
Focal hepatocyte necrosis[c]	0/5	0/5	0/5	1/5
Centrilobular hepatocyte enlargement[c]	0/5	2/5	3/5	4/5[d]
Female Rats				
Kidney				
Groups of basophilic/dilated tubules[c]	2/5	0/5	0/5	0/5
Liver				
Scattered mononuclear cell foci[c]	5/5	4/5	5/5	5/5
Focal hepatocyte necrosis[c]	0/5	0/5	1/5	0/5

[a]Safepharm Labs, Ltd. (1993).
[b]Following the methods in the *Risk Assessment Guidance for Superfund Volume I* (U.S. EPA, 2009) concentrations were converted to adjust for continuous exposure and HEC by using the following equations: $Conc_{ADJ}$ = Concentrations in mg/L × 1000 L/m^3 × (Hours per Day × Days Dosed ÷ Total Days); $Conc_{HEC}$ = $Conc_{ADJ}$ × Blood Air Partition Coefficient of 1; concentrations were calculated for an extrarespiratory effect for a Category 3 gas. Because the Blood Air Partition Coefficient lambda for humans is unknown, a default value of 1.0 is used for this ratio.
[c]Number of animals with endpoint/number of animals examined.
[d]Significantly different from control ($p < 0.05$) by Fisher's exact test (two-tailed) performed for this review.

Table B.4. Fluoride Concentration in Sternum and Teeth[a]				
Exposure Group (Human Equivalent Concentration, mg/m^3)				
Parameter	**0 mg/L (0)[b]**	**0.37 mg/L (92.5)[b]**	**1.50 mg/L (375)[b]**	**6.25 mg/L (1560)[b]**
Fluoride concentration (ppm)				
Male				
Sample size	5	5	5	5
Sternum[c]	100	339 [+239]	344 [+244]	556 [+456]
Teeth[c]	138	92 [−33]	273 [+98]	396 [186]
Female				
Sample size	5	5	5	5
Sternum[c]	149	277 [+86]	427 [+187]	534 [+258]
Teeth[c]	60	213 [+255]	292 [+387]	436 [+627]

[a]Safepharm Labs, Ltd. (1993).
[b]Following the methods in the *Risk Assessment Guidance for Superfund Volume I* (U.S. EPA, 2009) concentrations were converted to adjust for continuous exposure and HEC by using the following equations: $Conc_{ADJ}$ = Concentrations in mg/L × 1000 L/m^3 × (Hours per Day × Days Dosed ÷ Total Days); $Conc_{HEC} = Conc_{ADJ}$ × Blood Air Partition Coefficient of 1; concentrations were calculated for an extrarespiratory effect for a Category 3 gas. Because the Blood Air Partition Coefficient lambda for humans is unknown, a default value of 1.0 is used for this ratio.
[c]Mean [change compared to control].

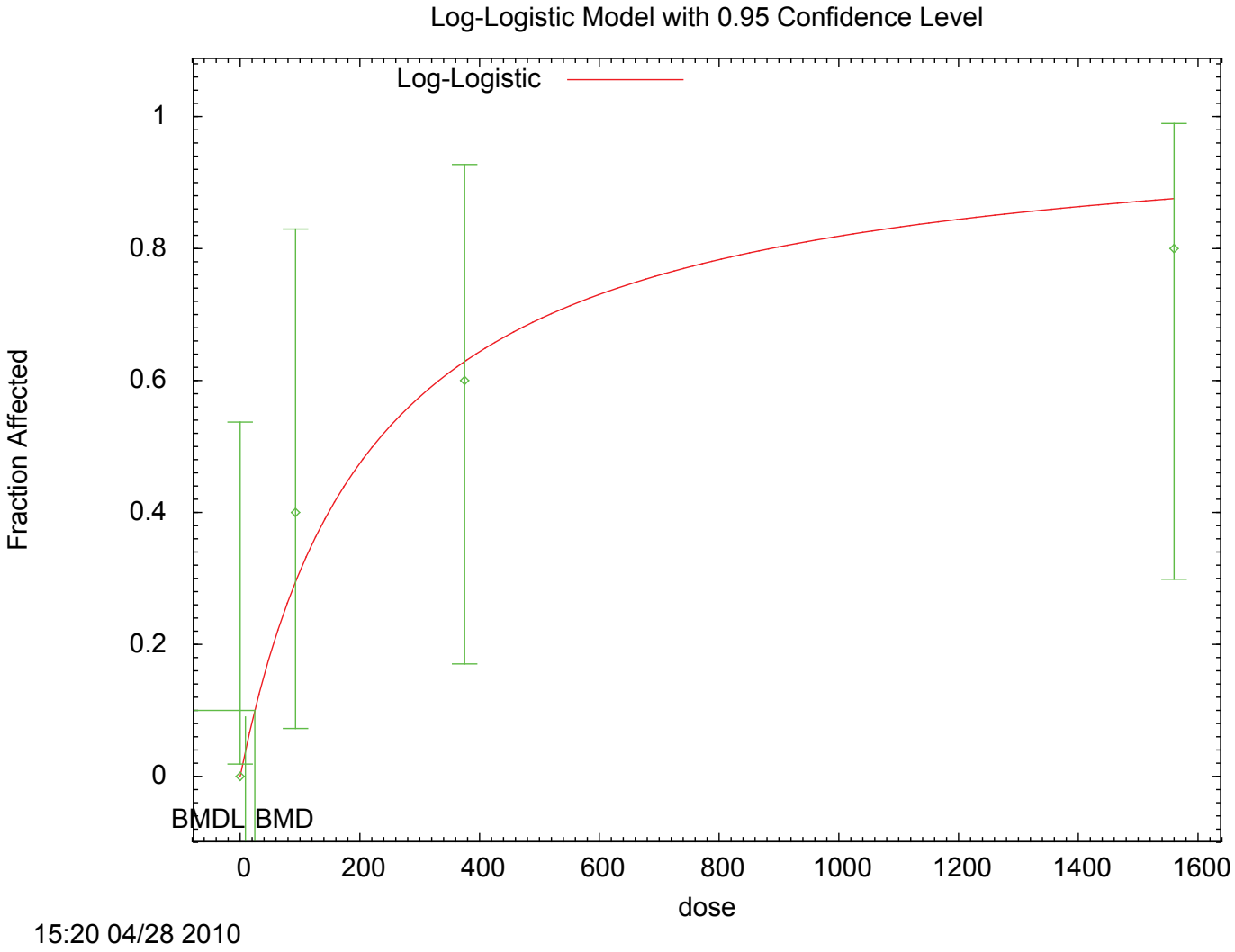
APPENDIX C. BMD OUTPUTS

Table C.1. Summary of BMDS Results for Fluorobenzene[a]

Endpoint	Gender Species	Model Type	BMRF	BMC	BMCL	BMC/BMCL	*p*-Value Test 1	*p*-Value Test 2	*p*-Value Test 3	*p*-Value Test 4	AIC	Scaled Residual of Interest	Model Selection Notes	Bound Flags?	Parameter Notes
Liver Centrilobular hepatocyte enlargement[b]	Male Rat	Dichotomous-Log-Logistic	0.1	2.5×10^{1}	8.9×10^{0}	2.8	N/A	N/A	N/A	0.908	20.9618	0	Lowest AIC Lowest BMCL hit bound (slope = 1)	Flag	Hit bound (slope = 1)
Relative Liver Weight[c]	Male Rat	Continuous-Hill	1	1.2×10^{2}	4.7×10^{1}	2.6	<.0001	0.999	0.985	NA	−39.5839	0.00037	Lowest BMCL p-score p < 0.1 Wrong variance model	No Flag	
Kidney Eosinophilic droplets proximal tubular epithelium	Male Rat	Dichotomous-Log-Probit	0.1	1.3×10^{2}	6.6×10^{1}	1.9	N/A	N/A	N/A	0.715	15.2874	−0.538	Lowest AIC hit bound (slope = 1)	Flag	Hit bound (slope = 1)
Relative Kidney Weight	Male Rat	Continuous-Linear	1	2.4×10^{2}	1.4×10^{2}	1.7	<.0001	<.0001	0.332	0.332	−74.9061	−0.0961	Lowest AIC Lowest BMCL	No Flag	
Relative Liver Weight	Female Rat	Continuous-Linear	1	4.0×10^{2}	2.4×10^{2}	1.7	1×10^{-3}	0.06	0.521	0.922	−43.2711	−0.677	Lowest AIC Lowest BMCL	No Flag	
Relative Lung Weight	Male Rat	Continuous-Linear	1	1.2×10^{3}	7.0×10^{2}	1.8	0.135	0.655	0.655	0.164	−116.618	0.322	Lowest AIC Lowest BMCL	No Flag	

[a]Safepharm Labs, Ltd. (1993).
[b]Endpoint used for POD.
[c]No models for this endpoint passed the selection criteria for an appropriate fit.

SafePharm_1993_Liver_Centril_M_LogLogistic_1




```
 ================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File:
C:\1\SafePharm_1993_Liver_Centril_M_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\1\SafePharm_1993_Liver_Centril_M_LogLogistic_1.plt
                                        Wed Apr 28 15:20:01 2010
 ================================================================

 [add notes here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
```

```
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =           0
                     intercept =    -5.73806
                         slope =           1


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background    -slope
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

              intercept

 intercept           1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background                0           *               *
*
      intercept         -5.39846           *               *
*
          slope                1           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -9.23213         4
   Fitted model        -9.48092         1      0.497573      3
0.9194
  Reduced model        -13.7628         1       9.06129      3
0.02849
```

AIC: 20.9618

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	5	0.000
92.5000	0.2950	1.475	2.000	5	0.515
375.0000	0.6291	3.146	3.000	5	-0.135
1560.0000	0.8759	4.379	4.000	5	-0.515

Chi^2 = 0.55 d.f. = 3 P-value = 0.9082

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMC = 24.5628

BMCL = 8.87128

APPENDIX D. REFERENCES

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