United States
Environmental Protection
Agency

EPA/690/R-09/019F
Final
9-29-2009

Provisional Peer-Reviewed Toxicity Values for

Diphenyl sulfone
(CASRN 127-63-9)

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 DIPHENYL SULFONE (CASRN 127-63-9)

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

No RfD, RfC, or cancer assessment for diphenyl sulfone (chemical structure shown in Figure 1) is available on IRIS (U.S. EPA, 2009), in the 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, 1994, 1991a). ATSDR (2009) has not published a Toxicological Profile for diphenyl sulfone and no Environmental Health Criteria Document is available (WHO, 2009). The American Conference of Governmental Industrial Hygienists (ACGIH, 2008), the Occupational Safety and Health Administration (OSHA, 2009), and the National Institute for Occupational Safety and Health (NIOSH, 2009) have not established occupational health standards for diphenyl sulfone. The carcinogenicity of diphenyl sulfone has not been assessed by the International Agency for Research on Cancer (IARC, 2009) or the National Toxicology Program (NTP, 2009, 2005).

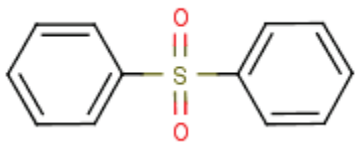

Figure 1. Chemical Structure of Diphenyl Sulfone

Literature searches were conducted from the 1960s through August 2009 for studies relevant to the derivation of provisional toxicity values for diphenyl sulfone. Databases searched include MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents.

REVIEW OF PERTINENT DATA

Human Studies

No human data having the ability to inform the derivation of either inhalation or oral exposure toxicity values for diphenyl sulfone have been located.

Animal Studies

Oral Exposure

One relevant animal toxicity study was located. Groups of CD Sprague-Dawley rats (15/sex/group) were fed diets containing 0, 100, 200, or 2,000 ppm of diphenyl sulfone (purity at least 99.5%) for 13−14 weeks (HLE, 1981). Because of the logistics of processing, the medium- and low-dose male rats—and some of the control males—were sacrificed after 14 weeks of treatment, rather than the target of 13 weeks. The study authors calculated the intake of diphenyl sulfone as 0, 8, 16, or 164 mg/kg-day in males and 0, 9, 19, or 206 mg/kg-day in females. Animals were observed daily for clinical signs of toxicity. Body weights and food consumption were recorded weekly. The eyes of all animals were examined with an ophthalmoscope before treatment, and the examination was repeated in control and high-dose animals during Weeks 6 and 13. Blood samples were collected from five males and five females per group during Weeks 1 and 12 to measure diphenyl sulfone concentrations in plasma (pooled by sex and group). In addition, after 0, 5, and 12 weeks, 16-hour fasting blood and urine samples were collected from 10 rats per sex in the control and high-dose groups for standard hematology and clinical chemistry analyses and urinalysis. The same numbers of medium and low-dose rats were also fasted. Although fluids were not routinely collected from these animals, certain investigations were extended to these groups to elucidate changes observed in the high-dose rats. At termination, each animal was necropsied. The final organ weights of the adrenal, brain, heart, kidneys, liver, lungs, pituitary, ovaries/testes, spleen, and thyroids were measured. Histopathological examination of the liver and kidneys was conducted on all animals, and 34 other tissues were examined in animals in the control and high-dose groups. In six animals per sex in the high-dose, medium-dose, and control groups, liver samples were examined by electron microscopy; in six animals per sex in all groups, liver homogenates were measured for aminopyrine-*N*-demethylase (APDM) activity, which is a biomarker of hepatic metabolic status.

According to the HLE (1981), no treatment-related deaths were observed. Treatment with diphenyl sulfone reportedly had no significant effect on the incidence of clinical signs. Body weights on Week 13 at the end of the study were significantly reduced by 11% in males and 9% in females of the high-dose group, and they were reduced—but not significantly—in males at the medium dose (see Table 1). Food consumption was about 5% lower than controls in high- and medium-dose males, but it was similar to controls in females. The study authors calculated that the efficiency of food conversion was reduced in high-dose animals throughout most of the study. From this, they concluded that the adverse effect on weight gain in high-dose rats was a primary effect of diphenyl sulfone rather than a palatability effect. Plasma measurements of diphenyl sulfone verified dose-related increases in absorption. No treatment-related ocular changes were observed. Statistically significant reductions were found for red cell hematological parameters: hemoglobin (Hgb) levels in high-dose males (Week 13) and females (Week 13), red blood cell (RBC) counts in high dose males (Week 13), and packed blood cell volumes (PCV) in high-dose males and females at Week 13 and medium-dose males at Week 14 (see Table 1). However, the study authors considered these changes to be within the

range of normal values. The study authors reported that no significant changes were observed in other hematological parameters (total and differential white cell counts, prothrombin clotting time, or activated partial thromboplastin coagulation time) (data not shown). Statistically significant changes in two clinical chemistry parameters were observed in high-dose rats: elevations in plasma cholesterol in males (Week 13), and reductions in plasma alkaline phosphatase (ALP) in males (Week 13); slight increases in cholesterol and triglycerides and a decrease in plasma ALP were observed in females, but they were not statistically significantly different from control (see Table 1). Furthermore, the biological significance of these changes is uncertain. The study authors reported that no other significant changes were observed in blood chemistry parameters (plasma glucose, blood urea nitrogen [BUN], albumin, total protein, sodium, potassium, cholesterol, alanine aminotransferase [ALT], or aspartate aminotransferase [AST]) (data not shown). The only treatment-related change in urinalysis parameters reported by the study authors was a slight increase in ketones and reducing substances in the urine of high-dose males and females. Treatment was reported to have no effect on urine pH or urine levels of bilirubin, urobilinogen, protein, glucose, or cells, or other solid constituents. The urinalysis data are not provided in the report.

According to HLE (1981), no gross treatment-related lesions were observed at necropsy. Liver and kidney weights were elevated in treated rats compared to controls (see Table 1); statistically significant elevations occurred in absolute liver and kidney weights in high-dose rats of both sexes, in relative liver weights in high- and mid-dose rats of both sexes, and in relative kidney weights in high- and mid-dose males and high- and low-dose females. Mean relative brain weights were significantly elevated in high-dose animals of both sexes compared to controls. The study authors reported no changes in the weights of other organs (data not shown). Histopathology was observed in the liver, kidney, and spleen (see Table 1). Lesions in the kidney, which were observed only in male rats, were characterized by the study authors as "tubular degeneration/regeneration and eosinophilic droplet formation in the proximal kidney tubules." Eosinophilic droplets were seen in all male groups including controls, but these droplets increased in incidence and severity with dose. Tubular degeneration and regeneration were observed only in high-dose male rats. The study authors stated that the accumulation of eosinophilic droplets (possibly reabsorbed protein) in kidney tubules of male rats was of uncertain toxicological significance because it commonly occurred in control males and the observed increases could have been adaptive responses to treatment. Considering sex-specificity, the proximal tubule location of droplet formation and the progression to tubular degeneration are consistent with hyaline droplet nephropathy associated with alpha $_{2u}$-globulin accumulation, which is specific to male rats (U.S. EPA, 1991b). However, there is no confirming evidence that the male renal pathology in this study was related to alpha $_{2u}$-globulin. Hemosiderosis in the spleen of high-dose rats is consistent with the hematological changes observed in this group, but it was considered incidental to treatment by the study authors. In the liver, hepatocellular hypertrophy was a dose-related finding. Ultrastructural analysis of the liver revealed a proliferation of smooth endoplasmic reticulum in livers from high-dose males (6/6) and females (6/6) and minimal changes in a third of the medium-dose males (2/6) examined. Some high-dose males (2/6) and females (1/6) also showed increased lipid vacuolization in hepatocytes. In addition, high-dose males and females showed significant elevations in liver aminopyrine-*N*-demethylase activity.

Table 1. Changes in Sprague-Dawley Rats Fed Diets Containing Diphenyl Sulfone for 13−14 Weeks[a]

	Dietary concentration (ppm)			
	Control	**100**	**200**	**2,000**
Males				
Dose (mg/kg-day)	0	8	16	164
Number of animals examined	15	15	15	15
Body weight (Week 13)	464 ± 52[b]	467 ± 45	438 ± 56	411 ± 27[c]
Hematology				
Hgb (g/dL, Week 13)	16.8	--	--	15.6[d]
Hgb (g/dL, Week 14)	15.4	15.0	14.8	--
RBC (mil/cmm, Week 13)	8.53	--	--	7.85[d]
RBC (mil/cmm, Week 14)	7.97	7.71	7.72	--
PCV (%, Week 13)	44	--	--	40[d]
PCV (%, Week 14)	41	40	39[c]	--
Clinical chemistry (Week 13)				
Cholesterol (mg/dL)	44	--	--	88[d]
Triglycerides (mg/dL)	78	--	--	75
ALP (IU/L)	271	--	--	153[d]
Organ weights				
Liver (g)	13.82	14.32	14.45	21.56[d]
Kidney (g)	2.42	2.63	2.51	3.57[d]
Brain (g)	1.96	2.00	1.97	2.02
Relative organ weights (% of body weight)				
Liver	3.001	3.100	3.330[d]	5.258[d]
Kidney	0.529	0.570	0.584[c]	0.869[d]
Brain	0.432	0.436	0.463	0.494[d]
Histopathology findings				
Kidneys (tubular degeneration/ regeneration)[f]	0/15[e]	--	--	15/15[g] (slight-to-moderate)
Kidneys (eosinophilic droplet formation)[f]	8/15 (minimal)	12/15 (minimal-to-slight)	14/15[g] (slight)	15/15[g] (moderate-to-marked)
Liver (cellular hypertrophy)[f]	6/15 (minimal)	11/15 (minimal-to-slight)	13/15[g] (minimal-to-slight)	15/15[g] (slight-to-moderate)
Spleen (hemosiderosis)	2/15	--	--	9/15[g]

Table 1. Changes in Sprague-Dawley Rats Fed Diets Containing Diphenyl Sulfone for 13−14 Weeks[a]

	Dietary concentration (ppm)			
	Control	**100**	**200**	**2,000**
Females				
Dose (mg/kg-day)	0	9	19	206
Number of animals examined	15	15	15	15
Body weight (Week 13)	258 ± 27[b]	261 ± 28	250 ± 18	235 ± 22
Hematology (Week 13)				
Hgb (g/dL)	16.3	--	--	15.3[d]
RBC (mil/cmm)	8.10	--	--	7.94
PCV (%)	43	--	--	41[c]
Clinical chemistry (Week 13)				
Cholesterol (mg/dL)	66	--	--	93
Triglycerides (mg/dL)	66	--	--	70
ALP (IU/L)	132	--	--	112
Organ weights				
Liver (g)	7.79	8.70	8.90	13.16[d]
Kidney (g)	1.39	1.53[c]	1.47[c]	1.60[d]
Brain (g)	1.79	1.82	1.81	1.82
Relative organ weights (% of body weight)				
Liver	3.131	3.443	3.610[c]	5.608[d]
Kidney	0.561	0.610[c]	0.598	0.680[d]
Brain	0.726	0.731	0.742	0.779[c]
Histopathology findings				
Kidneys (tubular degeneration/ regeneration/eosinophilic droplet formation)[f]	0/15[e]	--	--	0/15
Liver (cellular hypertrophy)[f]	6/15 (minimal)	14/15[g] (minimal-to-slight)	14/15[g] (minimal-to-slight)	15/15[g] (moderate-to-marked)
Spleen (hemosiderosis)	9/15	--	--	12/15

[a]HLE (1981).
[b]Mean ± standard deviation (standard deviations reported only for body weight data in original study).
[c]Significantly different from control at $p < 0.05$ (ANOVA, Students t-test).
[d]$p < 0.01$.
[e]Number affected/number examined.
[f]Data from source Table 7, as superseded by source Tables 8−10 and source text p. A34−35.
[g]Significantly different from control at $p < 0.05$ (Fisher Exact test performed for this review).

In summary, the HLE (1981) study revealed a number of significant effects following diphenyl sulfone exposure. Body weights at the end of the study were significantly reduced (9−11%) in the high-dose group due to a reduction in efficiency of food conversion. However, no significant reduction in body weight was observed in the low- or mid-dose treated rats. Dose-related renal effects were observed in male rats—including increased organ weight and eosinophilic droplet formation in corticotubular epithelium at ≥16 mg/kg-day and tubular degeneration/regeneration at 164 mg/kg-day. The available evidence suggests these changes were probably associated with alpha $_{2u}$-globulin nephropathy, which is specific to male rats (U.S. EPA, 1991b)—although this was not conclusively demonstrated. While increased kidney weight was observed in female rats at doses down to 9 mg/kg-day, the lack of associated renal histopathology in females at any dose suggests that the kidney weight changes in females were not toxicologically significant. Although no overt signs of liver damage (e.g., increases in serum biomarkers of hepatotoxicity, histological signs of liver degeneration) were observed at any exposure level, several dose-related hepatic effects (e.g., increased absolute and/or relative organ weights, hepatocellular hypertrophy, lipid vacuolization, proliferation in smooth endoplasmic reticulum, hepatic aminopyrine-*N*-demethylase activity) were observed in males and females following subchronic exposure to ≥16 mg/kg-day of diphenyl sulfone in the diet. For the purpose of this review, a LOAEL of 16 mg/kg-day and a NOAEL of 8 mg/kg-day are identified from the HLE (1981) study based on increased relative liver weight in male rats. Although the study initially appeared to have been generally well designed, an incident in which a control female escaped, became pregnant, littered, and was subsequently returned to the study raises some uncertainty regarding implementation of standard procedures.

Inhalation Exposure

No relevant data have been located regarding the toxicity of diphenyl sulfone to animals following inhalation exposure.

Other Studies

Diphenyl sulfone was tested for mutagenicity in a *Salmonella*/Microsome assay. Briefly, diphenyl sulfone was applied at concentrations of up to 5000 µg/plate to cultures of *Salmonella typhimurium* strains TA1535, TA100, TA1537, and TA98, in the presence or absence of S9 fraction. Diphenyl sulfone concentrations up to—and including—5000 µg did not induce mutagenic activity in any strain tested with or without metabolic activation (Bayer AG, 1991).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR DIPHENYL SULFONE

Limited information is available on the oral toxicity of diphenyl sulfone, and only one study, the HLE (1981) 13-week rat study, is of a duration relevant for assessing effects associated with this compound. However, based upon current standard operating procedure, unpublished principal or influential studies must be peer-reviewed before they can be considered for reference-value derivation. Since the HLE (1981) study is an unpublished TSCA submission, it is not known if the information has been peer-reviewed. As such, while subchronic and chronic oral reference values cannot be derived here, "screening-level" evaluations of oral diphenyl sulfone toxicity are provided in Appendix A.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR DIPHENYL SULFONE

A provisional RfC cannot be derived for diphenyl sulfone because inhalation toxicity data are not available in humans or animals.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR DIPHENYL SULFONE

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess* [the] *Carcinogenic Potential*" of diphenyl sulfone. Studies evaluating the carcinogenic potential of oral or inhalation exposure to diphenyl sulfone in humans or animals were not identified in the available literature.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for diphenyl sulfone is precluded by the lack of suitable data.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2008) Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). (2009) Toxicological profile information sheet. U.S. Department of Health and Human Services, Public Health Service. Online. http://www.atsdr.cdc.gov/toxprofiles/index.asp.

Bayer AG. (1991) Final report: salmonella/microsome test with cover letter dated 4/23/92. Submitted under TSCA; EPA Document No. 86-920000908; NTIS No. OTS0535645.

HLE (Hazleton Laboratories Europe, Ltd.). (1981) Initial submission: diphenyl sulfone: 13-week feeding study in rats with cover letter dated 8/29/92. Submitted under TSCA; EPA Document No. 88-920006821; NTIS No. OTS0543826.

IARC (International Agency for Research on Cancer). (2009) Search IARC monographs. Online. http://monographs.iarc.fr/.

NIOSH (National Institute for Occupational Safety and Health). (2009) NIOSH pocket guide to chemical Hazards. Index by CASRN.

NTP (National Toxicology Program). (2005) 11th Report on carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. Online. http://ntp-server.niehs.nih.gov/.

NTP (National Toxicology Program). (2009) Testing status of agents at NTP. Online. http://ntp.niehs.nih.gov:8080/index.html?col=010stat.

OSHA (Occupational Safety and Health Administration). (2009) OSHA Standard 1915.1000 for air contaminants. Part Z, Toxic and hazardous substances. Online. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

U.S. EPA (Environmental Protection Agency). (1991a) Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC.

U.S. EPA (Environmental Protection Agency). (1991b) Alpha $_{2u}$-globulin: association with chemically induced renal toxicity and neoplasia in the male rat. Risk Assessment Forum, Washington, DC; EPA/625/3-91/019F.

U.S. EPA (Environmental Protection Agency). (1994) Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC.

U.S. EPA (Environmental Protection Agency). (1997) Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC; EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA (Environmental Protection Agency). (2005) Guidelines for carcinogen risk assessment. Risk Assessment Forum, National Center for Environmental Assessment, Washington, DC; EPA/630/P-03/001F. Online. http://www.epa.gov/cancerguidelines/.

U.S. EPA (Environmental Protection Agency). (2006) 2006 Edition of the drinking water standards and Health advisories. Office of Water, Washington, DC; EPA/822/R-06/013. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf.

U.S. EPA (Environmental Protection Agency). (2009) Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/.

WHO (World Health Organization). (2009) Online catalogs for the Environmental Health Criteria series. Online. http://www.who.int/ipcs/publications/ehc/ehc_alphabetical/en/index.html.

APPENDIX A. DERIVATION OF A SUBCHRONIC AND CHRONIC ORAL SCREENING VALUE FOR DIPHENYL SULFONE (CASRN 127-63-9)

For reasons noted in the main PPRTV document, it is inappropriate to derive a subchronic or chronic oral p-RfD for diphenyl sulfone based on the HLE (1981) 13-week rat study. Specifically, as an unpublished, presumably nonpeer-reviewed TSCA submission, any useful data provided in such a reference is currently deemed inappropriate for the derivation of provisional toxicity values. However, the qualitative and quantitative information in the HLE (1981) study may be used to support derivation of provisional oral screening values for diphenyl sulfone (CASRN 127-63-9) that may be of use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix. Information contained in an appendix receives the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening 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.

Screening Subchronic Oral p-RfD

Limited information is available on the oral toxicity of diphenyl sulfone and only one study, the HLE (1981) 13-week rat study, is available for evaluation of diphenyl sulfone effects. This is a comprehensive subchronic study in which male and female rats were administered diphenyl sulfone via diet in doses of 0, 8, 16, or 164 mg/kg-day and 0, 9, 19, or 206 mg/kg-day, respectively for 13-weeks. The study examined a broad spectrum of gross, histological, hematological, and clinical chemistry parameters/endpoints and identifies a NOAEL of 8 mg/kg-day and LOAEL of 16 mg/kg-day based on significantly increased relative liver weight in exposed male rats, compared to control (female rats also exhibited a dose-dependent increase in relative liver weight with a NOAEL of 9 mg/kg-day and LOAEL of 19 mg/kg-day). Increased kidney weight was also observed in male and female rats; however, this observation was not dose-dependent in females (Table 1). Kidney histopathology consistent with alpha $_{2u}$-globulin nephropathy was observed in male rats. Conversely, no histopathology was observed in the kidneys of female rats at the highest dose tested (206 mg/kg-day). Thus, kidney effects are not considered further. High incidences of liver hypertrophy were observed in male and female rats at all diphenyl sulfone doses tested; however, there was a 40% incidence of this cellular phenotype in untreated controls of both sexes. As such, liver hypertrophy is not further considered. Other observations include hepatic changes indicative of increased metabolic activity, and hematological and splenic changes considered not to be treatment-related by the study authors. Therefore, increased relative liver weight has been selected as the critical effect. Dose-response modeling of the relative liver weight data is not possible because there are no variance data provided with the mean values in the HLE (1981) study (individual animal data are not available either). As such, the NOAEL of 8 mg/kg-day for significantly increased relative liver weight in male rats is selected as the point of departure for derivation of the subchronic oral screening value.

A **screening subchronic oral p-RfD** for diphenyl sulfone is derived by dividing the NOAEL of 8 mg/kg-day by a UF of 1000 as shown below:

Screening Subchronic Oral p-RfD = NOAEL ÷ UF
= 8 mg/kg-day ÷ 1000
= **0.008 or 8×10^{-3} mg/kg-day**

The composite UF of 1000 is composed of the following:

A 10-fold UF for laboratory animal-to-human interspecies differences (UF_A) is applied to account for the variability in extrapolating from rats to humans. No information is available on toxicokinetic or toxicodynamic differences or similarities for diphenyl sulfone in animals and humans. In the absence of data to quantify specific toxicokinetic and toxicodynamic differences, a default factor of 10 is applied.

A 10-fold UF for intraspecies differences (UF_H) is applied to account for variability in susceptibility in human populations. The default value of 10 is selected in the absence of information indicating the degree to which humans may vary in susceptibility to diphenyl sulfone toxicity.

A 10-fold UF for deficiencies in the diphenyl sulfone database (UF_D) is applied because the database for diphenyl sulfone includes only a single subchronic animal study, and no chronic oral toxicity studies in any species. Furthermore, the database lacks any information concerning reproductive and developmental endpoints following diphenyl sulfone exposure.

Screening Chronic Oral p-RfD

Derivation of the chronic oral screening value involves dividing the same subchronic NOAEL of 8 mg/kg-day for significantly increased liver weight (HLE, 1981) by a composite uncertainty factor (UF) of 10,000. The **screening chronic oral p-RfD** for diphenyl sulfone is calculated as follows:

Screening Chronic Oral p-RfD = NOAEL ÷ UF
= 8 mg/kg-day ÷ 10,000
= **0.0008 or 8×10^{-4} mg/kg-day**

The composite UF of 10,000 includes component factors of 10 for extrapolation from rats to humans, 10 for human variability, 10 for extrapolation from subchronic to chronic duration, and 10 for database insufficiencies, as explained below.

A 10-fold UF for laboratory animal-to-human interspecies differences (UF_A) is applied to account for the variability in extrapolating from rats to humans. No information is available on toxicokinetic or toxicodynamic differences or similarities for diphenyl sulfone in animals and humans. In the absence of data to quantify specific toxicokinetic and toxicodynamic differences, a default factor of 10 is applied.

A 10-fold UF for intraspecies differences (UF_H) is applied to account for potentially susceptible human subpopulations. In the absence of information on the variability in response of humans to diphenyl sulfone, the full value of 10 is applied.

A 10-fold UF is applied for using data from a subchronic study to assess potential effects from chronic exposure (UF_S), as data for evaluating response after chronic exposure are not available.

A 10-fold UF for deficiencies in the diphenyl sulfone database (UF_D) is applied because the database for diphenyl sulfone includes only a single subchronic animal study, and no chronic oral toxicity studies in any species. Furthermore, the database lacks any information concerning reproductive and developmental endpoints following diphenyl sulfone exposure.