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Provisional Peer-Reviewed Toxicity Values for

1,1'-Sulfonylbis(4-chlorobenzene)
(CASRN 80-07-9)

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

COMMONLY USED ABBREVIATIONS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,1'-SULFONYLBIS(4-CHLOROBENZENE) (CASRN 80-07-9)

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

The chemical 1,1'-sulfonylbis(4-chlorobenzene) is a monomer used in the plastics industry for creating polysulfone plastics, which are approved for food-contact use by the U.S. Food and Drug Administration (FDA) and a wide variety of other consumer plastics. They are also used in polyethersulfone plastics and as a component in reactive dyes in the textile industry. Despite the widespread potential exposures, no RfD, RfC, or cancer assessment for 1,1'-sulfonylbis(4-chlorobenzene) (see Figure 1 for chemical structure) is available on IRIS (U.S. EPA, 2008), in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997), or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). No relevant documents were located in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994). The Agency for Toxic Substances and Disease Registry (ATSDR, 2008) has not published a Toxicological Profile for 1,1'-sulfonylbis(4-chlorobenzene), and no Environmental Health Criteria Document is available from the World Health Organization (WHO, 2008).

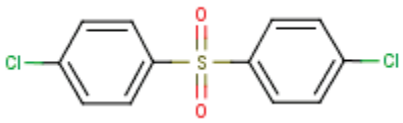

Figure 1. Structure of 1,1'-Sulfonylbis(4-chlorobenzene)

Neither the American Conference for Governmental Industrial Hygienists (ACGIH, 2008), Occupational Safety and Health Administration (OSHA, 2008) nor the National Institute of Occupational Safety and Health (NIOSH, 2008) has established occupational health standards for 1,1-sulfonylbis(4-chlorobenzene). The carcinogenicity of 1,1'-sulfonylbis(4-chlorobenzene) has not been assessed by the International Agency for

Research on Cancer (IARC, 2008), and 1,1-sulfonylbis(4-chlorobenzene) is not included in the National Toxicology Program's (NTP) Report on Carcinogens (NTP, 2005)—although NTP has evaluated the subchronic and chronic toxicity and carcinogenicity from oral exposure to 1,1'-sulfonylbis(4-chlorobenzene) in both mice and rats (NTP, 2001).

Literature searches were conducted from the 1960s through November of 2008 and updated in August 2009 for studies relevant to the derivation of provisional toxicity values for 1,1'-sulfonylbis(4-chlorobenzene). Databases searched include MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/ TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents (through August 2009).

REVIEW OF PERTINENT DATA

Human Studies

No studies regarding oral or inhalation exposure of humans to 1,1'-sulfonylbis(4-chlorobenzene) were located.

Animal Studies

Oral Exposure

Available subchronic and chronic oral studies of 1,1'-sulfonylbis(4-chlorobenzene) include a 14-week study in rats (Chhabra et al., 2001) and a 2-year study in rats and mice (NTP, 2001). A short-term toxicity study evaluating limited endpoints in rats (Poon et al., 1999) is discussed under Other Studies.

Subchronic Studies—In the subchronic toxicity study, F344 rats (10/sex/dose), were exposed continuously to 1,1'-sulfonylbis(4-chlorobenzene) (>99% pure) at 0, 30, 100, 300, 1000, or 3000 ppm in the diet for 14 weeks (Chhabra et al., 2001; NTP, 2001). Average daily doses were reported by the researchers to be approximately 0, 2, 6, 19, and 65 and 200 mg/kg-day in both males and females. Clinical observations and body weights were evaluated weekly and at the end of the study. A neurobehavioral screening battery that included tests for autonomic, convulsive, excitability, neuromuscular, sensorimotor, and general motor activity was administered on Week 12 to rats exposed to 0, 100, 300, or 1000 ppm. At study termination, blood samples were collected for hematology (erythrocyte, platelet and leukocyte counts, hematocrit, hemoglobin concentration, mean cell volume [MCV], mean cell hemoglobin [MCH] and mean cell hemoglobin concentration [MCHC]), and clinical chemistry (urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase [ALT], alkaline phosphatase [ALP], sorbitol dehydrogenase, creatine kinase, and total bile acids). At necropsy, selected organs (heart, right kidney, liver, ovary, right testis, thymus, and uterus) were weighed. A complete histopathological examination was conducted on control and high-dose rats, and target tissues were examined microscopically in animals from all dose groups.

All rats survived the duration of the experiment and no clinical signs related to exposure were observed (Chhabra et al., 2001; NTP, 2001). Tables 1 and 2 show the statistically significant changes in males and females, respectively. At the end of the experiment, male and female rats exposed to ≥300 ppm showed statistically significant, dose-related reductions in weight body weight. Final body weights of rats in the 300- and 1000-ppm groups were

approximately 96% and 91% of controls (respectively), while those in the 3000-ppm groups were 82−85% of control values. Feed consumption was reduced (23−39% less than controls) in the 3000-ppm group during the first week of the study, but it was similar to controls in all groups by the end of the study. A neurobehavioral screening battery revealed no statistically significant treatment-related effects in rats. A mild effect on the erythropoietic system was evidenced by slight—but statistically significant—decreases in hemoglobin, MCH, and MCHC, as well as significant increases in platelets, in both males (≥1000 ppm) and females (≥300 ppm). Clinical chemistry changes included slight—but statistically significant—increases in albumin and total protein concentrations in male and female rats exposed to ≥300 ppm and a dose-related decrease in ALP activity in males from all dose groups and in females at ≥100 ppm. Significant increases in sorbitol dehydrogenase activity were observed in rats of both sexes at 3000 ppm (83% and 45% higher than controls in males and females, respectively). In addition, a statistically significant increase in bile salt concentration was observed in 3000-ppm males (27% higher than controls). ALT activity was not increased at any dose; decreased activity (relative to controls) was observed in the lower dose groups. Slight—but statistically significant—increases in serum creatinine were observed in high-dose rats of both sexes; blood urea nitrogen was increased in high-dose males.

At necropsy, absolute and relative liver weights were significantly increased in a dose-related fashion in both male and female rats at ≥100 ppm (Chhabra et al., 2001; NTP, 2001; see Tables 1 and 2). In males, other significant organ weight changes were observed, primarily at 300 ppm and above, including increases in absolute and/or relative kidney and testes weights and decreased absolute and relative thymus weight. In females, relative—but not absolute—kidney weights were significantly elevated compared to controls at ≥1000 ppm; decreased body weight at these doses may have contributed to this change. There were no significant changes in ovary or uterus weights at any dose level. No gross lesions of any organ were observed. Histopathological examination of the liver revealed increased incidences of slight-to-mild centrilobular hypertrophy in males at ≥100 ppm and females at ≥300 ppm. The increase in cell size was reported to be due to both cytomegaly and karyomegaly (nuclear enlargement). In the kidney, there was a statistically significant, dose-related increase in the incidence of nephropathy in females at ≥1000 ppm (minimal severity in all dose groups) and a dose-related increase in the severity of nephropathy in males at ≥300 ppm, from minimal in controls and low-dose groups to marked in the high-dose group (9/10 controls and all treated males showed nephropathy). The observed nephropathy is characterized by foci of regenerating renal tubules with associated peritubular fibrosis and interstitial mononuclear inflammatory cell infiltration.

Table 1. Changes in Male Rats Exposed to 1,1'-Sulfonylbis(4-chlorobenzene) Via the Diet for 14 Weeks[a]

Parameter	Dietary Concentration in ppm (Dose in mg/kg-d)					
	0	30 (2 mg/kg-d)	100 (6 mg/kg-d)	300 (19 mg/kg-d)	1000 (65 mg/kg-d)	3000 (200 mg/kg-d)
Terminal body weight (g)	369 ± 4[b]	378 ± 7	366 ± 4	350 ± 4[c]	340 ± 6[d]	304 ± 8[d]
Hematology						
Hemoglobin (g/dL)	16.5 ± 0.2	16.6 ± 0.1	16.2 ± 0.2	16.3 ± 0.2	15.6 ± 0.1[d]	15.8 ± 0.2[d]
Reticulocytes (10^6/μL)	0.11 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.14 ± 0.01	0.15 ± 0.02[c]
MCH (pg)	17.4 ± 0.1	17.8 ± 0.1	17.6 ± 0.1	17.6 ± 0.1	17.3 ± 0.1	16.9 ± 0.3[c]
MCHC (g/dL)	34.0 ± 0.2	34.0 ± 0.1	33.9 ± 0.2	34.0 ± 0.2	33.5 ± 0.2	32.6 ± 0.3[d]
Platelets (10^3/μL)	754.7 ± 15.0	793.6 ± 56.5	769.1 ± 22.8	761.1 ± 13.3	837.8 ± 20.4[d]	948.8 ± 21.0[d]
Serum chemistry						
Albumin (g/dL)	4.9 ± 0.1	4.9 ± 0.1	5.1 ± 0.1	5.4 ± 0.1[d]	5.1 ± 0.0[d]	5.3 ± 0.1[d]
Total protein (g/dL)	7.4 ± 0.1	7.4 ± 0.2	7.7 ± 0.1	8.2 ± 0.1[d]	8.2 ± 0.1[d]	8.6 ± 0.1[d]
ALP (U/L)	602 ± 11	509 ± 27[d]	460 ± 7[d]	474 ± 9[d]	402 ± 8[d]	421 ± 8[d]
Sorbitol dehydrogenase (U/L)	23 ± 2	24 ± 2	20 ± 1	23 ± 3	27 ± 2	42 ± 4[d]
ALT (U/L)	73 ± 6	53 ± 4[c]	50 ± 3[d]	61 ± 6	63 ± 5	73 ± 6
Bile salts (μmol/L)	25.2 ± 2.4	23.6 ± 1.4	27.8 ± 2.9	25.0 ± 0.8	26.2 ± 0.5	32 ± 1.3[d]
Urea nitrogen (mg/dL)	20.5 ± 0.3	18.2 ± 0.5	19.8 ± 0.4	21 ± 0.3	21 ± 0.3	24 ± 0.3[d]
Creatinine (mg/dL)	0.68 ± 0.01	0.7 ± 0.02	0.69 ± 0.01	0.69 ± 0.01	0.71 ± 0.02	0.76 ± 0.02[d]
Organ weights						
Absolute kidney weight (g)	1.38 ± 0.03	1.37 ± 0.04	1.42 ± 0.03	1.43 ± 0.04	1.63 ± 0.04[d]	1.56 ± 0.03[d]
Relative kidney weight (g/g-bw)	0.35 ± 0.005	0.35 ± 0.005	0.37 ± 0.006[c]	0.39 ± 0.007[d]	0.46 ± 0.007[d]	0.50 ± 0.005[d]
Absolute liver weight (g)	15.5 ± 0.37	15.6 ± 0.5	18.2 ± 0.48[d]	20.1 ± 0.36[d]	25.0 ± 0.6[d]	26.4 ± 0.46[d]
Relative liver weight (g/g-bw)	3.96 ± 0.08	4.03 ± 0.07	4.77 ± 0.12[d]	5.48 ± 0.06[d]	7.08 ± 0.09[d]	8.47 ± 0.16[d]
Absolute R. testis weight (g)	1.49 ± 0.02	1.48 ± 0.04	1.51 ± 0.02	1.50 ± 0.01	1.57 ± 0.01[c]	1.54 ± 0.02[c]
Relative R. testis weight (g/g-bw)	0.38 ± 0.005	0.38 ± 0.006	0.40 ± 0.008	0.41 ± 0.005[d]	0.45 ± 0.009[d]	0.49 ± 0.011[d]
Absolute thymus weight (g)	0.35 ± 0.02	0.30 ± 0.02	0.31 ± 0.02	0.28 ± 0.01[d]	0.25 ± 0.01[d]	0.23 ± 0.02[d]
Relative thymus weight (g/g-bw)	0.088 ± 0.005	0.078 ± 0.003	0.081 ± 0.005	0.075 ± 0.003[c]	0.070 ± 0.003[d]	0.072 ± 0.004[d]

Table 1. Changes in Male Rats Exposed to 1,1'-Sulfonylbis(4-chlorobenzene) Via the Diet for 14 Weeks[a]

Parameter	Dietary Concentration in ppm (Dose in mg/kg-d)					
	0	**30 (2 mg/kg-d)**	**100 (6 mg/kg-d)**	**300 (19 mg/kg-d)**	**1000 (65 mg/kg-d)**	**3000 (200 mg/kg-d)**
Histopathology						
Centrilobular Hypertrophy (liver)	0/10[e]	0/10	7/10[d] (1.1)[f]	10/10[d] (2.0)	10/10[d] (2.0)	10/10[d] (2.0)
Nephropathy (kidney)	9/10 (1.0)	10/10 (1.0)	10/10 (1.0)	10/10 (1.9)	10/10 (2.9)	10/10 (3.8)

[a]Chhabra et al. (2001).
[b]Values are presented as means ± SE.
[c]Significantly different from control ($p < 0.05$).
[d]Significantly different from control ($p < 0.01$).
[e]Number of animals affected/number examined.
[f]Average severity grades of lesions in affected animals (1, minimal; 2, mild; 3, moderate; 4, marked) in parentheses.

Table 2. Changes in Female Rats Exposed to 1,1'-Sulfonylbis(4-chlorobenzene) Via the Diet for 14 Weeks[a]

Parameter	Dietary Concentration in ppm (Dose in mg/kg-d)					
	0	30 (2 mg/kg-d)	100 (6 mg/kg-d)	300 (19 mg/kg-d)	1000 (65 mg/kg-d)	3000 (200 mg/kg-d)
Terminal body weight (g)	204 ± 2[b]	201 ± 2	200 ± 2	196 ± 3[c]	185 ± 2[d]	174 ± 3[d]
Hematology						
Hemoglobin (g/dL)	15.8 ± 0.2	16.1 ± 0.1	15.7 ± 0.1	15.6 ± 0.2	15.0 ± 0.2[d]	14.8 ± 0.2[d]
Mean cell volume (fL)	55.2 ± 0.2	55.9 ± 0.2	55.6 ± 0.2	55.1 ± 0.2	54.4 ± 0.2[c]	54.1 ± 0.4[d]
MCH (pg)	19.2±0.1	19.4±0.1	19.2±0.1	18.7±0.1[d]	17.9±0.1[d]	17.8±0.1[d]
MCHC (g/dL)	34.9 ± 0.2	34.6 ± 0.2	34.5 ± 0.3	33.9 ± 0.3[c]	32.9 ± 0.2[d]	32.8 ± 0.2[d]
Platelets ($10^3/\mu L$)	736.4 ± 11.5	783.9 ± 14.9[c]	772.7 ± 23.2	790.4 ± 12.4[c]	843.9 ± 14.3[d]	826.9 ± 16.8[d]
Serum chemistry						
Albumin (g/dL)	5.1 ± 0.1	5.3 ± 0.1[c]	5.1 ± 0.1	5.4 ± 0.1[d]	6.0 ± 0.1[d]	6.1 ± 0.1[d]
Total protein (g/dL)	7.2 ± 0.1	7.6 ± 0.1[d]	7.5 ± 0.1[d]	8.0 ± 0.1[d]	9.1 ± 0.1[d]	9.5 ± 0.2[d]
ALP (U/L)	447 ± 16	432 ± 125	368 ± 14[d]	339 ± 15[d]	225 ± 8[d]	243 ± 9[d]
Sorbitol dehydrogenase (U/L)	20 ± 2	20 ± 1	20 ± 2	21 ± 1	27 ± 4	29 ± 4[c]
ALT (U/L)	52 ± 3	44 ± 1	41 ± 2[c]	40 ± 1[c]	48 ± 6	47 ± 4
Bile acids (µmol/L)	48.5 ± 5.3	54.2 ± 6.1	59.1 ± 5.1	72 ± 10.3	42.2 ± 2.4	49.4 ± 5.8
Urea nitrogen (mg/dL)	19.3 ± 0.6	18.7 ± 0.8	18.2 ± 0.5	19.6 ± 1	18.6 ± 0.5	21.8 ± 0.6
Creatinine (mg/dL)	0.67 ± 0.02	0.71 ± 0.02	0.68 ± 0.01	0.68 ± 0.01	0.68 ± 0.01	0.73 ± 0.02[c]
Organ Weights						
Absolute kidney weight (g)	0.75 ± 0.02	0.76 ± 0.01	0.77 ± 0.01	0.74 ± 0.02	0.79 ± 0.01	0.78 ± 0.02
Relative kidney weight (g/g-bw)	0.35 ± 0.006	0.37 ± 0.005	0.37 ± 0.006	0.37 ± 0.006	0.42 ± 0.004[d]	0.44 ± 0.007[d]
Absolute liver weight (g)	7.5 ± 0.17	7.7 ± 0.14	8.2 ± 0.10[c]	9.3 ± 0.26[d]	12.2 ± 0.27[d]	14.7 ± 0.24[d]
Relative liver weight (g/g-bw)	3.23 ± 0.04	3.72 ± 0.06	4.00 ± 0.04[d]	4.61 ± 0.08[d]	6.47 ± 0.12[d]	8.32 ± 0.15[d]
Histopathology						
Centrilobular hypertrophy (liver)	0/10[e]	0/10	0/10	10/10[d] (1.0)[f]	10/10[d] (1.9)	10/10[d] (1.9)
Nephropathy (kidney)	0/10	0/10	1/10 (1.0)	2/10 (1.0)	5/10[c] (1.0)	9/10[d] (1.0)

[a]Chhabra et al. (2001).
[b]Values are presented as means ± SE.
[c]Significantly different from control ($p < 0.05$).
[d]Significantly different from control ($p < 0.01$).
[e]Number of animals affected/number examined.
[f]Average severity grades of lesions in affected animals (1, minimal; 2, mild; 3, moderate; 4, marked) in parentheses.

The authors identified a NOAEL of 30 ppm (2 mg/kg-day) for this study (Chhabra et al., 2001; NTP, 2001). Effects observed at the next higher dose (100 ppm or 6 mg/kg-day) include increased absolute and relative liver weights, increased incidence of hepatocellular hypertrophy (males), decreased ALP and ALT, increased total serum protein (females), and a nonsignificant increase in the incidence of nephropathy (females). For the purpose of this review, the 100-ppm (6 mg/kg-day) dose is considered a LOAEL based on increased incidence of centrilobular hypertrophy and increased liver weight in male rats. Given the magnitude of the liver weight changes, the statistical significance of these changes, the accompanying histopathology, the serum chemistry changes (increased serum levels of bile salts, total protein, and sorbitol dehydrogenase) observed at the high dose in this study, this is viewed as a toxic effect. Additionally, the evidence for liver toxicity in the chronic study (see below) of rats (bile-duct hyperplasia in female rats; Chhabra et al., 2001; NTP, 2001) further supports these effects of early indicators of subsequent pathology. Evidence for liver toxicity was also observed in mice chronically exposed to 1,1'-sulfonylbis(4-chlorobenzene); hepatocellular necrosis was seen after subchronic exposure, and increased incidence of eosinophilic foci was seen after chronic exposure (Chhabra et al., 2001; NTP, 2001).

In the 14-week study in mice, groups of 10/sex/dose were fed diets containing 0, 30, 100, 300, 1000, or 3000 ppm of (> 99% pure) 1,1'-sulfonylbis(4-chlorobenzene), which the researchers estimated to be equivalent to 0, 3.5, 15, 50, 165, or 480 mg/kg-day in both males and females (Chhabra et al., 2001; NTP, 2001). The same study procedures described above for rats were followed for mice—except the neurobehavioral assessment was conducted during Week 12 for female mice exposed to 0, 300, 1000, or 3000 ppm, and blood samples were only analyzed for hematology and not clinical chemistry. All mice survived to the end of the study and no clinical signs related to exposure were noted. Significant changes are reported in Table 3. Body-weight gain was significantly reduced in treated males and females at ≥300 ppm. Final body weight was 91−92% of control in the 300-ppm groups and 85−87% of controls in the 1000- and 3000-ppm groups. Feed consumption was 47−52% lower than controls in the 3000-ppm groups during the first week of the study but similar to controls in all groups by Week 14. The neurological assessment found no effects in mice at any level. Hematological analyses revealed minimal changes in platelet counts and red cell indices that the authors indicated were within physiological ranges and, consequently, not biologically significant.

Both absolute and relative liver weights were statistically significantly increased in a dose-related manner in male and female mice (see Table 3) at ≥300 ppm (Chhabra et al., 2001; NTP, 2001). In addition, relative—but not absolute—organ-weight changes (testis and kidney in males, and ovary, uterus, and kidney in females) were statistically significantly increased at ≥1000 ppm; however, these changes were likely attributable to reduced body weights in these groups. Absolute—but not relative—thymus weight was statistically significantly decreased (20% less than controls, $p < 0.01$) in high-dose females. There was a statistically significant, dose-related increase in the incidence of centrilobular hypertrophy among male mice at ≥100 ppm and female mice at ≥1000 ppm. The lesions were morphologically similar to those in rats (described above) and increased in severity in relation to dose. In addition, hepatic necrosis (minimal severity) was seen in males at ≥100 ppm and females at ≥1000 ppm. The increase in incidence was statistically significant in males at ≥1000 ppm. Hepatic necrosis in these mice is characterized by multiple, randomly scattered small foci of coagulative necrosis. No other histological changes are reported in mice. The study authors did not identify effect levels for mice. For the purposes of this review, a NOAEL of 30 ppm (3.5 mg/kg-day) and a LOAEL of

100 ppm (15 mg/kg-day) are identified based on increased incidence of centrilobular hypertrophy in male mice. A nonsignificant increase in the incidence of hepatocellular necrosis (1/10 males) was also observed at this dose; this finding increased with dose and was not observed in control animals or those exposed to the NOAEL. Centrilobular hypertrophy is considered a sensitive indicator of toxicity for this chemical, given the available evidence for more explicitly toxic liver effects also occurring in both mice and rats. In the mouse, there were dose-related increase in liver cell necrosis in the subchronic study and eosinophilic foci in the chronic study and in the rats the serum chemistry findings in subchronic study and bile-duct hyperplasia in the chronic study. Serum chemistry was not analyzed in either the subchronic or chronic studies (see below) in mice, so there are no serum chemistry data to inform the assessment of liver toxicity in mice.

Chronic Studies—In the chronic study in rats (Chhabra et al., 2001; NTP, 2001), groups of 50 male and 50 female F344 rats were fed diets containing 0, 10 (males only), 30, 100, or 300 (females only) ppm of 1,1'-sulfonylbis(4-chlorobenzene) (>99% purity) for 2 years. The researchers reported average daily doses of 0, 0.5, 1.5, or 5 mg/kg-day in males and 1.6, 5.4, or 17 mg/kg-day in females. Survival and signs of illness were monitored twice daily; clinical observations were recorded monthly. Body weights were measured weekly for the first 13 weeks and monthly thereafter and at study termination. Blood samples were collected at approximately 2 weeks and 3, 12, and 18 months for determination of 1,1'-sulfonylbis(4-chlorobenzene); hematology was not assessed. At necropsy, a comprehensive set of organs and tissues were examined for grossly visible and microscopic lesions. Clinical pathology and organ weights are not assessed.

Survival was similar in control and treated rats, and no clinical findings were attributed to exposure (Chhabra et al., 2001; NTP, 2001). Feed consumption in treated groups was similar to controls. Body weights of mid- and high-dose males and females were less than controls for much of the study but remained within 10% of the control group for all but the high-dose females, which exhibited a >10% decrease in body weights compared to controls (based on graphical presentation of data; statistical analysis was not reported). Histopathology lesions related to treatment were found only in the liver. Statistically significant increased incidences of minimal-to-mild centrilobular hypertrophy (males and females), minimal bile-duct hyperplasia (females only), and minimal-to-mild centrilobular degeneration (females) were observed at ≥100 ppm (see Table 4). Hepatocyte hypertrophy was characterized by increased size of the centrilobular hepatocytes and fine cytoplasmic vacuolization accompanied by eosinophilic or basophilic stippling. Bile-duct hyperplasia was characterized by increased bile duct profiles within the portal areas. Centrilobular degeneration was noted to be only observed in those animals that had mononuclear cell leukemia in the liver; NTP (2001) suggested that this lesion was most likely a manifestation of anoxia due to large numbers of mononuclear leukemic cells infiltrating the centrilobular sinusoids. However, mononuclear cell leukemias are common in aging F344 rats, and the NTP data show high levels of these leukemias in the control rats as well. There appears to be no significant relationship between the chemical and these leukemias. No treatment-related nonneoplastic lesions were seen at 30 ppm. The authors identified a NOAEL of 30 ppm (1.5−1.6 mg/kg-day) (Chhabra et al., 2001; NTP, 2001) based on liver effects seen at higher doses. A LOAEL of 100 ppm (5−5.4 mg/kg-day) is identified based on increased incidences of bile-duct hyperplasia (females) and centrilobular hypertrophy (in males and females).

Table 3. Changes in Mice Exposed to 1,1'-Sulfonylbis (4-chlorobenzene) Via the Diet for 14 Weeks[a]

Parameter	Dietary Concentration in ppm (Dose in mg/kg-d)					
	0	**30 (3.5 mg/kg-d)**	**100 (15 mg/kg-d)**	**300 (50 mg/kg-d)**	**1000 (165 mg/kg-d)**	**3000 (480 mg/kg-d)**
Males						
Terminal body weight (g)	33.7 ± 0.5[b]	36.0 ± 0.5	33.5 ± 0.8	30.9 ± 0.4[c]	28.9 ± 0.4[c]	28.5 ± 0.3[c]
Organ weights						
Absolute liver weight (g)	1.71 ± 0.03	1.86 ± 0.04	1.79 ± 0.05	1.95 ± 0.04[c]	2.39 ± 0.06[c]	2.95 ± 0.06[c]
Relative liver weight (g/g-bw)	4.85 ± 0.09	4.93 ± 0.11	5.02 ± 0.08	5.89 ± 0.10[c]	7.65 ± 0.10[c]	9.91 ± 0.17[c]
Histopathology						
Centrilobular hypertrophy	0/10[d]	0/10	6/10[e] (1.0)[f]	10/10[e] (2.0)	10/10[e] (3.0)	10/10[e] (3.0)
Hepatocellular necrosis	0/10	0/10	1/10 (1.0)	3/10 (1.0)	7/10[e] (1.0)	8/10[e] (1.0)
Females						
Terminal body weight (g)	27.7 ± 0.7	29.3 ± 0.8	28.5 ± 0.6	25.3 ± 0.4[e]	24.1 ± 0.5[e]	23.9 ± 0.2[e]
Organ weights						
Absolute liver weight (g)	1.25 ± 0.04	1.34 ± 0.04	1.34 ± 0.02	1.56 ± 0.05[e]	1.80 ± 0.05[e]	2.30 ± 0.04[e]
Relative liver weight (g/g-bw)	4.39 ± 0.07	4.47 ± 0.08	4.75 ± 0.09[e]	6.04 ± 0.13[e]	7.14 ± 0.12[e]	9.09 ± 0.10[e]
Histopathology						
Centrilobular hypertrophy	0/10	0/10	0/10	0/10	10/10[e] (1.0)	10/10[e] (2.0)
Hepatocellular necrosis	0/10	0/10	0/10	0/10	1/10 (1.0)	2/10 (1.5)

[a]Chhabra et al. (2001).
[b]Values are presented as means ± SE.
[c]Significantly different from control ($p < 0.01$).
[d]Number of animals affected/number examined.
[e]Significantly different from control ($p < 0.05$).
[f]Average severity grades of lesions in affected animals (1, minimal; 2, mild; 3, moderate; 4, marked) in parentheses.

Table 4. Incidence of Nonneoplastic Liver Lesions in Rats Fed 1,1'-Sulfonylbis(4-chlorobenzene) for 2 Years[a]

Dietary concentration in ppm (dose in mg/kg-d)	Centrilobular Hypertrophy	Bile-Duct Hyperplasia	Centrilobular Degeneration
Males			
0	0/50[b]	46/50 (1.7)	18/50 (2.0)
10 (0.5 mg/kg-d)	1/50 (1.0)	47/50 (1.5)	15/50 (2.1)
30 (1.5 mg/kg-d)	3/50 (1.0)	44/50 (1.8)	20/50 (2.1)
100 (5.0 mg/kg-d)	16/50[c] (1.3)	48/50 (1.9)	23/50 (2.2)
Females			
0	0/50	5/50 (1.4)	1/50 (1.0)
30 (1.6 mg/kg-d)	2/50 (1.5)	12/50 (1.1)	5/50 (2.0)
100 (5.4 mg/kg-d)	24/50[c] (1.3)	21/50[c] (1.0)	10/50[c] (2.2)
300 (17 mg/kg-d)	38/50[c] (1.7)	32/50[c] (1.0)	7/50[d] (1.7)

[a]Chhabra et al. (2001).
[b]Number of animals affected/number examined. Average severity grades of lesions in affected animals (1, minimal; 2, mild; 3, moderate; 4, marked) in parentheses.
[c]Significantly different from control ($p < 0.01$).
[d]Significantly different from control ($p < 0.05$).

In the 2-year study in mice, groups of 50 male and 50 female B6C3F1mice were fed diets containing 1,1'-sulfonylbis(4-chlorobenzene) (>99% pure) at 0, 30, 100, or 300 ppm, corresponding to doses of 0, 4, 13, or 40 mg/kg-day in males and 0, 3, 10, or 33 mg/kg-day in females (Chhabra et al., 2001; NTP, 2001). Endpoints examined in the mouse study were the same as those in the corresponding rat study. Survival of treated mice was similar to controls, and no clinical signs related to treatment were observed. Feed consumption was similar to controls in all groups, but mean body weights among high-dose mice were less than the controls throughout most of the study; terminal body weights appeared to be within 10% of controls for male—but not female—mice based on data presented graphically (statistical analysis was not reported). Statistically significant, dose-related increases in the incidence of centrilobular hypertrophy in the liver were found in male mice at ≥30 ppm and female mice at ≥100 ppm (see Table 5). The lesions were morphologically similar to those in rats (described above) and increased in severity in relation to dose. The only other nonneoplastic lesion noted was a significant increase in eosinophilic foci in the livers of female mice treated with 300 ppm (see Table 5). The study authors did not identify effect levels for mice (Chhabra et al., 2001; NTP, 2001). A LOAEL of 30 ppm (4 mg/kg-day) is identified based on increased incidence of centrilobular hypertrophy in male mice; a NOAEL cannot be determined. Liver cell hypertrophy is considered adverse given the evidence for eosinophilic foci in female mice exposed chronically and liver cell necrosis in male and female mice exposed subchronically to 1,1'-sulfonylbis(4-chlorobenzene).

Table 5. Incidence of Nonneoplastic Liver Lesions in Mice Fed 1,1'-Sulfonylbis(4-chlorobenzene) for 2 Years[a]

Dietary concentration in ppm (dose in mg/kg-d)	Centrilobular Hypertrophy	Eosinophilic Focus
Males		
0	1/50[b] (1.0)	5/50
30 (4 mg/kg-d)	24/50[c] (1.0)	9/50
100 (13 mg/kg-d)	43/50[c] (1.4)	7/50
300 (40 mg/kg-d)	45/50[c] (2.8)	8/50
Females		
0	0/50	2/50
30 (3 mg/kg-d)	0/50	1/50
100 (10 mg/kg-d)	9/50[c] (1.0)	4/50
300 (33 mg/kg-d)	29/50[c] (1.4)	14/50[c]

[a]Chhabra et al. (2001).
[b]Number of animals affected/number examined. Average severity grades of lesions in affected animals (1, minimal; 2, mild; 3, moderate; 4, marked) in parentheses.
[c]Significantly different from control ($p < 0.05$).

No statistically significant increases in tumor incidence related to 1,1'-sulfonylbis(4-chlorobenzene) treatment were found in any dose group (rats or mice) during the 2-year studies (Chhabra et al., 2001; NTP, 2001). The NTP concluded that there was *no evidence of carcinogenic activity* of 1,1'-sulfonylbis(4-chlorobenzene) in rats or mice in this study.

Inhalation Exposure

No animal studies examining the effects of subchronic or chronic inhalation exposure to 1,1'-sulfonylbis(4-chlorobenzene) were located.

Other Studies

Acute/Short-term Studies

A short-term toxicity study evaluating hepatic enzyme induction was conducted by Poon et al. (1999). Groups of six weanling male Sprague-Dawley rats were exposed to 0 (4% corn oil), 10, 100, or 1000 ppm of 1,1'-sulfonylbis(4-chlorobenzene) (>99% purity) in the diet for 28 days. The authors reported that these dietary concentrations corresponded to doses of 0, 0.8, 8.1, or 75.6 mg/kg-day. Additional control and 1000-ppm exposure groups (6/group) were included for evaluation after 1, 2, and 3 weeks of exposure. Body weights and changes in food consumption were monitored weekly and clinical observations were made daily. Urine samples were collected weekly and analyzed for N-acetylglucosaminidase (NAG) activity, protein, and ascorbic acid. At termination at the end of exposure, blood was collected for hematology (erythrocyte count, hematocrit, MCV, MCH, platelet count, and total and differential white blood cell counts) and clinical chemistry (inorganic phosphate, total protein, ALP, aspartate aminotransferase [AST], bilirubin, calcium, cholesterol, glucose, uric acid, creatinine, and blood urea nitrogen). Lavage fluid from the lung was collected for analysis of NAG and

total protein, both biochemical markers for lung injury (Poon et al., 1999). The brain, heart, thymus, liver, kidney, and spleen were excised and weighed. Liver homogenates were collected for enzyme analyses (UDP-glucuronosyltransferase [UDPGT] activity, benzyloxyresorufin O-dealkylase [BROD], methoxyresorufin O-dealkylase [MROD], pentoxyresorufin O-dealkylase [PROD], ethoxyresorufin O-deethylase [EROD], glutathione S-transferase [GST] activity, and thiobarbituric acid-reactive substances [TBARS]), and parts of the liver, spleen, kidneys, brain, lungs, and abdominal fat were collected for analysis of 1,1'-sulfonylbis(4-chlorobenzene).

All animals survived to the end of the experimental period without clinical signs of toxicity, although hematuria was observed in one animal from each of the 1-, 3-, and 4-week groups exposed to 1000 ppm (Poon et al., 1999). After 4 weeks, body weight was statistically significantly reduced by about 7% in the high-dose group (relative to controls, $p < 0.05$), and there was a significant corresponding decrease in feed consumption in this group. Hematology analysis revealed a statistically significant increase in platelet count among high-dose rats; however, the authors reported that the levels were within the normal range of variation in rats. No significant changes were observed in total protein or NAG activity in lavage fluid or in urine samples.

Exposure to 1,1'-sulfonylbis(4-chlorobenzene) resulted in a number of hepatic effects, including serum chemistry changes, increased microsomal enzyme activities, and increased liver weight (Poon et al., 1999), as shown in Table 6. Serum chemistry findings included a statistically significant increase in cholesterol at 1000 ppm (nearly 3-fold increase over controls), and decrease in lactate dehydrogenase at ≥100 ppm. Marked increases in BROD and PROD activity were observed in all dose groups, and UDPGT and GST activities were increased more than 3-fold among high-dose rats. In contrast, MROD activity was significantly decreased in high-dose rats, and EROD activity was not affected by treatment. In addition, urinary ascorbic acid, a biomarker of hepatic enzyme induction in rats, was significantly elevated in all exposure groups. Other serum and urine chemistry parameters were not statistically significantly affected by exposure. After 4 weeks of exposure, relative liver weight was increased by 33% and 97% in the 100-ppm and 1000-ppm groups, respectively. The time-course study revealed that while liver weight and UDPGT and GST activities were maximally increased after 1 week of treatment, BROD and PROD levels tended to increase from Week 1 to Week 4. The only other statistically significant organ weight change was an increase in relative kidney weight in high-dose rats (20% higher than controls, $p < 0.05$).

Residue analysis showed that the highest levels of 1,1'-sulfonylbis(4-chlorobenzene) residues were in adipose tissue, followed by the liver and kidneys; low levels of 1,1'-sulfonylbis(4-chlorobenzene) were measured in the lungs (Poon et al., 1999). The kidney was the only organ that demonstrated increased 1,1'-sulfonylbis(4-chlorobenzene) accumulation over time during the time-course study.

Table 6. Hepatic Enzyme Induction and Related Effects in Male Rats Treated with 1,1-Sulfonylbis(4-chlorobenzene) Via Diet for 28 Days[a]

	Dose in mg/kg-d			
	Control[b]	**0.8[b]**	**8.1[b]**	**75.6[b]**
Clinical chemistry				
Serum cholesterol (mg/dL)	58.0 ± 6.6	61.3 ± 9.8	73.5 ± 11.2	161.8 ± 31.7[c]
Serum lactate dehydrogenase (IU/L)	2179 ± 775	1714 ± 638	1333 ± 500[c]	1234 ± 328[c]
Urinary ascorbic acid (mg/g creatinine)	84 ± 55	913 ± 445[c]	1929 ± 346[c]	1403 ± 651[c]
Hepatic enzyme activities				
BROD	0.09 ± 0.01	0.41 ± 0.15[c]	9.07 ± 5.33[c]	6.04 ± 2.07[c]
PROD	0.04 ± 0.01	0.16 ± 0.07[c]	0.62 ± 0.36[c]	1.0 ± 0.23[c]
EROD	0.07 ± 0.01	0.08 ± 0.02	0.06 ± 0.02	0.04 ± 0.02
MROD	0.07 ± 0.01	0.07 ± 0.02	0.05 ± 0.03	0.02 ± 0.01[c]
UDPGT	1.74 ± 0.85	2.83 ± 0.95	5.83 ± 1.31[c]	11.06 ± 2.13[c]
GST	943 ± 169	1223 ± 217	2734 ± 510[c]	4237 ± 757[c]
TBARS (nmol/mg protein)	0.44 ± 0.22	0.39 ± 0.10	0.47 ± 0.30	1.35 ± 0.40[c]
Organ weights				
Relative liver weight (% body weight)	3.52 ± 0.18	3.8 ± 0.36	4.68 ± 0.23[c]	6.92 ± 0.46[c]

[a]Poon et al. (1999).
[b]Mean ± standard deviation.
[c]Significantly different from control at $p < 0.05$.

BROD = benzyloxyresorufin O-dealkylase; PROD = pentoxyresorufin O-dealkylase; EROD = ethoxyresorufin O-deethylase; MROD = methoxyresorufin O-dealkylase; UDPGT = UDP-glucuronosyltransferase; GST = glutathione S-transferase; TBARS = thiobarbituric acid-reactive substances.

Genotoxicity

No evidence of mutagenicity was observed in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, 1537, or 1538 (DuPont, 1991; NTP, 2001), or in CHO/HGPRT cells (Microbiological Associates, Inc., 1991a; NTP, 2001) tested with or without metabolic activation. Evidence of weak mutagenic activity was observed in the mouse lymphoma L5178Y assay when tested without metabolic activation—but not with metabolic activation (Inveresk Research International, 1994). Tests for sister chromatid exchanges or chromosomal aberrations in CHO cells treated with 1,1'-sulfonylbis(4-chlorobenzene) gave equivocal and negative results (respectively; NTP, 2001). Conflicting results were observed in mouse micronucleus assays performed in vivo; 1,1'-sulfonylbis(4-chlorobenzene) induced a weak positive response in mice injected (intraperitoneally) with 200−800 mg/kg for 3 consecutive days (NTP, 2001) but a negative response in male and female mice given a single intraperitoneal injection of 196 to 1960 mg/kg (Microbiological Associates Inc., 1991b).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 1,1'-SULFONYLBIS(4-CHLOROBENZENE)

Oral studies of 1,1'-sulfonylbis(4-chlorobenzene) include subchronic and chronic studies in mice and rats, all conducted by NTP (2001) and published by Chhabra et al. (2001). Table 7 summarizes the available oral dose-response information. A short-term (28-day) study that focused on hepatic enzyme induction (Poon et al., 1999) provides supplemental information.

Table 7. Summary of Subchronic and Chronic Oral Toxicity Studies of 1,1'-Sulfonylbis(4-chlorobenzene)

Species, sex, number	Dose (mg/kg-d)	Exposure Regimen	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Responses at the LOAEL	Reference
Rat, 10/sex/ dose	0, 2, 6, 19, 65, 200	Diet for 14 wk	2	6	Increased incidence of centrilobular hypertrophy and increased liver weight in males	Chhabra et al., 2001; NTP, 2001
Mouse, 10/sex/ dose	0, 3.5, 15, 50, 165, 480	Diet for 14 wk	3.5	15	Increased incidence of centrilobular hypertrophy in males	Chhabra et al., 2001; NTP, 2001
Rat, 50/sex/ dose	0, 0.5, 1.5, 5 (M) 0, 1.6, 5.4, 17 (F)	Diet for 2 yr	1.5−1.6	5 −5.4	Increased incidence of bile-duct hyperplasia (females) and centrilobular hypertrophy (both sexes)	Chhabra et al., 2001; NTP, 2001
Mouse, 50/sex/ dose	0, 4, 13, 40 (M) 0, 3, 10, 33 (F)	Diet for 2 yr	NA	4	Increased incidence of centrilobular hypertrophy in males	Chhabra et al., 2001; NTP, 2001

The available studies suggest that the liver is the most sensitive target for 1,1'-sulfonylbis(4-chlorobenzene). Poon et al. (1999) showed that induction of hepatic drug metabolizing enzymes occurs at the lowest doses that have been tested (0.8 mg/kg-day). At higher doses, 1,1'-sulfonylbis(4-chlorobenzene) produces liver lesions that increase in incidence and severity with dose—including hepatocellular hypertrophy characterized by both cytomegaly and karyomegaly, bile-duct hyperplasia, eosinophilic foci, and necrosis (Chhabra et al., 2001; NTP, 2001). Increased liver weight was observed in all studies, and serum chemistry changes indicative of hepatotoxicity (increased sorbitol dehydrogenase and bile acids) were found at higher doses in the subchronic rat study (the only study that analyzed serum chemistry).

Subchronic p-RfD

Table 7 shows a summary of the subchronic rat and mouse data. In rats, a NOAEL and LOAEL of 2 and 6 mg/kg-day, respectively, have been identified based on increased liver weight and hepatocellular hypertrophy in males. In mice, a NOAEL and LOAEL of 3.5 and 15 mg/kg-day, respectively, have been identified based on hypertrophy in males (Chhabra et al., 2001; NTP, 2001). The data on hepatocellular hypertrophy in both species are not amenable to benchmark dose (BMD) modeling. This is primarily due to the shapes of the

dose-response curves where the large increase in incidence (from 0/10 to 7/10 in male rats, and 0/10 to 6/10 in male mice) between the control and the low-dose and a subsequent plateau in response levels at higher doses. That resulted in poor fits with the models in the EPA BMDS software package. Also, relative liver weight changes in male rats are not modeled because the data are confounded by decreases in body weight at the higher doses. While reduced overall body weights may have had some impact on absolute liver weights, any such impact is expected to be mitigated by the determination of the effect on relative liver weight, where body weight is actually used in the calculation to normalize for such variations. BMD modeling was conducted for increases in absolute liver weight in male rats (see Table 1).

Appendix A provides details of the modeling efforts and the selection of best fitting models. The 2-degree polynomial model with homogenous variance provides the best fit to the data on absolute liver weight in male rats after the three highest dose groups were dropped (no model fit was achieved with more dose groups); the BMD_{1SD} and $BMDL_{1SD}$ associated with this endpoint were 4.21 and 3.56 mg/kg-day, respectively. This $BMDL_{1SD}$ was selected as a suitable point of departure for derivation of the subchronic p-RfD. While comparisons have no weight programmatically, the $BMDL_{1SD}$ of 3.56 mg/kg-day for increased absolute liver weight in male rats is below the LOAELs for hypertrophy in both rats (6 mg/kg-day) and mice (15 mg/kg-day).

Physiologically based pharmacokinetic models as constructed by Matthews et al. (1996) and Parham et al. (2002) were of inadequate applicability to reduce the uncertainty factor used for animal to human extrapolation.

A **subchronic p-RfD** is derived by dividing the BMDL of 3.56 mg/kg-day by a UF of 1000, as shown below:

Subchronic p-RfD = BMDL ÷ UF
= 3.56 mg/kg-day ÷ 1000
= **0.004 mg/kg-day or 4×10^{-3} mg/kg-day**

The UF of 1000 is composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient.
- UF_D: A factor of 10 is applied for database inadequacies because data for evaluating developmental and reproductive toxicity are lacking. The database for 1,1'-sulfonylbis(4-chlorobenzene) includes comprehensive subchronic and chronic oral toxicity studies conducted by the NTP using both sexes of two species (Chhabra et al., 2001; NTP, 2001), as well as a limited short-term study in rats (Poon et al., 1999).

Confidence in the principal study (Chhabra et al., 2001; NTP, 2001) is high. Groups of 10 rats/sex/dose were used, a wide range of doses was tested, both a NOAEL and LOAEL were identified, and comprehensive toxicological endpoints were evaluated (body weight, clinical signs, neurobehavioral screening, hematology, clinical pathology, organ weights, and gross and

histological pathology). Confidence in the database is medium. Although comprehensive subchronic and chronic studies were conducted in rats and mice of both sexes by NTP, developmental and reproductive toxicity have not been evaluated. Medium confidence in the subchronic p-RfD follows.

Chronic p-RfD

Effects were observed at similar doses in mice and rats exposed chronically to 1,1'-sulfonylbis(4-chlorobenzene); the NOAEL and LOAEL in rats were ~2 and 5 mg/kg-day, while the LOAEL in male mice (a NOAEL was not identified) was 4 mg/kg-day (Chhabra et al., 2001; NTP, 2001). The data for centrilobular hypertrophy and bile-duct hyperplasia in female rats, and centrilobular hypertrophy in male mice were considered for use in the chronic p-RfD derivation. Although the incidence of centrilobular hypertrophy was also increased in male rats exposed at the LOAEL, the incidence of this effect in males was lower than in females exposed to the same dose. BMD modeling of the data on incidences of centrilobular hypertrophy and bile-duct hyperplasia in female rats (see Table 4) was conducted. The centrilobular hypertrophy data in male mice (see Table 5) are not amenable to BMD modeling; the data results in inadequate model fits due to the large increase in incidence (from 1/50 to 24/50) between controls and the lowest dose, and, additionally, there were no data points with response levels near the default benchmark response of 10% for quantal data.

Appendix B provides details of the modeling efforts and selection of best fitting models. The log-probit model provided the best fit to the data on centrilobular hypertrophy in female rats; the BMD_{10} and $BMDL_{10}$ associated with this endpoint were 1.97 and 1.62 mg/kg-day, respectively. The log-logistic model provided the best fit to the data on bile-duct hyperplasia in female rats; the BMD_{10} and $BMDL_{10}$ associated with this endpoint were 1.17 and 0.79 mg/kg-day, respectively. The lower $BMDL_{10}$ for bile-duct hyperplasia was selected as the point of departure for derivation of the chronic p-RfD. This value is somewhat lower than the LOAEL of 4 mg/kg-day for centrilobular hypertrophy in male mice.

A **chronic p-RfD** is derived by dividing the $BMDL_{10}$ of 0.79 mg/kg-day by a UF of 1000, as shown below:

$$\begin{aligned} \textbf{Chronic p-RfD} &= BMDL_{10} \div UF \\ &= 0.79 \text{ mg/kg-day} \div 1000 \\ &= \mathbf{0.0008 \text{ mg/kg-day or } 8 \times 10^{-4}} \end{aligned}$$

The UF of 1000 is composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient.

- UF_D: A factor of 10 is applied for database inadequacies because data for evaluating developmental and reproductive toxicity are lacking. The database for 1,1'-sulfonylbis(4-chlorobenzene) includes comprehensive subchronic and chronic oral toxicity studies conducted by the NTP using both sexes of two species (Chhabra et al., 2001; NTP, 2001), as well as a limited short-term study in rats (Poon et al., 1999).

Confidence in the principal study (Chhabra et al., 2001; NTP, 2001) is medium. Groups of 50 rats/sex/dose were used, three dose levels were tested, and both a NOAEL and LOAEL are identified, but the endpoints examined are limited to survival, body weight, and comprehensive gross and histological pathology. Confidence in the database is medium. Although comprehensive subchronic and chronic studies were conducted in rats and mice of both sexes by NTP (2001), developmental and reproductive toxicity have not been evaluated. Medium confidence in the chronic p-RfD follows.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 1,1'-SULFONYLBIS(4-CHLOROBENZENE)

No data are available on the effects of 1,1'-sulfonylbis(4-chlorobenzene) in humans or animals exposed via inhalation; derivation of provisional RfC values for 1,1'-sulfonylbis(4-chlorobenzene) is precluded by the absence of data.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,1'-SULFONYLBIS(4-CHLOROBENZENE)

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess* [the overall] *Carcinogenic Potential*" of 1,1'-sulfonylbis(4-chlorobenzene). This is primarily because of the lack of information on a second route of exposure. It should be noted that 1,1'-sulfonylbis(4-chlorobenzene) may be considered "*Not Likely to be Carcinogenic to Humans*" by the oral route of exposure based on animal evidence demonstrating a lack of carcinogenic effect in both sexes in well-designed and well-conducted studies in two appropriate animal species (U.S. EPA, 2005). These were large studies (50/species/sex) conducted by NTP (2001) in both sexes of two species, using 3 dose levels plus controls in each study. Survival was high in all treated and control groups; at study termination, 20−45 animals remained available for tumor evaluation in the various groups. Dose levels were selected based on subchronic studies, and changes in body weight and liver lesions (described above) suggest that the high dose in each study approached the MTD (maximum tolerated dose). There are no data on the potential carcinogenicity of 1,1'-sulfonylbis(4-chlorobenzene) in humans exposed orally.

Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is "*Inadequate Information to Assess* [the] *Carcinogenic potential*" of 1,1'-sulfonylbis(4-chlorobenzene) by the inhalation route of exposure. There are no data on the potential carcinogenicity of 1,1'-sulfonylbis(4-chlorobenzene) in humans exposed via inhalation,

and no inhalation bioassays are available. Genotoxicity data on this compound are limited, but generally, the data resulted in equivocal or negative findings. Some evidence suggests that 1,1'-sulfonylbis(4-chlorobenzene) has the potential for induction of chromosomal damage in the form of breakage or aneuploidy in vivo (NTP, 2001). Thus, while 1,1'-sulfonylbis(4-chlorobenzene) may be considered "not likely" by the oral route of exposure, the "inadequate" determination from the inhalation route yields an overall "*Inadequate Information to Assess* [the overall] *Carcinogenic Potential*" descriptor.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for 1,1'-sulfonylbis(4-chlorobenzene) is precluded by the lack of data showing a carcinogenic effect.

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APPENDIX A. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC RfD

Model-Fitting Procedure for Continuous Data:

The model-fitting procedure for continuous data is as follows. The simplest model (linear) is first applied to the data while assuming constant variance (EPA BMDS version 2.0). If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means is evaluated and the polynomial, power, and Hill models are fit to the data while assuming constant variance. Adequate model fit is judged by three criteria: goodness-of-fit *p*-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) whose dose is closest to the BMD corresponding to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMDL is selected as the POD when the difference between the BMDLs estimated from these models are more than 3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. 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 and the polynomial, power, and Hill models are fit to the data and evaluated while the variance model is applied. Model-fit and POD selection proceed as described earlier. 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 unsuitable for modeling.

Model-Fitting Results for Changes in Absolute Liver Weight in Male Rats (NTP, 2001):

The default benchmark response of one standard deviation from the control mean was used. Applying the procedure outlined above to the data for absolute liver weight in male rats, no model fit was achieved with the full data set, so the high dose groups were sequentially dropped from the analysis in an effort to achieve model fit. Adequate fits to the means and variance data were achieved with the linear and polynomial models (constant variance) after the three highest dose groups were dropped. Table A-1 shows the results. $BMDL_{1SD}$s from models providing adequate fit differed by less than 3-fold. In accordance with U.S. EPA (2000) guidance, the $BMDL_{1SD}$ associated with the lowest AIC was selected from among the models providing adequate fit. The 2-degree polynomial model had the lowest AIC; this model resulted in BMD_{1SD} and $BMDL_{1SD}$ values of 4.21 and 3.56 mg/kg-day, respectively.

Table A-1. Model Predictions for Changes in Absolute Liver Weight in Male Rats[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
All dose groups					
Hill, (constant variance)[c]	0.5878	0.04755	117.3108	4.27011	2.55666
Linear, Polynomial, and Power Models generate identical results (constant variance)[d]	0.5878	<.0001	182.4915	51.858	42.5989
Without high dose group					
Hill (constant variance)[c]	NA				
Linear and polynomial (all degrees) yield identical results (constant variance)[d]	0.4448	0.000578	108.2518	12.0538	10.011
Power (constant variance)[c]	NA				
Without two high dose groups					
Hill (constant variance)[c]	NA				
Linear and polynomial (all degrees) yield identical results (constant variance)[d]	0.6114	0.01782	75.19208	5.85109	4.57678
Power (constant variance)[c]	NA				
Without three high dose groups					
Hill (constant variance)[c]	NA				
Linear and 1-degree polynomial (constant variance)[d]	0.5906	0.1453	56.92811	2.96167	2.09017
2-degree polynomial (constant variance)[d]	**0.5906**	**0.7309**	**54.92518**	**4.20852**	**3.56358**
Power (constant variance)[c]	NA				

[a]NTP, 2001.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BMD/BMC = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL/BMCL = 95% lower confidence limit on the BMD/BMC; NA = Models generated errors, produced unusable outputs; SD = standard deviation.

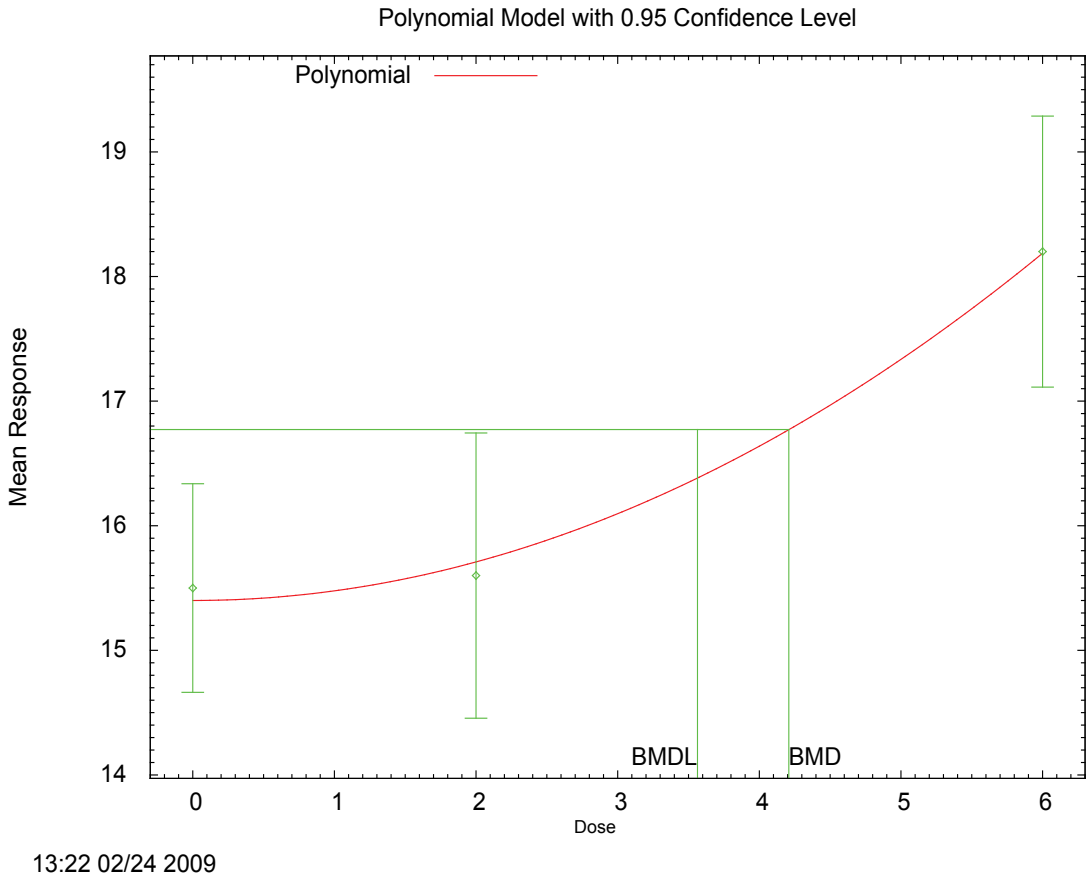

Figure A-1. Fit of 2-Degree Polynomial (Constant Variance) Model to Data for Changes in Absolute Liver Weight in Male Rats (NTP, 2001)

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

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR CHRONIC RfD

Model-Fitting Procedure for Quantal Noncancer Data:

The model-fitting procedure for dichotomous noncancer data is as follows. All available dichotomous models in the EPA BMDS (version 2.0) are fit to the incidence data using the extra risk option. The multistage model is run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Adequate model fit is judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMDL is selected as the point of departure when the difference between the BMDLs estimated from these models are more than 3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with U.S. EPA (2000) guidance, benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with an extra risk of 10% are calculated for all models.

Model-Fitting Results for the Incidence of Centrilobular Hypertrophy in Female Rats (NTP, 2001):

Applying the procedure outlined above to the data for centrilobular hypertrophy in female rats, adequate model fit was achieved with the log-logistic, log-probit, 1-degree multistage, and quantal linear models. Table B-1 shows the results. BMDLs from models providing adequate fit differed by less than 3-fold. In accordance with U.S. EPA (2000) guidance, the model with the lowest AIC was selected from among the models providing adequate fit. For this data set, the log probit model was selected, resulting in a benchmark dose (BMD_{10}) and associated 95% lower confidence limit ($BMDL_{10}$) of 1.97 and 1.62 mg/kg-day, respectively. Figure B-1 shows the model fit of the log probit model to the data.

Model-Fitting Results for the Incidence of Bile-Duct Hyperplasia in Female Rats (NTP, 2001):

Applying the procedure outlined above to the data for bile-duct hyperplasia in female rats, adequate model fit was achieved with all but the logistic and probit models. Table B-1 shows the results for the data. BMDLs from models providing adequate fit differed by less than 3-fold. In accordance with U.S. EPA (2000) guidance, the lowest AIC was selected from among models providing adequate fit. For this data set, the log-logistic model was selected resulting in a benchmark dose (BMD_{10}) and associated 95% lower confidence limit ($BMDL_{10}$) of 1.17 and 0.79 mg/kg-day, respectively. Figure B-2 shows the model fit of the log-logistic model to the data.

Table B-1. Model Predictions for Centrilobular Hypertrophy in Female Rats Exposed to 1,1'-Sulfonylbis(4-chlorobenzene) Via Diet for 2 Years[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[b]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma (power ≥ 1)	2	5.88	0.05	151.36	1.62	1.00
Logistic	2	23.89	0.00	172.18	3.59	2.93
Log logistic (slope ≥ 1)	2	3.46	0.18	148.79	1.82	1.14
Log probit (slope ≥ 1)	**3**	**3.01**	**0.39**	**146.17**	**1.97**	**1.62**
Multistage (degree = 1, betas ≥ 0)	3	5.93	0.11	150.19	1.20	0.97
Multistage (degree = 2, betas ≥ 0)	2	5.95	0.05	152.19	1.20	0.97
Multistage (degree = 3, betas ≥ 0)	2	5.95	0.05	152.19	1.20	0.97
Probit	2	22.96	0.00	170.33	3.43	2.85
Weibull (power ≥ 1)	2	6.03	0.05	151.72	1.48	0.99
Quantal linear	3	5.93	0.11	150.19	1.20	0.97

[a]NTP (2001).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike Information Criterion; BMD/BMC = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL/BMCL = 95% lower confidence limit on the BMD/BMC; NA = Not applicable; SD = standard deviation.

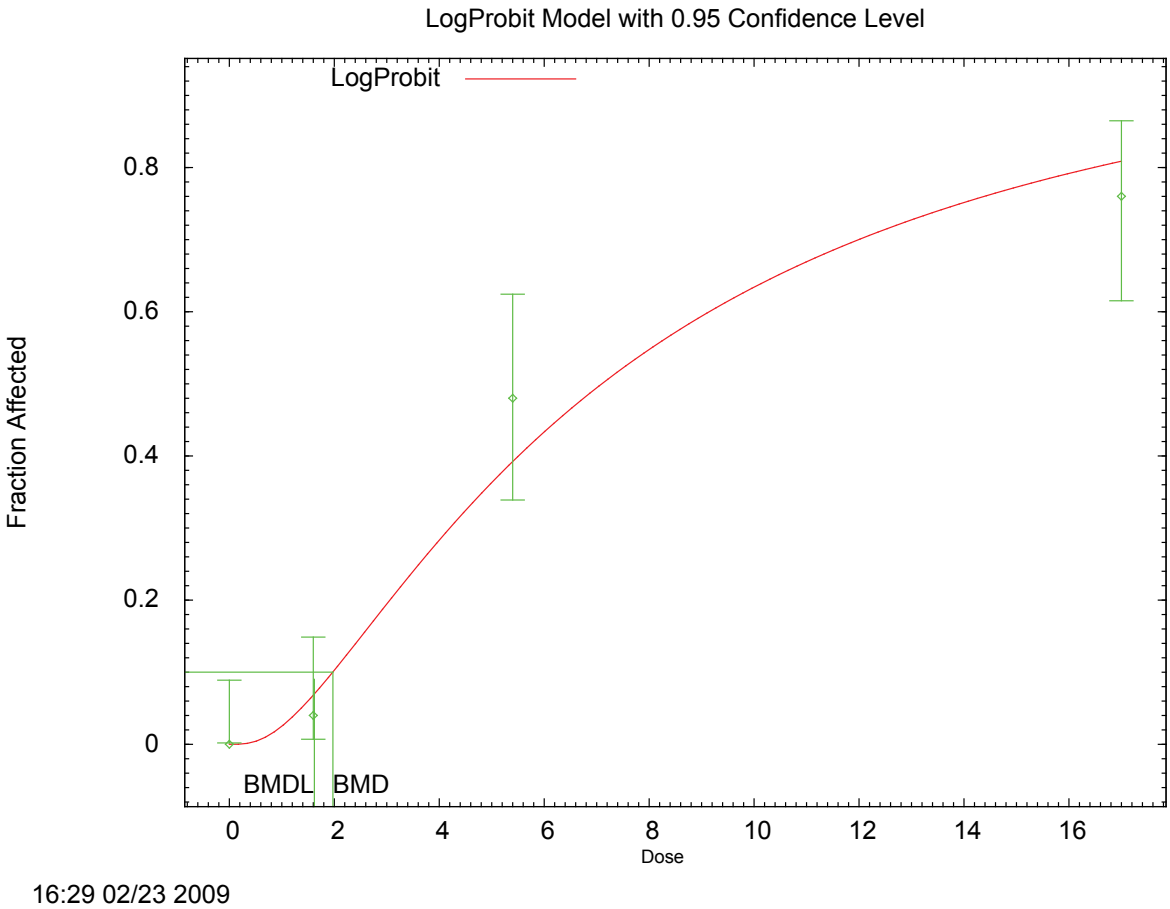

Figure B-1. Fit of Log Probit Model to Data on Centrilobular Hypertrophy (NTP, 2001)

BMDs and BMDLs indicated are associated with an extra risk of 10%, and are in units of mg/kg-day.

Table B-2. Model Predictions for Bile-Duct Hyperplasia in Female Rats Exposed to 1,1'-Sulfonylbis(4-chlorobenzene) Via Diet for 2 Years[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[b]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma (power ≥ 1)	2	1.68	0.43	226.67	1.79	1.33
Logistic	2	5.35	0.07	230.63	3.60	2.93
Log logistic (slope ≥ 1)	**2**	**0.19**	**0.91**	**225.18**	**1.17**	**0.79**
Log probit (slope ≥ 1)	2	4.64	0.10	229.73	3.27	2.39
Multistage (all degrees yield identical results, betas ≥ 0) Weibull (power ≥ 1) & quantal linear yield identical results	2	1.68	0.43	226.67	1.79	1.33
Probit	2	5.10	0.08	230.33	3.45	2.83

[a]NTP (2001).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike Information Criterion; BMD/BMC = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL/BMCL = 95% lower confidence limit on the BMD/BMC; NA = Not applicable; SD = standard deviation.

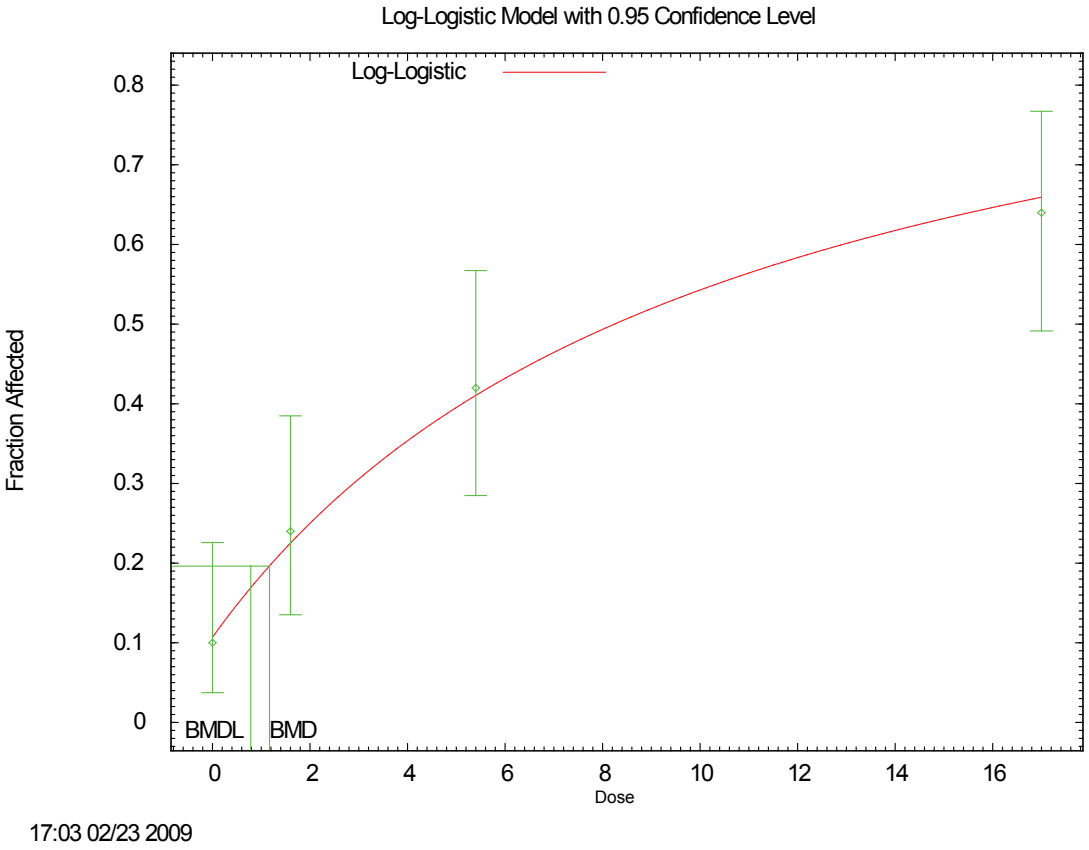

Figure B-2. Fit of Log-Logistic Model to Data on Bile-Duct Hyperplasia (NTP, 2001)

BMDs and BMDLs indicated are associated with an extra risk of 10%, and are in units of mg/kg-day