

Provisional Peer-Reviewed Toxicity Values for

Sulfolane
(CASRN 126-33-0)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

| | |
|----------------------|---|
| BMC | benchmark concentration |
| BMCL | benchmark concentration lower bound 95% confidence interval |
| BMD | benchmark dose |
| BMDL | benchmark dose lower bound 95% confidence interval |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| IUR | inhalation unit risk |
| LOAEL | lowest-observed-adverse-effect level |
| LOAEL _{ADJ} | LOAEL adjusted to continuous exposure duration |
| LOAEL _{HEC} | LOAEL adjusted for dosimetric differences across species to a human |
| NOAEL | no-observed-adverse-effect level |
| NOAEL _{ADJ} | NOAEL adjusted to continuous exposure duration |
| NOAEL _{HEC} | NOAEL adjusted for dosimetric differences across species to a human |
| NOEL | no-observed-effect level |
| OSF | oral slope factor |
| p-IUR | provisional inhalation unit risk |
| POD | point of departure |
| p-OSF | provisional oral slope factor |
| p-RfC | provisional reference concentration (inhalation) |
| p-RfD | provisional reference dose (oral) |
| RfC | reference concentration (inhalation) |
| RfD | reference dose (oral) |
| UF | uncertainty factor |
| UF _A | animal-to-human uncertainty factor |
| UF _C | composite uncertainty factor |
| UF _D | incomplete-to-complete database uncertainty factor |
| UF _H | interhuman uncertainty factor |
| UF _L | LOAEL-to-NOAEL uncertainty factor |
| UF _S | subchronic-to-chronic uncertainty factor |
| WOE | weight of evidence |

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR SULFOLANE (CASRN 126-33-0)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (<http://hhpprtv.ornl.gov>) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by this toxicity assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Sulfolane (2,3,5-tetrahydrothiophene-1,1-dioxide; tetramethylene sulfone), CAS No. 126-33-0, is used as an industrial solvent as well as a feedstock in polymer and electronics manufacturing. The chemical structure is shown in Figure 1. The chemical is listed as a high-production-volume chemical by the Organisation for Economic Cooperation and Development (OECD, 2004). Sulfolane has a low vapor pressure, suggesting it has low volatility; however, it is highly soluble in water. A table of physicochemical properties is provided below (see Table 1). The chemical formula is C₄H₈SO₂.

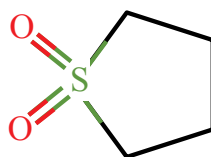


Figure 1. Sulfolane Structure

| Table 1. Physicochemical Properties Table for Sulfolane (CASRN 126-33-0) | |
|---|------------------------|
| Property (unit) | Value |
| Boiling point (°C) | 285 ^a |
| Melting point (°C) | 27.4–27.8 ^a |
| Density (g/cm ³) | 1.265 ^a |
| Vapor pressure (mm Hg at 27.6°C) | 0.0062 ^a |
| pH (unitless) | ND |
| Solubility in water (g/L at 25°C) | ≥100 ^b |
| Relative vapor density (air = 1) | 1.266 ^b |
| Molecular weight (g/mol) | 120.18 ^a |

^aATSDR (2010a).

^bOECD (2004).

ND = no data.

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for sulfolane is included in the United States Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) (U.S. EPA, 2011a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values are reported in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2011b). The Chemical Assessments and Related Activities (CARA) list does not include a Health and Environmental Effects Profile (HEEP) for sulfolane; there are no noncancer toxicity values (U.S. EPA, 1994). The toxicity of sulfolane has not been reviewed by the Agency for Toxic Substances and Disease

Registry (ATSDR) in a Toxicological Profile (ATSDR, 2010b), but ATSDR did perform a Health Consultation on sulfolane for the Alaska Department of Health and Social Services. ATSDR has recommended an oral exposure limit of 2.5 µg/kg-day based on an oral subchronic study in guinea pigs by Zhu et al. (1987) (ATSDR, 2010a). The toxicity of sulfolane has not been reviewed by the World Health Organization (WHO, 2010). The California Environmental Protection Agency (CalEPA, 2008, 2009) has not derived toxicity values for exposure to sulfolane. No occupational exposure limits for sulfolane have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010), the National Institute of Occupational Safety and Health (NIOSH, 2011), or the Occupational Safety and Health Administration (OSHA, 2010).

The HEAST (U.S. EPA, 2011b) does not report any values for cancer or a cancer weight-of-evidence (WOE) classification for sulfolane. The International Agency for Research on Cancer (IARC, 2010) has not reviewed the carcinogenic potential of sulfolane. Sulfolane is not included in the 12th Report on Carcinogens (NTP, 2011). CalEPA (2008) has not prepared a quantitative estimate of carcinogenic potential for sulfolane.

Literature searches were conducted on sources published from 1900 through September 2011 for studies relevant to the derivation of provisional toxicity values for sulfolane, CAS No. 126-33-0. Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUP, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for toxicity reference values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for sulfolane and includes all potentially relevant repeated-dose short-term-, subchronic-, and chronic-duration studies. The phrase "statistical significance," used throughout the document, indicates a *p*-value of <0.05, unless otherwise noted.

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry ^a | Critical effects | NOAEL ^a | BMDL/ BMCL ^a | LOAEL ^a | Reference (Comments) | Notes ^b |
|----------------------------------|--|------------------------|------------------|--------------------|----------------------------|--------------------|----------------------|--------------------|
| Human | | | | | | | | |
| 1. Oral^a | | | | | | | | |
| Subchronic | ND | | | | | | | NA |
| Chronic | ND | | | | | | | NA |
| Developmental | ND | | | | | | | NA |
| Reproductive | ND | | | | | | | NA |
| Carcinogenicity | ND | | | | | | | NA |
| 2. Inhalation^a | | | | | | | | |
| Subchronic | ND | | | | | | | NA |
| Chronic | ND | | | | | | | NA |
| Developmental | ND | | | | | | | NA |
| Reproductive | ND | | | | | | | NA |
| Carcinogenicity | ND | | | | | | | NA |

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry ^a | Critical effects | NOAEL ^a | BMDL/ BMCL ^a | LOAEL ^a | Reference (Comments) | Notes ^b |
|----------------------------|--|---|--|--|---|---|--|--------------------|
| Animal | | | | | | | | |
| 1. Oral^a | | | | | | | | |
| Subchronic | 10/10, CD, Rat, drinking water, 13 wk | 2.1, 8.8, 35.0, 131.7 (males) 2.9, 10.6, 42.0, 191.1 (females) | Statistically significant reductions in total white blood cell (WBC) and differential WBC counts (lymphocyte, basophils, monocyte, and large unstained cell [LUC]) counts in females; increased incidence and severity of cortical tubules with hyaline droplets in the kidneys of males | 8.8 (males) 2.9 (females) | No models fit to data (reduced WBCs in females) | 35.0 (males) 10.6 (females) | Huntingdon Life Sciences (2001) | PS, PR |
| Subchronic | 6-12/6-12, Crj:CD(S-D), Rat, gavage, 28 d | 0, 60, 200, or 700 | Slight reduction of locomotor activity and splenic weight in females; increased relative kidney weight in males; decreased body weight and food consumption in males and females; increased hyaline droplets and eosinophilic bodies in renal tubules of males | 60 (male hyaline droplets in kidney) 200 (female decreased spleen weight) | 267 (female spleen weight) | 200 (male hyaline droplets in kidney) 700 (female decreased spleen weight) | Ministry of Health and Welfare Japan (1996a) as cited by OECD (2004) | PR |
| Subchronic | 80 unspecified sex, and strain, Rat, unspecified oral exposure, 90 d | 0, 55.6, 167, or 500 | Decreased urine volume, increased urine gamma glutamyl transferase activity, decreased serum alkaline phosphatase, decreased "ICD ;(likely serum isocitrate dehydrogenase)," decreased thrombin. | ND ^c | ND | ND ^c | Zhu et al. (1987a) | PR |

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry ^a | Critical effects | NOAEL ^a | BMDL/ BMCL ^a | LOAEL ^a | Reference (Comments) | Notes ^b |
|-----------------|--|--------------------------|--|-------------------------------------|-------------------------|--------------------------------------|--|--------------------|
| Subchronic | 80 unspecified sex and strain, Guinea Pig, unspecified oral exposure, 90 d | 0, 55.6, 167, or 500 | Decreased ascorbic acid content in adrenal glands; decreased serum alkaline phosphatase levels; decreased WBC count | ND ^c | ND | ND ^c | Zhu et al. (1987b) | PR |
| Subchronic | 20/20, unspecified strain, Guinea Pig, unspecified oral exposure, 3 mo interim sacrifice | 0, 0.25, 2.5, 25, or 250 | Decreased marrow cell counts; shrinkage of the white pulp in the spleen | ND ^c | ND | ND ^c | Zhu et al. (1987c) | PR |
| Chronic | 20/20, unspecified strain, Guinea Pig, unspecified oral exposure, 6 mo | 0, 0.25, 2.5, 25, or 250 | Shrinkage of the white pulp in the spleen; fatty degeneration of liver | 0.25 | ND | 2.5 | Zhu et al. (1987c) | PR |
| Developmental | Unreported number of females, Kunming, Mouse, unreported method of oral administration, GDs 6–15 | 0, 93, 280, 840 | Increased fetal resorption; skeletal abnormalities (breastbone malposition, rib fusion) | 280 (maternal and developmental) | ND | 840 (maternal and developmental) | Zhu et al. (1987d) | PR |
| Reproductive | 12/12, Crj:CD(S-D), Rat, gavage, 41–50 d from 14 days pre-mating to lactation day 3 | 0, 60, 200, 700 | Mortality; decreased number of estrous cases; entire litter loss during lactation; increased number of still births; decreased body-weight gain and food consumption in males and females (pre-mating); decreased birth index and number of viable pups on Days 0 and 4 of lactation | 60 (reproductive and developmental) | ND | 200 (reproductive and developmental) | Ministry of Health and Welfare Japan (1999) as cited by OECD 2004 ^d | PR |
| Carcinogenicity | ND | | | | | | | NA |

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry ^a | Critical effects | NOAEL ^a | BMDL/ BMCL ^a | LOAEL ^a | Reference (Comments) | Notes ^b |
|----------------------------------|--|------------------------------|--|--------------------|----------------------------|--------------------|-------------------------|--------------------|
| 2. Inhalation^a | | | | | | | | |
| Subchronic | 8/7, S-D, Rat, repeated exposure, 8 hr/d, 5 d/wk, 37 d | 120 | Chronic liver inflammation; chronic lung inflammation | NA | ND | 120 | Andersen et al. (1977a) | PR |
| Subchronic | 15/0, 15/0, 8/7, S-D, Rat, continuous exposure, 23 hr/d, 90–110 d | 2.7, 3.8, 19.2 | No effects observed | 19.2 | ND | NA | Andersen et al. (1977b) | PR |
| Subchronic | 8/7, Hartley, Guinea Pig; repeated exposure, 8 hr/d, 5 d/wk, 37 d | 120 | Chronic lung inflammation | NA | ND | 120 | Andersen et al. (1977c) | PR |
| Subchronic | 15/0, 15/0, 8/7, 24/24, 15/15, Hartley, Guinea Pig, continuous exposure, 23 hr/d, 85–110 d | 2.7, 3.8, 19.2, 152, and 192 | Chronic pleuritis; WBC count significantly lower than preexposure levels; fatty vacuolation of the liver | 152 | ND | 192 | Andersen et al. (1977d) | PR |
| Subchronic | 2/0, Beagle, Dog, repeated exposure, 8 hr/d, 5 d/wk, 37 d | 120 | Chronic lung inflammation | NA | ND | 120 | Andersen et al. (1977e) | PR |

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry ^a | Critical effects | NOAEL ^a | BMDL/BMCL ^a | LOAEL ^a | Reference (Comments) | Notes ^b |
|-----------------|---|-------------------------|---|--------------------|------------------------|--------------------|-------------------------|--------------------|
| Subchronic | 1–4 males/group, Beagle, Dog, continuous exposure, 23 hr/d, 90-110 d | 2.7, 3.8, 19.2, and 192 | Convulsions, labored breathing, and aggressive behavior in all dogs; severe motor seizures; severe convulsion; chronically inflamed and hemorrhagic lungs | 19.2 | ND | 192 (FEL) | Andersen et al. (1977f) | PS, PR |
| Subchronic | 9/0, Squirrel Monkey (<i>Saimiri sciureus</i>), repeated exposure, 8 hr/d, 5 d/wk, 37 d | 120 | Chronic lung inflammation; extreme convulsions; blood-tinged fluid around eyes; pale livers and hearts; fatty metamorphosis of the liver | NA | ND | 120 (FEL) | Andersen et al. (1977g) | PR |
| Subchronic | 2–9 males/group, Squirrel Monkey, continuous exposure, 23 h/d, 90–110 d | 2.7, 3.8, 19.2, and 192 | Mortality and moribundity; chronic pleuritis | 19.2 | ND | 192 (FEL) | Andersen et al. (1977h) | PR |
| Chronic | ND | | | | | | | NA |
| Developmental | ND | | | | | | | NA |
| Reproductive | ND | | | | | | | NA |
| Carcinogenicity | ND | | | | | | | NA |

^aDosimetry: The units for oral exposures are expressed as mg/kg-day, while inhalation exposures units are expressed as mg/m³. NOAEL, BMDL/BMCL, and LOAEL values of long-term exposure (4 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure. Values for inhalation were not converted to HEC for respiratory effects due to inadequate information available on particle size of the vapor or for any similar vapor.

^bNotes: IRIS = utilized by IRIS, date of last update; PS = principal study, PR = peer reviewed, NPR = not peer reviewed.

^cIncomplete results and lack of description precludes assigning effect levels to the subchronic portion of this study.

^dTables and Figures are in English, the text is in Japanese.

NA = not applicable, ND = not determined, FEL = frank effect level.

HUMAN STUDIES

Oral Exposures

No studies were identified on the oral exposure of sulfolane to humans.

Inhalation Exposures

No studies were identified on the inhalation exposure of sulfolane to humans

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to sulfolane have been evaluated in several subchronic-duration studies (i.e., Huntingdon Life Sciences, 2001; Ministry of Health and Welfare Japan, 1996a, and as summarized in OECD 2004; Zhu et al., 1987), one 6-month chronic-duration study (Zhu et al., 1987), one developmental (Zhu et al., 1987), and one screening-level reproductive study (Ministry of Health and Welfare Japan, 1999, and, as summarized in OECD 2004). No carcinogenicity studies of animals orally exposed to sulfolane have been identified in the literature.

Subchronic Studies

Huntingdon Life Sciences (2001)

The 13-week drinking water study in rats (Huntingdon Life Sciences, 2001) is selected as the principal study for derivation of the subchronic and chronic p-RfDs. In a GLP-compliant, peer-reviewed¹ study by Huntingdon Life Sciences (2001), the study authors administered sulfolane (purity unreported) to CD rats (10/sex/group) in drinking water at concentrations of 0, 25, 100, 400, or 1600 mg/L for 13 weeks. The study authors calculated the actual dosages to be 2.1, 8.8, 35.0, and 131.7 mg/kg-day, respectively, for males and 2.9, 10.6, 42.0, and 191.1 mg/kg-day, respectively, for females. Analytical measurements performed by the study authors indicated that sulfolane was stable in drinking water for 8 days at ambient temperatures and that actual doses were within acceptable limits (96.3–109% of nominal concentrations). Animals were 26–30 days old when supplied by Charles River (UK) Limited, Margate, Kent, England. At the beginning of treatment, animals were 39–43 days old. Males weighed 167–215 g, and females weighed 142–180 g.

Animals were housed in a controlled environment. Temperatures were kept between 19–23°C, and relative humidity was kept between 40–70%. Lighting was supplied in a 12-hour light/dark cycle. The rodent facility was designed and maintained to prevent contamination with external biological and chemical agents. Rats were kept in stainless steel cages with five rats of the same sex in each cage. Food (Rat and Mouse No. 1 Maintenance Diet, Special Services, Ltd., Witham, Essex, England) was provided freely, except on nights before blood sampling. Public tap water was supplied ad libitum in polycarbonate water bottles. Diet and water analyses did not indicate any signs of contamination that may have affected the study.

The study authors examined animals at least twice per day for treatment-related effects and disease. Detailed physical examinations were performed once per week for each animal. Body weight was recorded during acclimatization, at Week 0, once per week throughout treatment, and again at study termination. Food consumption was measured by weighing supplied food and measuring spilled food. Mean weekly consumption and food conversion

¹Peer-reviewed independently as part of this review.

efficiency were calculated using these data. Water consumption was recorded weekly. All animals were given eye examinations before treatment, focusing on the adnexa, conjunctivae, cornea and sclera, anterior chamber and iris, lens, and vitreous and ocular fundus. Any animals with ocular abnormalities were replaced with healthy animals. During Week 13 of treatment, study authors examined the eyes of animals in the control and high-dose groups.

The study authors performed functional observational battery tests at various times throughout the study. Before treatment and once weekly throughout treatment, animals were examined in the hand for exophthalmos, fur condition, lacrimation, piloerection, reactivity to handling, ease of removal from cage, salivation, and vocalization on handling. Afterward, activity counts, arousal, convulsion, defecation count, gait, grooming, palpebral closure, posture, rearing count, tremor, twitches, and urination were assessed during a 1-minute period in a standard area. Before treatment and during Weeks 6 and 12, animals were examined for approach response, auditory startle reflex, body temperature, body weight, grip strength (forelimbs and hindlimbs), landing foot splay, tail pinch response, pupil reflex, righting reflex, and touch response. Motor activity was measured before treatment and during Weeks 6 and 12 using infrared sensor equipment on animals for 1 hour.

During Week 13, blood samples were collected and examined for hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte count, platelet count, mean cell hemoglobin (MCH), mean cell volume (MCV), and mean cell hemoglobin concentration (MCHC). Romanowsky stains of blood films were examined using light microscopy for abnormal morphology and unusual cell types. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were also measured in additional samples. Blood cell counts also reported large unstained cells (LUCs), which are thought to be larger than normal or atypical lymphocytes. During Week 13, blood plasma was analyzed for alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, total cholesterol, creatinine, urea, total protein, albumin, albumin/globulin ratio, and sodium and potassium concentrations.

At sacrifice, the study authors performed a full necropsy including examination of the external body and orifices; neck; and cranial, thoracic, abdominal, and pelvic cavities including their viscera. The study authors recorded organ weights (with bilateral organs weighed together) for the adrenals, brain, epididymides, heart, kidneys, liver, ovaries, spleen, testes, thymus, and uterus with cervix. The following organs were preserved with 10% neutral buffered formalin (except testes and epididymides, which were preserved in Bouin's fluid and then 70% industrial methylated spirits) and examined microscopically: adrenals, aorta, brain, cecum, colon, duodenum, epididymides, femur (with joint), heart, ileum, jejunum, kidneys, liver, lungs (with bronchi), lymph nodes, mammary area, esophagus, ovaries, pancreas, pituitary, prostate, rectum, salivary gland, sciatic nerve, seminal vesicles, skin, spinal cord, spleen, sternum, stomach, testes, thymus, thyroid with parathyroids, trachea, urinary bladder, and uterus with cervix.

In control and high-dose animals, tissue samples were sectioned and stained from the adrenals (cortex and medulla), brain (cerebellum, cerebrum, and midbrain), femur, heart, ileum, kidneys, liver, lungs, mammary area (including overlying skin), spinal cord, stomach, thyroid, uterus, and testes. The study report indicates that kidneys were examined in the 2.1-, 8.8-, and 35.0-mg/kg-day groups (males) and 2.9-, 10.6-, and 42.0-mg/kg-day groups (females). The study authors also examined any abnormal tissues observed in control and all treatment groups.

The study authors did not observe any deaths or treatment-related clinical signs in either males or females. Study authors did not observe treatment-related findings in body weight (see Table B.1), food and water consumption, ocular examinations, functional observational battery tests, organ weight, or macroscopic tissue examination in males or females. Food conversion efficiency was slightly lower than controls during Week 1 in animals receiving the highest dose level (see Table B.2). However, after this time point, food efficiency was roughly comparable with controls in all groups. Females receiving 2.9 mg/kg-day of sulfolane had increased body-weight gain compared with controls but it was not significant. Females exhibited statistically significant decreases in total white blood cells (WBCs), lymphocyte, monocyte, basophil, and LUC counts compared with controls in the 10.6-, 42.0-, and 191.1-mg/kg-day dose groups (see Table B.3). Information was not provided about neutrophils or other cell types, and it is assumed these did not change. Males did not experience similar decreases in these cell counts. There were other intergroup hematological differences reaching statistical significance, with little or no biological relevance, including slightly prolonged prothrombin times in high-dose males and increased mean cell volumes and reduced activated partial thromboplastin times in high-dose females. LUCs were significantly lower in males at 35.0 and 131.7 mg/kg-day compared with control, but the study authors noted there were high values in two of the control animals. Basophils were also significantly different from controls at the two highest doses in both genders.

Males in the high-dose group (i.e., 131.7 mg/kg-day) experienced lowered ALT activities and elevated creatinine concentrations in Week 13 that were statistically significantly different than controls (see Table B.4). Males in the high-dose group had statistically lower AST activities, but authors noted that the mean value in controls was higher due to unusually high levels in two animals. The high-dose animals also displayed reduced plasma sodium concentration compared with controls, but the study authors attributed this decrease to a very low value in one control animal. Histopathological examinations indicated that males dosed with 35.0 and 131.7 mg/kg-day had an increasing incidence and severity of hyaline droplets in the cortical tubules of the kidneys, and increased cortical tubular basophilia; this effect was considered treatment related (see Table B.5). High-dose males also experienced a slightly elevated incidence of granular casts of the renal medulla compared with controls. These effects were not seen in females.

Although there was no assay of functional manifestation of the white cell decreases such as decreased inflammation or compromised immune function, or other effects to the organs of the immune system, the decreases in white cell counts seen in female rats are broad (seen in several cell types), statistically significant, and dose related. Additionally, there was a statistically significant decrease in the spleen weights at the high dose, which supports the immune suppression effect. Also, this effect has been consistently reported in several other studies of sulfolane exposures (albeit at higher exposures) in a different rat strain (Crj:CD[S-D]), species (guinea pigs), and route of exposure (inhalation) (Zhu et al., 1987; Andersen et al., 1977). A LOAEL of 10.6 mg/kg-day and NOAEL of 2.9 mg/kg-day were identified in female rats based on significant decreases in total WBCs, lymphocyte, monocyte, basophil, and LUC counts.

Ministry of Health and Welfare Japan (1996a, cited in OECD, 2004)

In a GLP-compliant, peer-reviewed study, the Ministry of Health and Welfare Japan (1996a, cited in OECD, 2004) administered sulfolane (vehicle and purity unreported) by gavage

to 5-week old male and female Crj:CD(S-D) rats (source unreported) at dose levels of 0, 60, 200, or 700 mg/kg-day for 28 days. The study report was written in Japanese, but it is summarized here based on secondary information from the Organisation for Economic Cooperation and Development (OECD, 2004). Additionally, the data tables in the Ministry of Health and Welfare Japan study report are available in English. There were 6 animals/sex in the 60- and 200-mg/kg-day groups and 12 animals/sex for the groups dosed at 0 and 700 mg/kg-day. After 28 days of treatment, 6 animals in the control and 6 in the 700 mg/kg-day groups were observed for a 14-day recovery period. The exact methods, animal husbandry, and statistical procedures performed by the Ministry of Health and Welfare Japan were not reported by the OECD.

There were no deaths in the control or treatment groups. Males in the 700-mg/kg-day group experienced significantly ($p < 0.01$) lower absolute body weight compared with controls throughout treatment (12–14% body-weight depression from Days 3–28), while high-dose females only differed significantly ($p < 0.01$) from controls for the first 14 days of treatment (11% absolute body-weight depression only on Day 3) (see Table B.6). High-dose males experienced significantly ($p = 0.01$) decreased food consumption for the first 3 weeks of treatment, while females had significantly ($p < 0.01$) decreased food consumption the first week of treatment (see Table B.7). High-dose females experienced decreased locomotor activity (3/12 animals; see Table B.8) during the beginning of the treatment period. Hematology revealed that all dosed male groups had significantly ($p = 0.05$) slightly decreased (2–3%) mean cell hemoglobin concentration (MCHC) after 28 days of treatment, but there was no decrease observed after the 14-day recovery period (see Table B.9). WBC counts in males of the high-dose group were significantly higher ($p = 0.05$) compared with control only after the recovery period and not after the 28-day treatment period. Because only the control and the high-dose groups were examined after recovery, a dose response could not be evaluated. Effects on WBCs in treated females were not observed. High-dose females had significantly reduced mean red blood cell counts (RBCs) and significantly increased mean cell volume (MCV) compared with controls after recovery ($p = 0.01$; see Table B.9). The high-dose males had decreased chloride (<2%) and increased cholinesterase activity (60%) and total bilirubin (29%), but all three parameters returned to normal after the recovery period. The high-dose females had elevated ALT (46% above control) and decreased glucose (15% below control) (see Table B.10). High-dose male rats experienced significantly increased ($p = 0.05$) relative kidney, brain and heart weight (see Table B.11), and increased incidence and severity of hyaline droplets and eosinophilic bodies in the renal tubules at both 200 and 700 mg/kg-day (see Table B.12). Based on observed kidney effects in male rats, a LOAEL of 200 mg/kg-day and a NOAEL of 60 mg/kg-day were identified.

Zhu et al. (1987)

In a single published study that was translated from Chinese for this review, Zhu et al. (1987) conducted a series of studies on the acute, subchronic (90-day), and chronic (6-month) oral toxicity of sulfolane in mice, white rats, and guinea pigs. Study authors also conducted a teratogenicity test and several genotoxicity tests (Ames, bone marrow micronucleus test, and sister chromatid exchange test). The studies are referred to as Zhu et al. (1987a) for the subchronic test on white rats, Zhu et al. (1987b) for the subchronic test on guinea pigs, Zhu et al. (1987c) for the chronic, 6-month toxicity test on guinea pigs, Zhu et al. (1987d) for the developmental toxicity test, and Zhu et al. (1987e) (see Table 4A) for the genotoxicity tests. The Zhu et al. (1987) study is considered a peer-reviewed study because it was reported in a Health Consultation by ATSDR (2010a). The study authors did not state whether the experiment

adhered to GLP guidelines and did not provide data tables in the translation. This report appears to be an extended abstract of the original study with very little useful information for risk assessment purposes. There is, for example, no clear indication of histopathological examination of any tissues in any test described, save for the spleen and liver in the 6-month study. This lack of results precludes assigning any effect levels at least to the 90-day test reports.

Zhu et al. (1987a)

Zhu et al. (1987a) conducted an oral toxicity study on 80 white rats (sex, age, strain not specified) at doses of 0, 55.6, 167, or 500 mg/kg-day sulfolane (purity, vehicle not specified) for 90 days. Study authors did not specify the type (e.g., gavage, drinking water, diet) or frequency of oral administration. It is unclear from the translated study report whether the dosing units were reported as mg/kg food or mg/kg body weight; however, the review by ATSDR (2010a) cites the units as mg/kg body weight per day. After 90 days, the study authors sacrificed animals by femoral artery bleed and measured biochemical parameters, “organ index,” and pathology with no mention of histopathology. The study authors did not delineate the specific biochemical parameters examined, nor did they specify the meaning of “organ index.” Additionally, the study authors did not provide data tables nor report the type of statistical procedures performed, but they did provide *p*-values to indicate statistical significance.

In rats, no significant changes in biochemical parameters or pathology were reported in the low- and mid-dose groups. However, the study authors reported significant changes in the high-dose group (500 mg/kg-day) including changes in urine volume, increased gamma glutamyl transferase activity in the urine, decreased serum alkaline phosphatase (ALP) activity, decreased ICD (undefined in the study report, but likely serum isocitrate dehydrogenase), and decreased thrombin. The study authors stated that other examined parameters did not exhibit statistically significant changes.

Zhu et al. (1987b)

Zhu et al. (1987b) conducted an oral toxicity study on 80 guinea pigs total (sex, age, group size, strain not clearly indicated) at doses of 0, 55.6, 167, or 500 mg/kg-day sulfolane (purity, vehicle not specified) for 90 days (see description of doses in Zhu et al., 1987a). After 90 days, study authors sacrificed animals by femoral artery bleed and measured specific biochemical parameters, “organ index,” and pathology with no mention of histopathology. The study authors did not delineate the specific biochemical parameters examined, nor did they specify the meaning of “organ index.” Additionally, the study authors did not report the type of statistical procedures performed, but they did provide *p*-values to indicate statistical significance. In guinea pigs, WBC counts were significantly ($p < 0.05$) decreased relative to controls values in all dose groups, although no other indication of dose response is described or given.

Chronic Study

Zhu et al. (1987c)

Study authors conducted a 6-month, chronic toxicity study where guinea pigs (20/sex/dose) were orally dosed with sulfolane (vehicle and purity not reported) at dose levels of 0, 0.25, 2.5, 25, or 250 mg/kg-day. The translation of the study did not specify the type or frequency of oral exposure (e.g., gavage, diet, drinking water). The study authors conducted biochemical and pathological evaluations on a subset of animals during an interim sacrifice at 3 months and at the end of the study at 6 months. This information is the only experimental design information provided in the translation. The translation did not state the specific

biochemical parameters, organs examined, or whether the “pathology” mentioned was gross pathology or histopathological. The study authors did not provide data tables; however, study authors did provide some values for biochemical parameters and incidence of pathology in the written narrative. The translated study did not mention any methods for statistical analysis. The data from the interim sacrifice at 3 months is considered subchronic-duration data.

At the 3-month interim sacrifice, the study authors reported that ALT, AST, and marrow cell number were lower than controls (see Table B.13). It is not clear from the study report which values were statistically significant. Incidence for shrinkage of white pulp in the spleen in the 0-, 0.25-, 2.5-, 25-, and 250-mg/kg-day groups were reported as 0/14, 0/14, 1/14, 2/14, and 6/14, respectively. The study authors did not present any statistical analysis on data for incidence of white pulp shrinkage in the spleen. Shrinkage in this area may be related to decreased cellularity, which may occur after exposure to agents that cause necrosis of lymphocytes, T-lymphocytes in particular (Elmore, 2006). At 6 months, the study authors reported that the “organ coefficient” of the male guinea pig liver was 40.2 and significantly different from the control group, but the study authors did not specify the meaning of this term. The study authors also reported a dose-response relationship in the increased incidence of fatty degeneration of the liver. This fatty degeneration of the liver is given once in the report, apparently as a total incidence for control and increasing exposures (0/25, 0/22, 2/26, 4/25, and 7/22), and then again as “significant degeneration” at 2.5 mg/kg-day (1/26), 25 mg/kg-day (2/25), and 250 mg/kg-day (5/22). Likewise, shrinkage of splenic white pulp was noted in these “significant” liver exposure groups: 2/26 at 2.5 mg/kg-day, 2/25 at 25 mg/kg-day, and 7/22 at 250 mg/kg-day (see Table B.13). Based on these reported histopathological results, a NOAEL of 0.25 mg/kg-day and a LOAEL of 2.5 mg/kg-day are designated.

Developmental Study

Zhu et al. (1987d)

Zhu et al. (1987d) conducted a developmental toxicity study where female Chinese Kunming mice (number not reported) were orally administered sulfolane (purity not reported) in distilled water vehicle at dose levels of 0, 93, 280, or 840 mg/kg-day on Gestational Days (GDs) 6–15. A positive control (*N,N*-methylene-bis-2-amino-5-sulfhydryl-1,3,4-thiadianole) and negative control (distilled water) were also administered to pregnant mice. On GD 18, fetuses were removed, and bodies, organs, and skeletons were examined for abnormalities. The study authors provided no other experimental details or methods of statistical analysis. Study authors reported that the incidence of skeletal abnormalities in the highest dose group (840 mg/kg-day) was significantly higher ($p < 0.01$, statistical test not reported) than the negative control. Study authors also stated that the number of fetal resorptions at the highest dose was greater than that of the negative control (30.16% versus 13.53%, respectively), but statistical significance was not specified. There were no skeletal abnormalities observed in pups in the 280-mg/kg-day group. Data from the study indicate a maternal and developmental NOAEL of 280 mg/kg-day and corresponding LOAEL of 840 mg/kg-day. Although study authors did not indicate whether GLP was followed, the study is considered acceptable because both skeletal and visceral observations of the pups were made, and abnormalities in pups were detected after treatment with sulfolane.

Reproductive Study

Ministry of Health and Welfare Japan (1999)

The Ministry of Health and Welfare Japan (1999) conducted a one-generation reproductive/developmental toxicity screening test that was peer-reviewed by OECD (2004).

The study report is written in Japanese, but it is summarized here based on secondary information from OECD (2004). Additionally, the data tables in the Ministry of Health and Welfare Japan study report are available in English. The study followed OECD 421 guidelines and was conducted under GLP standards. Study authors administered sulfolane (purity unreported) in water by gavage to 10-week-old Crj:CD(S-D) rats (12/sex/group) at doses of 0, 60, 200, or 700 mg/kg-day for 41–50 days. The dosing period extended from 14 days before mating to Lactation Day 3. Males and females were cohoused at a ratio of 1:1 for 14 days until proof of copulation. Clinical observations for general appearance were conducted twice per day for the parental generation and once per day for pups. During the mating period, body weight and food consumption were measured twice per week and then once per week in females during the gestation and lactation period. Estrous cycle was monitored daily until successful copulation. Study authors recorded the following parameters: number of successful copulated pairs, copulation index, pairing days until copulation, number of pregnant females, fertility index, number of corpora lutea, number of implantation sites, implantation index, number of living pregnant females, number of pregnant females with parturition, gestation length, number of pregnant females with live pups on Day 0, gestation index, number of pregnant females with live pups on Day 4, delivery index, number of pups alive on Day 0 of lactation, live birth index, sex ratio, number of pups alive on Day 4 of lactation, viability index, and body weight of live pups (on Days 0 and 4). At necropsy, study authors collected organ weights in the parental generation for testes, epididymides, and ovaries. Microscopic examinations of these organs were conducted for animals in the high-dose group only. Pups were examined macroscopically but apparently did not include a detailed organ or skeletal examination.

One high-dose male and one high-dose female died during the treatment period. High-dose animals of both sexes experienced statistically significantly decreased body-weight gain and food consumption during premating; body-weight gain in high-dose males was significantly ($p < 0.01$) decreased throughout the duration of the study (see Tables B.14 and B.15). Study authors also reported soiled fur, diarrhea, and soft stool in males at the 700-mg/kg-day dose group. In females of the 700-mg/kg-day dose group, study authors observed soiled fur during premating and increased relative ovary weight at necropsy (see Table B.16). Females dosed with 700 mg/kg-day had fewer estrous cycles (see Table B.17). The high-dose female group also experienced significantly decreased ($p < 0.01$) birth index, live birth index, and number of pups (on Lactation Days 1 and 4, data shown for LD-4 only; see Table B.18). The number of stillbirths was also significantly increased ($p < 0.01$) in this group. Four dams from this group experienced total litter loss during lactation. Furthermore, the females dosed with 200 mg/kg-day had significantly ($p < 0.05$) decreased delivery and birth indices (see Table B.18). Mean pup weight was significantly decreased on Lactation Day 0 and 4 in the 700-mg/kg-day group ($p < 0.01$) (see Table B.19). Mean litter weights were significantly decreased ($p < 0.05$) compared to control at ≥ 200 mg/kg-day. At necropsy, study authors did not observe external anomalies in any of the treated pups. A NOAEL of 60 mg/kg-day for reproductive and developmental toxicity based on decreased delivery and birth indexes was identified. The LOAEL was 200 mg/kg-day.

Limitations of the study report include lack of individual body weight, food consumption, uterine weight, and ovarian follicle counts data. Female estrous cycles were counted for 14 days prior to mating, but authors did not report measures of cycle length. Although male rats were examined for reproductive organ atrophy and sperm count, sperm motility and morphology were not measured by study authors.

Carcinogenicity Studies

No human or animal studies pertaining to carcinogenicity of sulfolane via the oral exposure route were identified in the literature.

Inhalation Exposures

The effects of inhalation exposure of animals to sulfolane have been evaluated in one subchronic study testing multiple species (i.e., Andersen et al., 1977). No chronic-duration, developmental, reproductive, or carcinogenicity studies via inhalation exposures have been identified in the literature.

Subchronic Study

Andersen et al. (1977)

In a published, peer-reviewed study, Andersen et al. (1977) conducted a series of tests investigating the subchronic inhalation toxicity of sulfolane to rats, guinea pigs, dogs, and squirrel monkeys. For the subchronic studies, both discontinuous repeated and continual-exposure regimens were implemented by study authors. The methods and results for each exposure group, species, and dosing regimens were not clearly reported. For the sake of clarity, the study is divided into eight separate summaries (Andersen et al., 1977a–h) based on species and exposure regimen (repeated versus continual). The citation and associated experimental design for the subchronic studies are summarized in Table 3. Particle measurements given in the report, “a mean particle size between 1–4 microns in diameter” are sufficient to validate the study by indicating that the material could be breathed into the respiratory tract. This information is, however, not sufficient to perform more formal dosimetry that requires a measurement of mass median aerodynamic diameter (MMAD) and the variability, the sigma g, about that MMAD; therefore, formal dosimetry conversion to HEC for respiratory and extrapulmonary effects is not conducted for this study. Exposure concentrations are duration adjusted from intermittent exposure to continuous exposure 24 hours/day, 7 days/week ($CONC_{adj} = CONC_{study} [in\ mg/m^3] \times [Hours\ per\ Day\ Exposed \div 24] \times [Days\ Exposed \div Total\ Study\ Days]$).

**Table 3. Study Design and Citations for Andersen et al. (1977)
Subchronic-Duration Inhalation Studies**

| Citation | Species and Exposure Regimen |
|------------------------|---|
| Andersen et al., 1977a | Rat, repeated exposure, 8 hr/d, 5 d/wk |
| Andersen et al., 1977b | Rat, continual exposure, 23 hr/d, 7 d/wk |
| Andersen et al., 1977c | Guinea pig, repeated exposure, 8 hr/d, 5 d/wk |
| Andersen et al., 1977d | Guinea pig, continual exposure, 23 hr/d, 7 d/wk |
| Andersen et al., 1977e | Dog, repeated exposure, 8 hr/d, 5 d/wk |
| Andersen et al., 1977f | Dog, continual exposure, 23 hr/d, 7 d/wk |
| Andersen et al., 1977g | Monkey, repeated exposure, 8 hr/d, 5 d/wk |
| Andersen et al., 1977h | Monkey, continual exposure, 23 hr/d, 7 d/wk |

For the various exposure regimens, study authors concluded that 20 mg/m³ (19.2 mg/m³ adjusted for continuous exposure) was the no-effect level for the four species of animals tested (i.e., rats, guinea pigs, dogs, and squirrel monkeys). Thus, the results from all species are mutually supportive. However, for this review, a NOAEL and LOAEL are established for each species and exposure regimen.

Andersen et al. (1977a)

Andersen et al. (1977a) exposed eight male and seven female Sprague-Dawley rats via whole-body inhalation exposure to a concentration of 495 ± 75 mg/m³ (mean ± standard deviation) aerosolized sulfolane-W (sulfolane plus 3% water to prevent freezing, purity unreported) for 8 hours/day, 5 days/week, for 27 exposure days over a total study duration of 37 days. It is unclear from the study report whether a separate, untreated control group was tested. Study authors indicate changes “compared with controls” in the text; however, the use of an untreated control group was not stated in the experimental design. Adjusted daily concentration was calculated for a total study duration of 37 days (includes weekends) over 24 hours/day, 7 days/week is 120 mg/m³. Test concentrations within chambers were determined by chromatographic analysis at 6-hour intervals. Rats were housed in Rochester-type chambers with sulfolane reservoirs, and input lines were wrapped in heat tape and maintained above room temperature to prevent freezing. Airflow through the chambers was maintained at 1 m³/min. Dry chow (unreported brand) and water were provided ad libitum. Authors did not report if the study was conducted according to GLP standards.

Authors determined body weights, total and differential leukocyte counts, hemoglobin concentrations, and hematocrit levels prior to and following exposure. The timepoint of postexposure sampling for the repeat-dose study is not clearly stated in the study report. Additional analyses performed after exposure included creatinine and urea nitrogen levels, cholesterol, lactate dehydrogenase (LDH), AST, ALT, and ALP activity. Rats were observed at unreported intervals for clinical signs of toxicity and abnormal behavior. Authors collected 24-hour urine samples and recorded pH, protein, sugar, ketone bodies, and occult blood. Histopathological analysis was performed on tissues from the lung, bronchus, heart, kidney, bile duct, liver, spleen, stomach, intestine, pancreas, cerebellum, esophagus, thyroid, trachea, lymph node, bladder, and aorta of an unreported number of animals. Authors used Student's *t*-test to compare preexposure and postexposure levels ($p < 0.05$).

Andersen et al. (1977a) observed no mortalities or significant differences in hematology or body weight between preexposure and postexposure levels. A small, nonsignificant decrease in WBC count in sulfolane-treated rats versus control was reported; however, specific values were not reported. Authors observed chronic lung inflammation in all animals but provided no information regarding severity. Study authors reported chronic liver inflammation in 1/5 males and 3/3 females; however, they did not address the inconsistencies between the number of animals reported in each dose group ($n = 8$ males, 7 females) and the number of animals examined for pathology ($n = 5$ males, 3 females). Authors concluded that sulfolane vapor is not toxic to rats under these experimental conditions. However, based on chronic lung and liver inflammation observed in rats at the only concentration tested, a LOAEL of 120 mg/m³ is established.

Andersen et al. (1977b)

Andersen et al. (1977b) administered sulfolane by whole-body inhalation exposure to Sprague-Dawley rats at concentrations of $2.8 \pm 1.4 \text{ mg/m}^3$ for 90 days ($n = 15$ males), $4.0 \pm 1.0 \text{ mg/m}^3$ for 110 days ($n = 15$ males), or $20 \pm 6.7 \text{ mg/m}^3$ for 95 days ($n = 8$ males, 7 females) for 23 hours/day, 7 days/week. Adjusted daily concentrations calculated for continuous exposure over 24 hours/day, 7 days/week are 2.7, 3.8, and 19.2 mg/m^3 . No control group was examined for this study. The test substance used, the method of test concentration determination, and animal husbandry are as reported in Andersen et al. (1977a). Authors did not report if this study was conducted in compliance with GLP standards.

Animals were weighed and blood drawn for analysis prior to exposure, after 30 exposure days, after 60 exposure days, and “at the end of exposure.” The exact time interval for postexposure examination is unclear. Authors examined all endpoints reported in Andersen et al. (1977a) and used Student’s *t*-test to compare preexposure and postexposure data.

Andersen et al. (1977b) reported no mortalities or significant changes in hematology, biochemistry, or body weight between preexposure and postexposure observations. One rat (sex not reported) at the 19.2 mg/m^3 concentration was observed to have a small circumscribed peripheral liver lesion, and 2/7 females at the same exposure had slightly elevated AST, ALT, and LDH activity levels. Authors reported that the liver lesion was not considered to be related to sulfolane exposure, and the dose-related nature of the clinical chemistry observations was unclear. A NOAEL of 19.2 mg/m^3 is established.

Andersen et al. (1977c)

Andersen et al. (1977c) also exposed 8 male and 7 female Hartley-derived guinea pigs to a concentration of $495 \pm 75 \text{ mg/m}^3$ sulfolane by whole-body inhalation exposure for 8 hours/day, 5 days/week, for 27 exposure days. The test chemical used is described in Andersen et al. (1977a). Adjusted daily concentration calculated for a total study duration of 37 days (includes weekends) and 24-hour treatment is 120 mg/m^3 . It is unclear if an untreated control group was used in this study. Determinations of test concentrations within chambers and husbandry are as described in Andersen et al. (1977a).

Study authors weighed animals and examined hematology prior to exposure. Total and differential leukocyte counts, hemoglobin concentrations, and hematocrit were determined and reevaluated after exposure (exact time interval for postexposure examination is unclear). Endpoints examined are those reported in Andersen et al. (1977a).

Andersen et al. (1977c) reported no significant differences in preexposure and postexposure body weight, hematology, or biochemistry. Preexposure and postexposure WBC, hematocrit, and hemoglobin counts are reported in Table B.20. Although a control group is reported in this table, authors do not mention an untreated group, and it is unclear what this “control” group represents. Authors reported that some degree of chronic lung inflammation (incidence and severity unreported) was observed in all animals. Authors concluded that sulfolane vapor is not toxic to guinea pigs under these experimental conditions. However, based on lung inflammation in guinea pigs, a LOAEL of 120 mg/m^3 is established. The LOAEL represents the only dose tested in this experiment.

Andersen et al. (1977d)

Andersen et al. (1977d) exposed Hartley-derived guinea pigs via whole-body inhalation to sulfolane at concentrations of $2.8 \pm 1.4 \text{ mg/m}^3$ for 90 days ($n = 15$ males), $4.0 \pm 1.0 \text{ mg/m}^3$ for 110 days ($n = 15$ males), $20 \pm 6.7 \text{ mg/m}^3$ for 95 days ($n = 8$ males, 7 females), $159 \pm 68 \text{ mg/m}^3$ for 85 days ($n = 24$ males, 24 females), or $200 \pm 48 \text{ mg/m}^3$ for 90 days ($n = 15$ males, 15 females) exposure for 23 hours/day, 7 days/week. The test chemical used is described in Andersen et al. (1977a). Adjusted daily concentrations calculated for continuous exposure over 24 hours/day, 7 days/week are 2.7, 3.8, 19.2, 152, and 192 mg/m^3 , respectively. It is unclear if an untreated control group was used in this study. Some data tables within the study report indicate a control group, but study authors do not explicitly mention this group in the methods section. Determination of test concentrations within chambers and husbandry are as described in Andersen et al. (1977a).

Study authors weighed animals and drew blood for analysis prior to exposure, after 30 exposure days, after 60 exposure days, and “following exposure” (Andersen et al., 1977d). The exact time interval of postexposure examination is unclear. Guinea pigs (exact number unreported) in the 152-mg/m^3 exposure-group were also bled from the toe at 10-day intervals. Authors report that in the 192-mg/m^3 exposure group, eight males and two females were bled after 20 exposure-days and that five males and five females were removed at 30 and 60 exposure-days for examination of body weight, hematology, biochemistry, and necropsy. Tissues from half of these animals were histopathologically examined. Authors examined all endpoints reported previously (Andersen et al., 1977a) and used Student’s *t*-test to compare preexposure and postexposure data.

Authors reported no mortalities, signs of clinical toxicity, or changes in body weight, hematology, biochemistry, or treatment-related pathology at exposures $\leq 152 \text{ mg/m}^3$. In the 19.2-mg/m^3 exposure group, study authors observed pale livers that they did not consider related to sulfolane treatment, but they did not provide details regarding incidence or severity of the effect.

Authors reported significantly decreased WBC count in the highest exposure group (192 mg/m^3) compared with preexposure levels on Days 20, 30, and 90—but not Day 60 (see Table B.21). However, the data table provided by study authors includes an untreated control group that is not mentioned in their explanation of methods, and it is unclear what this “control” group represents. The WBC count data are not amenable to BMD modeling because the number of animals in each exposure group was not clearly stated. No significant changes in body weight or enzyme activity levels were observed at the 192 mg/m^3 level, although slight, nonsignificant increases in plasma AST and ALT activities were observed at 30 and 60 days. No significant changes in hematocrit or hemoglobin counts were observed at any postexposure sampling period at the 152- or 192-mg/m^3 groups. Chronic pleuritis was observed in all 10 guinea pigs in the 192-mg/m^3 group necropsied at 30 days. Authors reported fatty vacuolization in 4/5 guinea pig livers at 30 days, 6/7 at 60 days, and 4/5 at 90 days; however, the inconsistencies between the number of animals reported to be necropsied previously in the study (0 at 30 days, 5 of each sex at 60 and 90 days) and those reported to be observed (5 at 30 days, 7 at 60 days, and 5 at 90 days) were not addressed. Based on chronic pleuritis, decreased WBC counts, and fatty vacuolization in liver of guinea pigs, a NOAEL of 152 mg/m^3 is established, with a corresponding LOAEL of 192 mg/m^3 .

Andersen et al. (1977e)

Andersen et al. (1977e) also exposed two male beagle dogs to a concentration of $495 \pm 75 \text{ mg/m}^3$ sulfolane by whole-body inhalation exposure for 8 hours/day, 5 days/week, for 27 exposure days. The test chemical used is described in Andersen et al. (1977a). The adjusted daily concentration calculated for a total study duration of 37 days (includes weekends) and 24 hours/day, 7 days/week is 120 mg/m^3 . No untreated control group was used in this study. Determination of test concentrations within chambers and husbandry are as described previously (Andersen et al., 1977a).

Parameters examined in Andersen et al. (1977e) are as described in Andersen et al. (1977a) with the exception that urine samples were not collected. Authors observed no significant changes in body weight, hematology, biochemistry, or pathology. Chronic lung inflammation was observed in both animals (severity not reported). A LOAEL of 120 mg/m^3 is established based on chronic lung inflammation.

Andersen et al. (1977f)

The subchronic inhalation study (Andersen et al., 1977f) is selected as the principal study for derivation of the subchronic RfC and screening chronic RfC. Andersen et al. (1977f) exposed male beagle dogs to concentrations of $2.8 \pm 1.4 \text{ mg/m}^3$ sulfolane for 90 days ($n = 1$), $4.0 \pm 1.0 \text{ mg/m}^3$ for 110 days ($n = 1$), $20 \pm 6.7 \text{ mg/m}^3$ for 95 days ($n = 2$), or $200 \pm 48 \text{ mg/m}^3$ for 90 days ($n = 4$) by whole-body inhalation exposure for 23 hours/day, 7 days/week. Adjusted daily concentrations calculated for continuous treatment over 24 hours/day, 7 days/week are 2.7, 3.8, 19.2, and 192 mg/m^3 , respectively. The test chemical used is described in Andersen et al. (1977a). No untreated control group was used in this study. Determination of test concentrations within chambers and husbandry methods are described previously (Andersen et al., 1977a).

Authors examined parameters previously detailed in Andersen et al. (1977a) with the exception that urine samples were not collected. Authors observed no mortalities, signs of clinical toxicity, changes in body weight, hematology, biochemistry, or pathology for the three low-exposure levels ($\leq 19.2 \text{ mg/m}^3$).

At the 192 mg/m^3 exposure-level, authors reported intermittent convulsions (incidence and severity not reported) and frequent displays of fiercely aggressive behavior both toward other dogs and their handlers. During periods of convulsive activity, authors noted episodic, slow, and labored breathing. Authors sacrificed one dog on Exposure Day 11 after the animal experienced many severe generalized motor seizures. Another dog was sacrificed on Exposure Day 29 after becoming so aggressive as to be considered a danger to the handlers. A third dog was removed from the testing chamber after 13 exposure days due to dangerously aggressive behavior. After a 29-day recuperative period, the dog was returned to the testing chamber but died 7 days later (Exposure Day 49) during a violent convulsion. The fourth dog was removed from the chamber on Exposure Day 27 (specific reason not given), allowed to recuperate for 3 days, and survived the full 90 days. Gross pathologic evaluation showed that three of four dogs had pneumonia, and in two of these cases, histologic examination revealed chronically inflamed and hemorrhagic lungs. Authors concluded that these effects were probably due to a combination of pulmonary and nervous system toxicity. Clinical chemistry measurements taken at Day 60 revealed grossly elevated plasma AST, ALT, and LDH levels in one dog (360, 111, and 96 IU/L, respectively; study authors did not report values for an untreated control).

No effects were observed at the 19.2 mg/m³ exposure level, while animals at the next-highest dose exhibited frank effects such as severe motor seizures, convulsions, and death. Based on information in the study, a FEL of 192 mg/m³ and a NOAEL of 19.2 mg/m³ are identified. The NOAEL is used as the POD for derivation of the subchronic and screening chronic p-RfC.

Andersen et al. (1977g)

Andersen et al. (1977g) also exposed nine male squirrel monkeys (*Saimiri sciureus*) to a concentration of 495 ± 75 mg/m³ sulfolane by whole-body inhalation exposure for 8 hours/day, 5 days/week, for 27 exposure days. The test chemical used is described in Andersen et al. (1977a). Adjusted daily concentration calculated for a total study duration of 37 days (includes weekends) and continuous exposure 24 hours/day, 7 days/week is 120 mg/m³. No untreated control group was used in this study. Determinations of test concentrations within chambers and husbandry are described previously (Andersen et al., 1977a).

Parameters examined by Andersen et al. (1977g) are as described previously (Andersen et al., 1977a) with the exception that urine samples were not collected. Three animals died, one each on Days 7, 9, and 15. Five others were sacrificed in extremis between Days 9 and 17. Authors noted blood tinged fluid around the eyes (incidence and severity not reported). Pathology revealed pale livers and hearts (incidence and severity not reported), and authors reported 5/6 monkeys had fatty metamorphosis of the liver. Authors also reported a slight, statistically nonsignificant decrease in WBC count and some degree of chronic lung inflammation in all animals (severity not reported). Based on mortality observed at the only concentration tested, an FEL of 120 mg/m³ is established.

Andersen et al. (1977h)

Andersen et al. (1977h) exposed male squirrel monkeys (*Saimiri sciureus*) to concentrations of 2.8 ± 1.4 mg/m³ sulfolane for 90 days (*n* = 9), 4.0 ± 1.0 mg/m³ for 110 days (*n* = 9), 20 ± 6.7 mg/m³ for 95 days (*n* = 6), or 200 ± 48 mg/m³ for 90 days (*n* = 2) by whole-body inhalation exposure for 23 hours/day, 7 days/week. The test chemical used is described in Andersen et al. (1977a). The adjusted daily concentrations calculated for continuous exposure over 24 hours/day, 7 days/week are 2.7, 3.8, 19.2, and 192 mg/m³, respectively. No untreated control group was used in this study. Determinations of test concentrations within chambers and husbandry are as described in Andersen et al. (1977a).

Authors examined parameters detailed in Andersen et al. (1977a) with the exception that urine samples were not collected. Authors observed no mortalities, signs of clinical toxicity, changes in body weight, hematology, biochemistry, or pathology for the three low-exposure levels (≤19.2 mg/m³). At the 192 mg/m³ exposure level, one animal died on Day 3, and the other was sacrificed in a moribund state on Day 4. Authors reported that both animals were heavily infested with parasites and that this could have contributed to their susceptibility. Authors also noted that the monkey sacrificed on Day 4 had chronic pleuritis. No other information was provided. In this exposure regimen, a FEL (death) of 192 mg/m³ and a NOAEL of 19.2 mg/m³ are identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

The database of other experiments on sulfolane includes genotoxicity, effects on thermoregulation, toxicokinetics, and neurotoxicity. The genotoxicity studies are summarized in Table 4A while other studies are summarized in Table 4B.

Table 4A. Summary of Sulfolane Genotoxicity

| Endpoint | Test System | Dose/ Concentration ^a | Results ^b | | Comments | References |
|--|--|-------------------------------------|-----------------------|--------------------|---|---|
| | | | Without Activation | With Activation | | |
| Genotoxicity studies in prokaryotic organisms | | | | | | |
| Reverse mutation | <i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537, TA1538 <i>E. coli</i> WP2, WP2uvrA | 0–52,000 µg/plate | – | – | No precipitation at any concentration with or without S9 | Ministry of Health and Welfare Japan (1996b) as reported in OECD (2004); Shell Oil Company (1982) ; Phillips Petroleum Co. (1994); Zhu et al. (1987e) |
| SOS repair induction | ND | | | | | |
| Genotoxicity studies in nonmammalian eukaryotic organisms | | | | | | |
| Mutation | <i>S. cerevisiae</i> | 0–5 mg/mL | – | – | | Shell Oil Company (1982) |
| Recombination induction | ND | | | | | |
| Chromosomal aberration | ND | | | | | |
| Chromosomal malsegregation | ND | | | | | |
| Mitotic arrest | ND | | | | | |
| Genotoxicity studies in mammalian cells—in vitro | | | | | | |
| Mutation | Mouse lymphoma L5178Y TK cells | 0–1000 µg/mL | + | + | Considered positive by study authors but no dose-response observed | Phillips Petroleum Co. (1994); also reported in OECD (2004), however OECD cites study as “Phillips Petroleum Co. (1982)” |
| Chromosomal aberrations | CHL/IU | 0, 0.3, 0.6, or 1.2 mg/mL | – | – | No structural aberrations/polyploidy induced in continuous (24 or 48 hr) or short-term (6 hr) treatment | Ministry of Health and Welfare Japan (1996c) as reported in OECD (2004) |
| Chromosomal aberrations | Rat liver, RL4 cells | 0–1000 µg/mL | – | NA | | Shell Oil Company (1982) |

Table 4A. Summary of Sulfolane Genotoxicity

| Endpoint | Test System | Dose/ Concentration ^a | Results ^b | | Comments | References |
|--|---|-------------------------------------|-----------------------|--------------------|---------------------------------|-------------------------------|
| | | | Without Activation | With Activation | | |
| Sister chromatid exchange (SCE) | Chinese hamster ovary cells | 0–6400 µg/mL | – | – | Growth inhibition at 6400 µg/mL | Phillips Petroleum Co. (1994) |
| Sister chromatid exchange (SCE) | Human peripheral lymphocytes | 0, 0.01, 0.1, 1, 10 mg/mL | – | NR | Growth inhibition at 10 mg/mL | Zhu et al. (1987e) |
| DNA damage | ND | | | | | |
| DNA adducts | ND | | | | | |
| Genotoxicity studies in mammals—in vivo | | | | | | |
| Mouse bone marrow micronucleus test | 7-wk-old mouse (strain, sex not specified); orally administered sulfolane | 62.5, 125, 250, 500, 1000 mg/kg | – | | | Zhu et al. (1987e) |
| Chromosomal aberrations | ND | | | | | |
| Sister chromatid exchange (SCE) | ND | | | | | |
| DNA damage | ND | | | | | |
| DNA adducts | ND | | | | | |
| Mouse biochemical or visible specific locus test | ND | | | | | |
| Dominant lethal | ND | | | | | |
| Genotoxicity studies in subcellular systems | | | | | | |
| DNA binding | ND | | | | | |

^aLowest effective dose for positive results, highest dose tested for negative results.

^b+ = positive, – = negative, NA = not applicable, ND = no data, NR = not reported.

Table 4B. Other Studies

| Test | Materials and Methods | Results | Conclusions | References |
|--|--|---|---|----------------------------|
| Carcinogenicity other than oral/inhalation | ND | | | |
| Short-term studies | ND | | | |
| Metabolism/toxicokinetics | Male Wistar rat, female rabbit (species unspecified); 100 mg in 2 mL water i.p. injection. | One major metabolite identified (3-hydroxysulfone); metabolite comprised 85% of urinary radioactivity. | Sulfolane is excreted mainly through urine after i.p. injection. | Roberts and Warwick (1961) |
| Metabolism/toxicokinetics | Rat, 500 and 1000 mg/kg i.v. | Sulfolane was excreted unchanged in urine; percentage of dose excreted unchanged in the urine was >50% between Days 0 and 2 at 1000 mg/kg; plasma half-life was 3.5–5 hr. | Sulfolane was rapidly distributed in rat after i.v. administration. | Andersen et al. (1976) |
| Metabolism/toxicokinetics | 12 Sprague-Dawley (S-D) rat, 0.2 mL [³ H]-sulfolane (95.3% radiochemical purity, 1.733 mCi/mg specific radioactivity) injected into ligated sections of GI tract. 55 S-D rat, oral dose (40uCi/100g bodyweight), blood and organs weighed and measured for distribution. Pregnant S-D rat (number unspecified) killed 2 hr after administration and examined for distribution to embryo. 3 Male S-D rat, biliary tract plunging tubes collected bile every 10 min within 72 hr after oral dose of [³ H]-sulfolane. 5 male S-D rat, oral doses, urine and feces collected every 10 min for 72 hr. | Major absorption site was small intestine, half life for absorption is 0.15 hr; T _{max} (time to maximum plasma concentration) is 1.16 hr; [³ H]-sulfolane present in every organ with peak levels at 1 hr, decreasing thereafter; at the peak, levels highest in liver, followed by the kidney and lung; elimination half life of [³ H]-sulfolane was longest in brain tissue (31.22 ± 4.68 d); blood concentration in embryos mirrored pregnant dams, while the placenta had a higher concentration; biliary excretion only 3% of administered dose after 72 hr; excretion in urine and feces accounted for 31 and 15% of administered dose, respectively; kinetic constant for sulfolane is 4.47 hr ⁻¹ . | Sulfolane is rapidly and completely absorbed and distributed throughout the body; excretion occurs mainly through the urine, with some excretion through the feces. | Zhu et al. (1988) |

Table 4B. Other Studies

| Test | Materials and Methods | Results | Conclusions | References |
|--------------------------------|--|--|---|------------------------|
| Mode of action/ mechanistic | ND | | | |
| Immunotoxicity | ND | | | |
| Neurotoxicity | Male S-D-derived rat, Hartley derived guinea pig, New Zealand white rabbit, and Swiss albino mouse; doses administered i.v., orally, i.p, and s.c. (exact doses not provided). LD ₅₀ values calculated from mortality after 1-wk observation. | Hunched posture, increased auditory sensitivity, hyperreactivity, and rapid respiration in rats and mice; at lethal doses, all species experienced clonic-tonic convulsions; LD ₅₀ values determined for i.v. administration were approximately half the value of those for i.p., oral, and subcutaneous administrations for all species. | Authors concluded that sulfolane has an excitatory effect on the central nervous system following acute administration. | Andersen et al. (1976) |
| Neurotoxicity | Male S-D rat; single i.p. injection of either saline or 200, 400, or 800 mg/kg-bw; body temperature and metabolic rate were recorded at ambient temperatures of 15°C, 25°C, or 35°C. | No effect of sulfolane at 35°C; at lower ambient temperature, hypothermia and hypometabolism were induced by sulfolane in the rat. | Authors concluded that “hypometabolic and hypothermic efficacy of sulfolane is dependent on ambient temperature.” | Gordon et al. (1984) |
| Neurotoxicity | Male S-D rat; single i.p. injection of either saline or 800 mg/kg; metabolic rate, tail skin temperature, colonic (deep body) temperature, and preferred body temperature were recorded at ambient temperatures of 15°C or 25°C. | Sulfolane reduced metabolic rate and colonic temperature at both ambient temperatures tested; preferred ambient temperature and tail skin temperature unaffected by treatment. | Authors concluded sulfolane toxicity is greater at increased ambient temperatures. | Gordon et al. (1985) |

Table 4B. Other Studies

| Test | Materials and Methods | Results | Conclusions | References |
|---------------|---|---|--|-------------------------|
| Neurotoxicity | Male Long-Evans hooded rat; single i.p. injection of either saline or 200, 400, or 800 mg/kg-bw; body temperature and motor activity were measured at ambient temperatures of 20.8°C or 32.3°C. | Hypothermia at doses ≥ 400 mg/kg-bw at 20.8°C; hypothermia attenuated at 32.3°C; at both temperatures, motor activity decreased at doses ≥ 400 mg/kg-bw. | Authors concluded that increasing ambient temperature attenuates hypothermia in sulfolane-treated rats, but sulfolane-induced hypoactivity was still evident when tested at both the higher and lower ambient temperatures. | Ruppert and Dyer (1985) |
| Neurotoxicity | Male Long-Evans hooded rat; single i.p. injection of either saline or 200, 400, or 800 mg/kg-bw sulfolane; visual evoked potentials (VEP) were measured by surgically-implanted electrodes. | No clinical changes in behavior; dose-dependent increase in latency of visual evoked potentials (statistically significant at ≥ 400 mg/kg-bw); dose-dependent hypothermia. | Authors concluded that acute administration of sulfolane produced clear alterations of visual system function and hypothermia. However, when hypothermia was attenuated by increasing ambient temperature, VEP latencies diminished, indicating that latencies were likely secondary to sulfolane-induced hypothermia. | Dyer et al. (1986) |
| Neurotoxicity | Male CD-1 mouse; single i.p. injection of saline or 200, 400, 600, or 800 mg/kg sulfolane in volume of 0.3 mL/100 g bw; Experiment 1 measured preferred ambient temperature immediately following injection; Experiment 2 measured metabolic rate and colonic temperature at ambient temperatures of 20°C, 30°C, or 35°C immediately following injection. | Sulfolane-treated mice had significantly lower metabolic rate and body temperature at lower ambient temperatures ($< 30^\circ\text{C}$). Mice exhibited behavioral preference for lower ambient temperature after treatment with sulfolane. Percent mortality after a LD_{50} dose of sulfolane increased with increasing ambient temperature. | Authors concluded that sulfolane-treated mice exhibited both autonomic and behavioral decrease in body temperature in order to reduce toxic effects of sulfolane. | Gordon et al. (1986) |

Table 4B. Other Studies

| Test | Materials and Methods | Results | Conclusions | References |
|---------------|---|---|--|--------------------------|
| Neurotoxicity | Male Long-Evans hooded rat; single i.p. injection of saline or 200, 400, or 800 mg/kg; Experiment 1 measured presence of audiogenic (AG) seizures and potentiation of pentylenetetrazol (PTZ) seizures; second and third experiments measured effect of body temperature on seizure occurrence using 400- and 800-mg/kg groups (Experiment 2) and the 800-mg/kg group (Experiment 3). | AG seizures occurred in half of the high-dose animals in first two experiments; sulfolane-induced hypothermia showed a protective effect and reduced AG seizure characteristics; doses of 800 mg/kg increased PTZ seizure severity and at 400 and 800 mg/kg, seizure duration was significantly increased; AD seizure activity was not affected significantly by treatment. | Doses of 800 mg/kg sensitized typically resistant rats to AG seizures and increased severity and duration of PTZ seizures; the data suggest that sulfolane treatment does not significantly affect the hippocampus. | Burdette and Dyer (1986) |
| Neurotoxicity | Male New Zealand White rabbit; single injection of 100, 300, or 1000 µg sulfolane in a 3-µL volume of saline directly into preoptic/anterior hypothalamic (POAH) area via stereotaxically implanted cannula; single injection of 300, 100, or 3000 µg in a 3-µL volume of saline directly into intracerebroventricular (ICV) area; POAH temperature, ear temperature, and metabolic rate were measured. | No statistically significant thermoregulatory effects upon direct injection into POAH; however, significant hyperthermia observed at 60–120 min postdosing upon injection into the ICV at 3000 µg. | Study authors concluded that sulfolane did not directly act on the thermoregulatory neurons of the CNS since no changes in temperature were observed when injected directly into the POAH. This finding contrasts previous findings of systemic (i.p.) injection of sulfolane where hypothermia was induced. | Mohler and Gordon (1989) |

ND = not data.

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

The genotoxicity of sulfolane has been evaluated in bacterial and eukaryotic in vitro systems and has yielded predominantly negative results. In bacterial cells, sulfolane was negative for inducing reverse mutations in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strains WP2 and WP2uvrA at concentrations up to 52,000 µg/plate, with or without metabolic activation (\pm S9). Study authors reported that no test compound precipitation or cytotoxicity occurred at concentrations up to 52,000 µg/plate. The only positive result for genotoxicity was reported in an unpublished mouse lymphoma assay by Phillips Petroleum Co. (1994) where study authors exposed L5178Y cells (T/K^{+/-}) to sulfolane at concentrations of 0, 60, 90, 135, 202, 301, 449, 670, or 1000 µg/mL; however, OECD (2004) noted that there was no dose response observed, and the survival percentage was not affected by increasing doses. Therefore, OECD considered the positive result as an incorrect interpretation by Phillips Petroleum Co. (1994). Sulfolane was negative for inducing mutations in a nonmammalian eukaryotic test system (*S. cerevisiae*) at concentrations up to 5 mg/mL (\pm S9) and negative for inducing chromosomal aberrations in CHL/IU and rat liver RL4 cells. Sulfolane did not induce sister chromatid exchange in Chinese hamster ovary cells at concentrations up to 6400 µg/mL, or in human peripheral lymphocytes at 10 mg/ml.

Carcinogenicity Studies

No human or animal studies pertaining to the carcinogenicity of sulfolane via the oral exposure route were identified in the literature.

Other Toxicity Studies (Exposures Other Than Oral or Inhalation)

Information is not available in this regard.

Short-term Studies

Information is not available in this regard.

Metabolism/Toxicokinetic Studies

Zhu et al. (1988), Roberts and Warwick (1961), and Andersen et al. (1976) provide information on the toxicokinetics and metabolism of sulfolane. Data indicate that sulfolane is rapidly and completely absorbed and distributed throughout the body when dosed orally, i.p., or i.v., and excretion occurs mainly through the urine. Further information is provided in Table 4B.

Mode of Action/Mechanistic

Information is not available in this regard.

Immunotoxicity

Information is not available in this regard.

Neurotoxicity

Sulfolane has been shown to elicit changes in thermoregulation of experimental animals Gordon et al. (1984), Ruppert and Dyer (1985), Mohler and Gordon (1989), Dyer et al. (1986), Gordon et al. (1986). Overall, the study authors observed that sulfolane-treated rodents demonstrated increased survivability at lower ambient temperatures. The various studies are presented in Table 4B.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present a summary of noncancer reference and cancer values, respectively. IRIS data are indicated in the table, if available.

| Table 5. Summary of Noncancer Reference Values for Sulfolane (CASRN 126-33-0) | | | | | | | |
|--|--------------------|---|--------------------------|-------------------|------------|-----------------------|---------------------------------|
| Toxicity Type (units) | Species/Sex | Critical Effect | p-Reference Value | POD Method | POD | UF_C | Principal Study |
| Subchronic p-RfD (mg/kg-d) | Rat/F | Decreased total and differential WBC counts (lymphocytes, basophils, monocytes, and LUCs) | 1×10^{-2} | NOAEL | 2.9 | 300 | Huntingdon Life Sciences (2001) |
| Chronic p-RfD (mg/kg-d) | Rat/F | Decreased total and differential WBC counts (lymphocytes, basophils, monocytes, and LUCs) | 1×10^{-3} | NOAEL | 2.9 | 3000 | Huntingdon Life Sciences (2001) |
| Subchronic p-RfC (mg/m ³) | Dog/M | Chronically inflamed and hemorrhagic lungs; neurological effects | 2×10^{-2} | NOAEL | 19.2 | 1000 | Andersen et al. (1977f) |
| Screening chronic p-RfC (mg/m ³) | Dog/M | Chronically inflamed and hemorrhagic lungs; neurological effects | 2×10^{-3} | NOAEL | 19.2 | 10,000 | Andersen et al. (1977f) |

| Table 6. Summary of Cancer Values for Sulfolane (CASRN 126-33-0) | | | | |
|---|--------------------|-------------------|---------------------|------------------------|
| Toxicity Type | Species/Sex | Tumor Type | Cancer Value | Principal Study |
| p-OSF | None | None | None | None |
| p-IUR | None | None | None | None |

DERIVATION OF ORAL REFERENCE DOSES

There are five subchronic-duration studies, one chronic-duration study, one developmental study and one reproductive study available involving oral exposures to sulfolane (see Table 2). The most acceptable study to use for deriving an oral reference value is a GLP compliant, peer-reviewed study (Huntingdon Life Sciences, 2001) that identified reduced WBC counts in female rats exposed to sulfolane in drinking water for 13 weeks. Although alternative studies are available (i.e., Ministry of Health and Welfare Japan, 1996a; Zhu et al., 1987), these reports are originally published in a foreign language (Japanese and Chinese, respectively), and the available translations do not contain detailed documentation of experimental methods and study design. The 28-day repeated dose study performed by the Ministry of Health and Welfare Japan (1996a) was reviewed and translated by OECD (2004), but OECD did not provide husbandry data and did not explicitly list the pathology parameters examined. In the translation of the Zhu et al. (1987) paper, information is not provided on the type or frequency of oral exposure, strain of animals used, specific biochemical parameters examined, specific organs examined, type of pathology examined, or methods for statistical analysis. It is unknown whether Zhu et al. (1987) followed GLP guidelines. The methods in the Huntingdon Life Sciences study are well documented, and the study adheres to GLP guidelines. Additionally, the study authors conducted the drinking water study at a lower dose range and examined a wider array of endpoints than the other available studies, and thus, the study was able to detect more sensitive effects of sulfolane. The subchronic-duration study by Huntingdon Life Sciences (2001) is, therefore, selected to derive the subchronic and chronic p-RfDs.

Sulfolane exposure of rats via the drinking water for 13 weeks showed kidneys and WBC as targets of toxicity. The kidney effects in males (hyaline droplets in cortical tubules and increased incidence of cortical tubule basophilia) fit two of the three criteria to be considered related to male rat-specific alpha_{2u}globulin nephropathy (as cited in U.S. EPA, 1991). Kidney effects specific to male rats involving alpha_{2u}globulin are generally thought to be not applicable to humans since humans do not possess alpha_{2u}globulin. However, because the immunohistochemical staining of kidney sections for alpha_{2u}globulin was not performed in the Huntingdon Life Sciences (2001) study, the presence of alpha_{2u}globulin is not confirmed and the human relevance of this effect cannot be discounted. However, the male rat kidney effects occur at higher doses and are less sensitive than the WBC effects observed in the Huntingdon Life Sciences (2001) study. Therefore, reduced WBC counts in female rats were chosen as the critical effect.

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The study by Huntingdon Life Sciences (2001) is selected as the principal study for derivation of the subchronic p-RfD. The critical endpoint is decreased total and differential WBC count (lymphocytes, basophils, monocytes, and LUCs) in female rats. The study was independently peer reviewed by three scientific experts in the summer of 2011, and this peer review supported the study conclusions.² The study was performed according to GLP guidelines and otherwise meets the standards of study design and performance, with numbers of animals, examination of potential toxicity endpoints, and presentation of information. Details are provided in the “Review of Potentially Relevant Data” section.

²Peer-review report available upon request.

BMD modeling of total WBC count in female rats was attempted using the available continuous models (polynomial, power, Hill, linear) in EPA's BMD software (Version 2.1.2) consistent with EPA's BMD EPA technical guidance (U.S. EPA, 2000). A benchmark response (BMR) of one standard deviation change from the control mean was selected in the absence of a biological rationale for using an alternative BMR. The BMD analysis resulted in significant lack of fit (goodness-of-fit $p < 0.10$) for all continuous models employing nonconstant (modeled) variance (see Table C.1). The homogeneity variance p -value of less than <0.1 indicates that nonconstant variance is the appropriate variance model (and therefore it is inappropriate to assume constant variance for these data).

Because these data were not amenable to BMD modeling, a NOAEL/LOAEL approach was employed to identify the point of departure (POD). The leukocyte data indicate a consistently observed effect, and identify a NOAEL of 2.9 mg/kg-day in females, and thus can be established as a POD for deriving the oral subchronic and chronic RfDs. The LOAEL for this same effect in females is 10.6 mg/kg-day.

No dosimetric adjustments are made because sulfolane was administered continuously via drinking water, and the study authors calculated average daily dose based on body weight and drinking water consumption data in the principal study.

The subchronic p-RfD for sulfolane, based on a NOAEL of 2.9 mg/kg-day in female rats, is derived as follows:

$$\begin{aligned}\text{Subchronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 2.9 \text{ mg/kg-day} \div 300 \\ &= \mathbf{1 \times 10^{-2} \text{ mg/kg-day}}\end{aligned}$$

Table 7 summarizes the uncertainty factors (UFs) for the subchronic p-RfD of sulfolane.

| Table 7. Uncertainty Factors for Subchronic p-RfD of Sulfolane | | | |
|---|--------------|--|---|
| UF | Value | Justification | Notes |
| UF _A | 10 | A UF _A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. | |
| UF _D | 3 | A UF _D of 3 is applied because there is an acceptable developmental study in mice (Zhu et al., 1987d), but there is only a screening-level one-generation reproduction study in rats (Ministry of Health and Welfare Japan, 1999) via the oral route. | The developmental study in mice was conducted soundly and identified teratogenic effects and is, therefore, considered a valid study. |
| UF _H | 10 | A UF _H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans. | |
| UF _L | 1 | A UF _L of 1 is applied for using a POD based on a NOAEL. | |
| UF _S | 1 | A UF _S of 1 is applied because a subchronic study was utilized. | |
| UF _C ≤3000 | 300 | | |

Table 8 shows the confidence descriptors for the subchronic RfD.

| Table 8. Confidence Descriptors for the Subchronic p-RfD for Sulfolane | | |
|---|--------------------------------|---|
| Confidence Categories | Designation^a | Discussion |
| Confidence in study | H | Confidence in the key study is high. The Huntingdon Life Sciences (2001) study was independently peer reviewed, and was conducted in compliance with GLP. |
| Confidence in database | M | The database includes subchronic toxicity studies in two species (rat and guinea pig), two chronic toxicity studies (in mice and guinea pigs), one developmental study in mice but no 2-generation reproductive developmental toxicity studies. |
| Confidence in subchronic p-RfD ^b | M | The overall confidence in the subchronic p-RfD value is medium. |

^aL = low; M = medium; H = high.

^bThe overall confidence cannot be greater than lowest entry in table.

Derivation of a Chronic Provisional RfD (Chronic p-RfD)

The peer-reviewed study by Huntingdon Life Sciences (2001) is selected as the principal study for derivation of the chronic p-RfD. For the same reasons listed above in the subchronic p-RfD discussion, the study by Huntingdon Life Sciences (2001) meets standards of study design and performance. Details are provided in the “Review of Potentially Relevant Data” section.

The chronic p-RfD for sulfolane, based on a NOAEL of 2.9 mg/kg-day in female rats, is derived as follows:

$$\begin{aligned}
 \text{Chronic p-RfD} &= \text{NOAEL} \div \text{UF} \\
 &= 2.9 \text{ mg/kg-day} \div 3000 \\
 &= 1 \times 10^{-3} \text{ mg/kg-day}
 \end{aligned}$$

Table 9 summarizes the UFs for the chronic p-RfD of sulfolane. Table 10 shows the confidence descriptors for the chronic p-RfD.

| Table 9. Uncertainty Factors for the Chronic p-RfD of Sulfolane | | | |
|--|-------|--|---|
| UF | Value | Justification | Notes |
| UF _A | 10 | A UF _A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. | |
| UF _D | 3 | A UF _D of 3 is applied because there is an acceptable developmental study in mice (Zhu et al., 1987d) but only a screening-level one-generation reproduction study in rats (Ministry of Health and Welfare Japan, 1999) via the oral route. | The developmental study in mice was conducted soundly and identified teratogenic effects and is, therefore, considered a valid study. |
| UF _H | 10 | A UF _H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans. | |
| UF _L | 1 | A UF _L of 1 is applied for using a POD based on a NOAEL. | |
| UF _S | 10 | A UF _S of 10 is applied because a subchronic study is utilized. | |
| UF _C ≤3000 | 3000 | | |

Table 10. Confidence Descriptors for Chronic p-RfD for Sulfolane

| Confidence Categories | Designation^a | Discussion |
|---|--------------------------------|--|
| Confidence in study | H | The HLS study is GLP compliant, peer reviewed, and met the standards for an acceptable study |
| Confidence in database | M | There is an acceptable developmental study but not a two-generational reproductive study |
| Confidence in subchronic p-RfD ^b | M | The overall confidence descriptor is medium. |

^aL = Low, M = Medium, H = High.

^bThe overall confidence cannot be greater than lowest entry in table.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

The study by Andersen et al. (1977f) is selected as the principal study for the derivation of the subchronic p-RfC. The critical endpoint is chronically inflamed and hemorrhagic lungs and neurological effects in male beagle dogs. The study was conducted before GLP guidelines were instituted. Details of the study are provided in the “Review of Potentially Relevant Data” section. The other inhalation studies performed by Andersen et al. (1977a–e,g,h) in several different animal species did not provide more sensitive effects or had improper animal husbandry. A rat study (Andersen et al., 1977b) had the same NOAEL but did not identify a LOAEL. The data are not amenable to benchmark dose modeling. The Andersen et al. (1977f) study provides the lowest POD for developing a subchronic p-RfC, and that POD is protective of all effects seen in all species in all exposure regimens examined in Andersen et al (1977a–h).

The POD in this study is an unadjusted NOAEL of 20 mg/m³ as reported by the study authors. Dosimetric adjustments were performed for continuous exposure duration. Conversion to HEC is not performed for the respiratory effects due to inadequate information (no MMAD determination) on aerosol particle size. Conversion to HEC is not performed for extrapulmonary (neurologic) effects due to inadequate chemical-specific information about partition coefficients between blood and air.

$$\begin{aligned}
 \text{NOAEL}_{\text{ADJ}} &= \text{NOAEL} \times (\text{Hours per Day Dosed} \div 24) \times (\text{Days Dosed} \div \text{Total Study Days}) \\
 &= 20 \text{ mg/m}^3 \times (23 \div 24) \times (95 \text{ Days Dosed} \div 95 \text{ Total Study Days}) \\
 &= 20 \times 0.958 \\
 &= 19.2 \text{ mg/m}^3
 \end{aligned}$$

$$\begin{aligned}
 \text{Subchronic p-RfC} &= \text{NOAEL}_{\text{ADJ}} \div \text{UF} \\
 &= 19.2 \text{ mg/m}^3 \div 1000 \\
 &= 2 \times 10^{-2} \text{ mg/m}^3
 \end{aligned}$$

Table 11 summarizes the UFs for the subchronic p-RfC of sulfolane.

| Table 11. Uncertainty Factors for Subchronic p-RfC of Sulfolane | | | |
|--|--------------|--|---|
| UF | Value | Justification | Notes |
| UF _A | 10 | A UF _A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between dogs and humans. | Dosimetric conversion is not performed due to missing aerosol size information. |
| UF _D | 10 | A UF _D of 10 is applied because there are no acceptable two-generation reproduction studies or developmental studies via the inhalation route. | |
| UF _H | 10 | A UF _H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans. | |
| UF _L | 1 | A UF _L of 1 is applied because a NOAEL is used. | |
| UF _S | 1 | A UF _S of 1 is applied because a subchronic study is utilized. | |
| UF _C ≤3000 | 1000 | | |

The confidence of the subchronic p-RfC for sulfolane is low as explained in Table 12 below.

| Table 12. Confidence Descriptors for Subchronic p-RfC for Sulfolane | | |
|--|--------------------------------|---|
| Confidence Categories | Designation^a | Discussion |
| Confidence in study | L | The study by Andersen et al. (1977a–h) does not provide particle size information for subchronic studies, and the methods are not clearly reported. |
| Confidence in database | L | The database for subchronic inhalation exposure includes the single study by Andersen et al. (1977a–h). |
| Confidence in subchronic p-RfD ^b | L | The overall confidence descriptor is low. |

^aL = Low, M = Medium, H = High.

^bThe overall confidence cannot be greater than lowest entry in table.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

No chronic p-RfC can be derived for the following reason: the composite UF for the chronic p-RfC is >3000. Therefore, the value is relegated to a screening-level value, and discussion for the derivation of a screening chronic p-RfC is available in Appendix A.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 13 identifies the cancer weight-of-evidence (WOE) descriptor for sulfolane.

| Table 13. Cancer WOE Descriptor for Sulfolane | | | |
|---|--------------------|---|--|
| Possible WOE Descriptor | Designation | Route of Entry (Oral, Inhalation, or Both) | Comments |
| <i>“Carcinogenic to Humans”</i> | Not selected | NA | |
| <i>“Likely to Be Carcinogenic to Humans”</i> | Not selected | NA | |
| <i>“Suggestive Evidence of Carcinogenic Potential”</i> | Not selected | NA | |
| <i>“Inadequate Information to Assess Carcinogenic Potential”</i> | Selected | Both | No carcinogenicity studies on human or animal exposure to sulfolane via the oral or inhalation route are available in the literature. |
| <i>“Not Likely to Be Carcinogenic to Humans”</i> | Not selected | NA | |

NA = Not Applicable.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define mode of action as “a sequence of key events and processes starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation” (p. 1–10). Examples of possible modes of carcinogenic action for a given chemical include “mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immunologic suppression” (p. 1–10). Based on the available literature, sulfolane is not genotoxic. Because there are no available studies on the carcinogenicity of sulfolane, the mode-of-action discussion is precluded.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

There are insufficient data to assess the carcinogenic potential of sulfolane via the oral route; therefore, derivation of a p-OSF is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

There are insufficient data to assess the carcinogenic potential of sulfolane via the inhalation route; therefore, derivation of a p-IUR is precluded.

APPENDIX A. PROVISIONAL SCREENING VALUES

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

DERIVATION OF SCREENING PROVISIONAL INHALATION REFERENCE CONCENTRATION

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

Similar to the subchronic p-RfC, the study by Andersen et al. (1977f) is selected as the principal study for the derivation of the screening chronic p-RfC. The critical endpoint is chronically inflamed and hemorrhagic lungs and neurological effects in male beagle dogs. The POD in the Andersen et al. (1977f) study is an unadjusted NOAEL of 20 mg/m³ as reported by the study authors. Dosimetric adjustments were performed for continuous exposure duration. Conversion to HEC is not performed due to inadequate information on aerosol particle size (no information was given to determine the MMAD).

$$\begin{aligned} \text{NOAEL}_{\text{ADJ}} &= \text{NOAEL} \times (\text{Hours per Day Dosed} \div 24) \times (\text{Days Dosed} \div \text{Total Study Days}) \\ &= 20 \text{ mg/m}^3 \times (23 \div 24) \times (95 \text{ Days Dosed} \div 95 \text{ Total Study Days}) \\ &= 20 \times 0.958 \\ &= 19.2 \text{ mg/m}^3 \end{aligned}$$

$$\begin{aligned} \text{Screening Chronic p-RfC} &= \text{NOAEL}_{\text{ADJ}} \div \text{UF} \\ &= 19.2 \text{ mg/m}^3 \div 10,000 \\ &= 2 \times 10^{-3} \text{ mg/m}^3 \end{aligned}$$

Table A.1 summarizes the UFs for the screening chronic p-RfC of sulfolane. The composite UF of 10,000 relegates this to a screening value. Confidence in the screening value is by definition, low.

Table A.1. Uncertainty Factors for Screening Chronic p-RfC of Sulfolane

| UF | Value | Justification | Notes |
|--------------------------|--------------|--|---|
| UF _A | 10 | A UF _A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between dogs and humans. | Dosimetric conversion is not performed due to missing aerosol size information. |
| UF _D | 10 | A UF _D of 10 is applied because there are no acceptable two-generation reproduction studies or developmental studies via the inhalation route, and there is no indication of any other relevant studies that may be relevant for database UF. | |
| UF _H | 10 | A UF _H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans. | |
| UF _L | 1 | A UF _L of 1 is applied because a NOAEL was used. | |
| UF _S | 10 | A UF _S of 10 is applied because a subchronic study is utilized and extrapolated for a chronic exposure duration. | |
| UF _C ≤3000 | 10,000 | | |

APPENDIX B. DATA TABLES

| Table B.1. Mean Body Weight and Survival of Male and Female CD Rats After Exposure to Sulfolane for 13 Weeks in Drinking Water^a | | | | | | |
|---|------------|---|------------------|------------------|-------------------|---------------------|
| Parameter | | Exposure Group, mg/L (Average Daily Dose, mg/kg-d)^b | | | | |
| Male | | 0 | 25 (2.1) | 100 (8.8) | 400 (35.0) | 1600 (131.7) |
| No. of animals | | 10 | 10 | 10 | 10 | 10 |
| Body weight ^c (g) | Week 0 | 192 ± 9.6 | 196 ± 6.5 (102) | 188 ± 9.5 (98) | 190 ± 7.8 (99) | 193 ± 12.8 (101) |
| | Week 1 | 251 ± 10.7 | 253 ± 8.7 (101) | 247 ± 11.9 (98) | 250 ± 11.9 (100) | 243 ± 16.5 (97) |
| | Week 2 | 306 ± 13.2 | 313 ± 10.3 (102) | 305 ± 11.8 (100) | 310 ± 18.1 (101) | 302 ± 20.8 (99) |
| | Week 3 | 348 ± 17.7 | 357 ± 10.1 (103) | 348 ± 15.0 (100) | 350 ± 23.3 (101) | 347 ± 26.6 (100) |
| | Week 4 | 385 ± 18.7 | 395 ± 13.5 (103) | 383 ± 19.2 (99) | 388 ± 31.6 (101) | 385 ± 29.5 (100) |
| | Week 5 | 418 ± 21.7 | 427 ± 11.1 (102) | 412 ± 24.3 (99) | 412 ± 32.2 (99) | 416 ± 34.0 (100) |
| | Week 6 | 437 ± 23.1 | 453 ± 14.3 (104) | 437 ± 29.0 (100) | 435 ± 34.3 (100) | 441 ± 36.7 (101) |
| | Week 7 | 457 ± 25.8 | 467 ± 14.6 (102) | 457 ± 34.5 (100) | 455 ± 35.0 (100) | 464 ± 38.3 (102) |
| | Week 8 | 478 ± 26.1 | 490 ± 17.3 (103) | 478 ± 34.1 (100) | 475 ± 37.9 (99) | 488 ± 39.2 (102) |
| | Week 9 | 498 ± 28.5 | 514 ± 16.9 (103) | 497 ± 38.8 (100) | 494 ± 42.2 (99) | 509 ± 42.1 (102) |
| | Week 10 | 515 ± 30.4 | 529 ± 20.7 (103) | 511 ± 45.9 (99) | 511 ± 41.9 (99) | 525 ± 43.7 (102) |
| | Week 11 | 524 ± 31.5 | 538 ± 22.8 (103) | 522 ± 43.8 (100) | 523 ± 45.8 (100) | 541 ± 44.7 (103) |
| | Week 12 | 541 ± 34.9 | 558 ± 27.5 (103) | 540 ± 49.6 (100) | 541 ± 48.6 (100) | 558 ± 47.9 (103) |
| Week 13 | 538 ± 32.2 | 553 ± 26.4 (103) | 539 ± 47.9 (100) | 536 ± 48.7 (100) | 556 ± 51.0 (103) | |
| Body weight gain (g) | Week 0–13 | 346 ± 37.4 | 357 ± 26.1 (103) | 351 ± 48.2 (101) | 346 ± 43.7 (100) | 363 ± 43.0 (105) |
| Survival ^d | | 10/10 (100) | 10/10 (100) | 10/10 (100) | 10/10 (100) | 10/10 (100) |

Table B.1. Mean Body Weight and Survival of Male and Female CD Rats After Exposure to Sulfolane for 13 Weeks in Drinking Water^a

| Parameter | | Exposure Group, mg/L (Average Daily Dose, mg/kg-d) ^b | | | | |
|----------------------|-----------|---|----------------------------------|------------------|------------------|-----------------|
| Female | | 0 | 25 (2.9) | 100 (10.6) | 400 (42.0) | 1600 (191.1) |
| No. of animals | | 10 | 10 | 10 | 10 | 10 |
| Body weight (g) | Week 0 | 163 ± 10.8 | 160 ± 10.4 (98) | 159 ± 7.5 (98) | 160 ± 5.3 (98) | 158 ± 11.2 (97) |
| | Week 1 | 187 ± 14.3 | 185 ± 14.2 (99) | 185 ± 8.7 (99) | 187 ± 6.7 (100) | 178 ± 13.0 (95) |
| | Week 2 | 208 ± 14.4 | 210 ± 14.5 (101) | 208 ± 9.5 (100) | 210 ± 8.8 (101) | 200 ± 16.5 (96) |
| | Week 3 | 226 ± 15.6 | 227 ± 15.5 (100) | 222 ± 12.4 (98) | 225 ± 10.1 (100) | 216 ± 18.7 (96) |
| | Week 4 | 238 ± 16.1 | 245 ± 15.1 (103) | 235 ± 14.6 (99) | 237 ± 12.7 (100) | 228 ± 18.0 (96) |
| | Week 5 | 248 ± 15.4 | 257 ± 20.1 (104) | 248 ± 14.0 (100) | 251 ± 12.5 (101) | 237 ± 18.0 (96) |
| | Week 6 | 254 ± 17.6 | 266 ± 18.5 (105) | 254 ± 15.0 (100) | 261 ± 13.4 (103) | 246 ± 20.5 (97) |
| | Week 7 | 262 ± 19.2 | 274 ± 18.3 (105) | 259 ± 15.8 (99) | 268 ± 15.6 (102) | 250 ± 22.0 (95) |
| | Week 8 | 267 ± 18.5 | 281 ± 19.3 (105) | 262 ± 17.8 (98) | 271 ± 16.0 (101) | 259 ± 19.4 (97) |
| | Week 9 | 272 ± 18.9 | 290 ± 22.6 (107) | 275 ± 16.3 (101) | 284 ± 17.5 (104) | 265 ± 20.8 (97) |
| | Week 10 | 279 ± 16.5 | 297 ± 24.3 (106) | 278 ± 16.1 (100) | 291 ± 17.6 (104) | 272 ± 22.2 (97) |
| | Week 11 | 284 ± 18.0 | 300 ± 23.3 (106) | 280 ± 18.0 (99) | 292 ± 20.2 (103) | 276 ± 23.3 (97) |
| | Week 12 | 287 ± 18.0 | 304 ± 22.3 (106) | 282 ± 19.5 (98) | 295 ± 18.1 (103) | 279 ± 20.9 (97) |
| | Week 13 | 283 ± 19.8 | 303 ± 26.0 (107) | 282 ± 17.1 (100) | 292 ± 19.9 (103) | 276 ± 22.2 (98) |
| Body weight gain (g) | Week 0–13 | 120 ± 12.1 | 143 ± 19.4 ^c (119) | 123 ± 12.4 (103) | 132 ± 23.3 (110) | 118 ± 16.3 (98) |
| Survival | | 10/10 (100) | 10/10 (100) | 10/10 (100) | 10/10 (100) | 10/10 (100) |

^aHuntingdon Life Sciences (2001).

^bAverage daily doses (mg/kg-day) were calculated by study authors.

^cWeights expressed as mean ± SD (% of control).

^dSurvival expressed as number surviving/total number (% survival).

^eSignificantly different from control ($p < 0.05$); test was not reported.

Table B.2. Mean Food Conversion Efficiency in Male and Female CD Rats After Exposure to Sulfolane for 13 Weeks in Drinking Water^a

| Parameter | | Exposure Group, mg/L (Average Daily Dose, mg/kg-d) ^b | | | | |
|------------------------------|-----------|---|----------|------------|------------|--------------|
| Male | | 0 | 25 (2.1) | 100 (8.8) | 400 (35.0) | 1600 (131.7) |
| No. of animals | | 10 | 10 | 10 | 10 | 10 |
| Food efficiency ^c | Week 1 | 28.5 | 27.3 | 29.2 | 29.0 | 26.2 |
| | Week 2 | 23.6 | 26.1 | 26.2 | 26.8 | 27.3 |
| | Week 3 | 18.9 | 19.0 | 19.6 | 18.2 | 21.2 |
| | Week 4 | 18.1 | 17.8 | 17.1 | 17.9 | 18.2 |
| | Week 5 | 15.8 | 14.6 | 14.1 | 11.7 | 15.7 |
| | Week 6 | 9.3 | 11.7 | 11.9 | 11.1 | 12.4 |
| | Week 7 | 9.9 | 7.0 | 10.1 | 9.9 | 10.7 |
| | Week 8 | 10.2 | 10.8 | 10.3 | 10.1 | 11.6 |
| | Week 9 | 9.8 | 11.2 | 9.6 | 9.3 | 10.1 |
| | Week 10 | 8.3 | 7.1 | 6.9 | 8.4 | 7.6 |
| | Week 11 | 4.7 | 4.8 | 5.8 | 5.9 | 8.1 |
| | Week 12 | 8.0 | 9.0 | 8.8 | 8.8 | 7.9 |
| | Week 13 | ND | ND | ND | ND | ND |
| Overall | Week 1–13 | 12.9 | 12.9 | 13.4 | 12.9 | 13.6 |
| Female | | 0 | 25 (2.9) | 100 (10.6) | 400 (42.0) | 1600 (191.1) |
| No. of animals | | 10 | 10 | 10 | 10 | 10 |
| Food efficiency ^c | Week 1 | 16.8 | 17.7 | 18.9 | 19.6 | 14.8 |
| | Week 2 | 14.8 | 17.0 | 16.7 | 16.3 | 16.0 |
| | Week 3 | 12.5 | 11.6 | 10.3 | 10.5 | 11.1 |
| | Week 4 | 9.0 | 12.3 | 8.7 | 8.7 | 8.2 |
| | Week 5 | 6.9 | 7.7 | 8.8 | 9.6 | 6.5 |
| | Week 6 | 3.9 | 6.6 | 4.4 | 6.8 | 6.6 |
| | Week 7 | 5.0 | 5.2 | 3.2 | 5.4 | 3.3 |
| | Week 8 | 4.0 | 4.9 | 2.4 | 2.1 | 5.6 |
| | Week 9 | 4.4 | 5.9 | 9.7 | 8.9 | 4.7 |
| | Week 10 | 4.9 | 5.1 | 1.9 | 4.9 | 4.9 |
| | Week 11 | 3.9 | 1.9 | 1.4 | 0.7 | 1.9 |
| | Week 12 | 2.6 | 3.4 | 1.3 | 2.1 | 2.2 |
| | Week 13 | NE | NE | 0.2 | NE | NE |
| Body weight gain (g) | Week 1–13 | 6.7 | 7.6 | 6.8 | 7.3 | 6.5 |

^aHuntingdon Life Sciences (2001).

^bAverage daily doses (mg/kg-day) were calculated by study authors.

^cFood conversion efficiency expressed as mean (%) and calculated as overall body-weight gain divided by total food consumed.

ND = not examined; body-weight loss or stasis, NE = not examined

Table B.3. Selected Hematology Data for Rats Exposed to Sulfolane for 13 Weeks in Drinking Water^a

| Parameter | Exposure Group, mg/L (Average Daily Dose, mg/kg-d) ^b | | | | | |
|-----------------------------------|---|---------------|---------------------|--------------------------------|---------------------------------|---------------------------------|
| | Male | 0 | 25 (2.1) | 100 (8.8) | 400 (35.0) | 1600 (131.7) |
| No. of animals | | 9 | 10 | 10 | 9 | 9 |
| MCV (fL) ^c | | 54.6 ± 0.89 | 53.8 ± 1.60 (99) | 53.3 ± 1.41 (98) | 54.4 ± 1.84 (100) | 54.7 ± 1.58 (100) |
| WBC (× 10 ⁹ /L) | | 11.60 ± 2.719 | 11.61 ± 2.078 (100) | 10.90 ± 1.534 (94) | 9.47 ± 2.071 (82) | 11.34 ± 2.074 (98) |
| Lymphocyte (× 10 ⁹ /L) | | 9.65 ± 2.430 | 9.77 ± 1.758 (101) | 8.73 ± 1.267 (90) | 7.90 ± 1.764 (82) | 9.67 ± 1.919 (100) |
| Basophil (× 10 ⁹ /L) | | 0.02 ± 0.007 | 0.02 ± 0.009 (100) | 0.02 ± 0.005 (100) | 0.01 ± 0.007 ^c (0.5) | 0.01 ± 0.007 ^d (0.5) |
| Monocyte (× 10 ⁹ /L) | | 0.36 ± 0.145 | 0.36 ± 0.104 (100) | 0.38 ± 0.119 (106) | 0.27 ± 0.134 (75) | 0.25 ± 0.071 (69) |
| LUC (× 10 ⁹ /L) | | 0.22 ± 0.127 | 0.14 ± 0.042 (64) | 0.16 ± 0.048 (73) | 0.12 ± 0.050 ^c (55) | 0.14 ± 0.039 ^d (64) |
| PT (sec) | | 13.4 ± 0.80 | 14.0 ± 1.32 (104) | 13.3 ± 0.53 (99) | 13.4 ± 1.27 (100) | 14.3 ± 0.40 ^d (107) |
| APTT (sec) | | 17.8 ± 2.24 | 18.2 ± 3.17 (102) | 16.8 ± 2.34 (94) | 17.8 ± 2.28 (100) | 16.9 ± 2.25 (95) |
| | Female | 0 | 25 (2.9) | 100 (10.6) | 400 (42.0) | 1600 (191.1) |
| No. of Animals | | 10 | 10 | 9 | 9 | 10 |
| MCV (fL) | | 55.4 ± 1.39 | 55.1 ± 1.76 (99) | 54.2 ± 1.19 (98) | 55.2 ± 1.25 (100) | 56.7 ± 1.39 ^d (102) |
| WBC (× 10 ⁹ /L) | | 7.97 ± 2.213 | 7.63 ± 2.653 (96) | 5.41 ± 1.392 ^c (69) | 5.53 ± 1.756 ^c (69) | 4.54 ± 1.019 ^c (57) |
| Lymphocyte (× 10 ⁹ /L) | | 6.98 ± 2.146 | 6.36 ± 2.452 (91) | 4.39 ± 1.308 ^c (63) | 4.63 ± 1.564 ^c (66) | 3.73 ± 0.941 ^c (53) |
| Basophil (× 10 ⁹ /L) | | 0.01 ± 0.006 | 0.01 ± 0.006 (100) | 0.00 ± 0.005 ^d (0) | 0.00 ± 0.007 ^d (0) | 0.00 ± 0.004 ^c (0) |
| Monocyte (× 10 ⁹ /L) | | 0.22 ± 0.080 | 0.23 ± 0.119 (105) | 0.13 ± 0.053 ^d (59) | 0.13 ± 0.040 ^d (59) | 0.10 ± 0.040 ^c (45) |
| LUC (× 10 ⁹ /L) | | 0.11 ± 0.040 | 0.11 ± 0.056 (100) | 0.06 ± 0.023 ^d (55) | 0.06 ± 0.026 ^c (55) | 0.04 ± 0.019 ^c (36) |
| PT (sec) | | 13.8 ± 0.97 | 14.1 ± 0.84 (102) | 13.8 ± 0.85 (100) | 14.1 ± 0.52 (102) | 14.0 ± 0.94 (101) |
| APTT (sec) | | 17.4 ± 5.21 | 14.8 ± 1.65 (85) | 15.4 ± 2.02 (89) | 14.7 ± 1.33 (84) | 14.2 ± 2.61 ^d (82) |

^aHuntingdon Life Sciences (2001).

^bAverage daily doses (mg/kg-day) were calculated by study authors.

^cExpressed as group mean ± SD (% of controls).

^dSignificantly different from control ($p \leq 0.05$); Williams' test or Shirley's test.

^eSignificantly different from control ($p \leq 0.01$); Williams' test.

APTT = activated partial thromboplastin time PT = partial thromboplastin time.

Table B.4. Selected Clinical Chemistry Data for Rats Exposed to Sulfolane for 13 Weeks in Drinking Water^a

| Parameter | Exposure Group mg/L (Average Daily Dose, mg/kg-d) ^b | | | | |
|------------------------|--|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| | 0 | 25 (2.1) | 100 (8.8) | 400 (35.0) | 1600 (131.7) |
| Male | | | | | |
| No. of animals | 10 | 10 | 10 | 10 | 10 |
| ALT (U/L) ^c | 49 ± 7.3 | 43 ± 9.1 (88) | 45 ± 11.9 (92) | 43 ± 9.5 (88) | 38 ± 7.7 ^d (78) |
| AST (U/L) | 100 ± 55.1 | 77 ± 9.5 (77) | 83 ± 21.1 (83) | 82 ± 30.1 (82) | 68 ± 10.0 ^c (68) |
| Creatinine (µmol/L) | 49 ± 3.5 | 48 ± 3.0 (98) | 49 ± 2.9 (100) | 51 ± 2.1 (104) | 53 ± 1.8 ^c (108) |
| Sodium (mmol/L) | 141 ± 1.1 | 140 ± 1.3 (99) | 141 ± 0.9 (100) | 140 ± 0.9 ^d (99) | 138 ± 5.1 ^c (98) |
| Total protein (g/L) | 68 ± 2.3 | 69 ± 2.1 (101) | 68 ± 2.5 (100) | 67 ± 2.4 (99) | 67 ± 2.2 (99) |
| Female | | | | | |
| No. of animals | 10 | 10 | 10 | 10 | 10 |
| ALT (U/L) | 48 ± 37.5 | 54 ± 34.3 (113) | 43 ± 10.9 (90) | 43 ± 14.8 (90) | 36 ± 6.1 (75) |
| AST (U/L) | 81 ± 28.9 | 97 ± 61.2 (120) | 85 ± 22.7 (105) | 76 ± 18.4 (94) | 72 ± 16.2 (89) |
| Creatinine (µmol/L) | 52 ± 3.1 | 54 ± 5.5 (104) | 56 ± 6.9 (108) | 55 ± 6.2 (106) | 53 ± 4.5 (102) |
| Sodium (mmol/L) | 141 ± 1.0 | 140 ± 0.6 ^d (99) | 139 ± 0.9 ^c (99) | 140 ± 0.8 ^c (99) | 140 ± 0.8 ^c (99) |
| Total protein (g/L) | 75 ± 3.9 | 75 ± 2.8 (100) | 75 ± 5.0 (100) | 72 ± 2.6 (196) | 73 ± 3.0 (97) |

^aHuntingdon Life Sciences (2001).

^bAverage daily doses (mg/kg-day) were calculated by study authors.

^cExpressed as group mean ± SD (% of controls).

^dSignificantly different from control ($p \leq 0.05$); Williams' test or Shirley's test.

^eSignificantly different from control ($p \leq 0.01$); Williams' test or Shirley's test.

Table B.5. Selected Histopathological Data in the Kidney for Rats Exposed to Sulfolane for 13 Weeks in Drinking Water^a

| Parameter | Exposure Group mg/L (Average Daily Dose, mg/kg-d) ^b | | | | | |
|--|--|-----------------|-------------------|-------------------|---------------------|--------------|
| | Male | 0 | 25 (2.1) | 100 (8.8) | 400 (35.0) | 1600 (131.7) |
| Cortical tubular basophilia ^c | | 3/10 (30) | 4/10 (40) | 3/10 (30) | 3/10 (30) | 7/10 (70) |
| Cortical tubules with hyaline droplets | | 4/10 (40) | 2/10 (20) | 4/10 (40) | 9/10 (90) | 9/10 (90) |
| Granular casts—medulla | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) | 2/10 (20) |
| Cortical scarring | | 1/10 (1) | 0/10 (0) | 0/10 (0) | 1/10 (10) | 1/10 (10) |
| Medullary cyst(s) | | 3/10 (30) | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Interstitial nephritis | | 1/10 (10) | 0/10 (0) | 2/10 (20) | 0/10 (0) | 1/10 (10) |
| Mineralizations, corticomedullary | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Hyaline tubular casts | | 0/10 (0) | 1/10 (10) | 0/10 (0) | 0/10 (0) | 1/10 (10) |
| Hydronephrosis | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 1/10 (10) | 2/10 (20) |
| Hyperplasia, papillary epithelium | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 1/10 (10) | 1/10 (10) |
| Cortical cyst(s) | | 0/10 (0) | 1/10 (10) | 1/10 (10) | 1/10 (10) | 0/10 (0) |
| Papilla—dilated ducts | | 0/10 (0) | 1/10 (10) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Female | 0 | 25 (2.9) | 100 (10.6) | 400 (42.0) | 1600 (191.1) | |
| Cortical tubular basophilia | | 0/10 (0) | 1/10 (10) | 0/10 (0) | 0/10 (0) | 1/10 (10) |
| Cortical tubules with hyaline droplets | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Granular casts—medulla | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Cortical scarring | | 0/10 (0) | 1/10 (10) | 2/10 (20) | 1/10 (10) | 1/10 (10) |
| Medullary cyst(s) | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Interstitial nephritis | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 1/10 (10) | 1/10 (10) |
| Mineralizations, corticomedullary | | 1/10 (10) | 0/10 (0) | 1/10 (10) | 0/10 (0) | 3/10 (30) |
| Hyaline tubular casts | | 0/10 (0) | 1/10 (10) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Hydronephrosis | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 1/10 (10) | 0/10 (0) |
| Hyperplasia, papillary epithelium | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Cortical cyst(s) | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) |
| Papilla—dilated ducts | | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) |

^aHuntingdon Life Sciences (2001).

^bAverage daily doses (mg/kg-day) were calculated by study authors.

^cResults presented no. of animals with lesion/no. of animals tested (% incidence).

Table B.6. Mean Body Weight and Survival of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | Exposure Group, mg/kg-d | | | | |
|---------------------------------|-------------------------|-----------|---------------|---------------|----------------------------|
| | 0 | 60 | 200 | 700 | |
| Males—treatment period | | | | | |
| No. of animals | 12 | 6 | 6 | 12 | |
| Body weight ^b (g) | Day 1 | 151 ± 3 | 151 ± 3 (100) | 151 ± 4 (100) | 151 ± 3 (100) |
| | Day 3 | 165 ± 4 | 165 ± 4 (100) | 166 ± 6 (101) | 146 ± 5 ^c (88) |
| | Day 7 | 203 ± 7 | 200 ± 5 (99) | 199 ± 5 (98) | 177 ± 6 ^c (87) |
| | Day 10 | 228 ± 10 | 225 ± 7 (99) | 222 ± 5 (97) | 198 ± 6 ^c (87) |
| | Day 14 | 263 ± 13 | 260 ± 10 (99) | 255 ± 6 (97) | 226 ± 7 ^c (86) |
| | Day 17 | 288 ± 17 | 284 ± 11 (99) | 278 ± 8 (97) | 247 ± 9 ^c (86) |
| | Day 21 | 319 ± 21 | 312 ± 12 (98) | 307 ± 8 (96) | 276 ± 12 ^c (87) |
| | Day 24 | 340 ± 23 | 330 ± 14 (97) | 324 ± 10 (95) | 292 ± 13 ^c (86) |
| | Day 28 | 365 ± 27 | 351 ± 17 (96) | 348 ± 7 (95) | 317 ± 15 ^c (87) |
| | Gain 1–28 | 214 ± 25 | 200 ± 16 (93) | 197 ± 7 (92) | 166 ± 15 ^c (78) |
| Survival ^c | 12/12 (100) | 6/6 (100) | 6/6 (100) | 12/12 (100) | |
| Males—recovery period | | | | | |
| Body weight ^b (g) | Day 28 | 371 ± 29 | NE | NE | 341 ± 15 ^c (92) |
| | Day 31 | 390 ± 31 | NE | NE | 345 ± 15 ^c (88) |
| | Day 35 | 413 ± 35 | NE | NE | 371 ± 17 ^d (90) |
| | Day 28 | 430 ± 38 | NE | NE | 386 ± 19 ^d (90) |
| | Day 42 | 446 ± 44 | NE | NE | 406 ± 22 (91) |
| | Gain 28–42 | 75 ± 15 | NE | NE | 92 ± 13 (123) |
| Survival ^c | 12/12 (100) | NE | NE | 12/12 (100) | |

Table B.6. Mean Body Weight and Survival of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | | Exposure Group, mg/kg-d | | | |
|---------------------------------|-------------|-------------------------|---------------|----------------|---------------------------|
| Females—treatment period | | | | | |
| Body weight ^b (g) | Day 1 | 134 ± 4 | 134 ± 4 (100) | 135 ± 5 (101) | 134 ± 4 (100) |
| | Day 3 | 142 ± 5 | 143 ± 7 (101) | 140 ± 7 (99) | 127 ± 5 ^c (89) |
| | Day 7 | 159 ± 6 | 160 ± 6 (101) | 157 ± 7 (99) | 146 ± 6 ^c (92) |
| | Day 10 | 167 ± 8 | 169 ± 7 (101) | 169 ± 9 (101) | 157 ± 8 ^d (94) |
| | Day 14 | 180 ± 11 | 180 ± 6 (100) | 181 ± 11 (101) | 169 ± 8 ^d (94) |
| | Day 17 | 190 ± 12 | 190 ± 7 (100) | 191 ± 13 (101) | 178 ± 8 (94) |
| | Day 21 | 199 ± 13 | 200 ± 9 (101) | 202 ± 14 (102) | 189 ± 9 (95) |
| | Day 24 | 206 ± 15 | 203 ± 9 (99) | 208 ± 15 (101) | 195 ± 10 (95) |
| | Day 28 | 215 ± 16 | 213 ± 9 (99) | 217 ± 18 (101) | 205 ± 10 (95) |
| | Gain 1–28 | 81 ± 14 | 79 ± 6 (98) | 82 ± 15 (101) | 72 ± 10 (89) |
| Survival ^c | 12/12 (100) | 6/6 (100) | 6/6 (100) | 12/12 (100) | |
| Females—recovery period | | | | | |
| Body weight ^b (g) | Day 28 | 214 ± 23 | NE | NE | 207 ± 13 (97) |
| | Day 31 | 219 ± 25 | NE | NE | 222 ± 14 (101) |
| | Day 35 | 226 ± 26 | NE | NE | 233 ± 17 (103) |
| | Day 28 | 233 ± 32 | NE | NE | 239 ± 20 (103) |
| | Day 42 | 239 ± 34 | NE | NE | 246 ± 22 (103) |
| | Gain 28–42 | 25 ± 12 | NE | NE | 40 ± 11 (160) |
| Survival ^c | 12/12 (100) | NE | NE | 12/12 (100) | |

^aMinistry of Health and Welfare Japan (1996a).

^bWeights expressed as mean ± SD (% of control).

^cSurvival expressed as number surviving/total number (% survival).

^dSignificantly different from control ($p = 0.05$); test was not reported.

^eSignificantly different from control ($p = 0.01$); test was not reported.

NE = not examined.

Table B.7. Mean Food Consumption Data of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | | Exposure Group (mg/kg-d) | | | |
|-----------------------------------|--------|--------------------------|--------------|--------------|---------------------------|
| | | 0 | 60 | 200 | 700 |
| Males—treatment period | | | | | |
| No. of cages | | 12 | 6 | 6 | 12 |
| Food consumption ^b (g) | Week 1 | 25 ± 1 | 25 ± 3 (100) | 25 ± 2 (100) | 18 ± 3 ^c (72) |
| | Week 2 | 29 ± 3 | 29 ± 3 (100) | 29 ± 2 (100) | 24 ± 2 ^c (83) |
| | Week 3 | 30 ± 2 | 30 ± 2 (100) | 31 ± 1 (103) | 27 ± 2 ^c (90) |
| | Week 4 | 32 ± 4 | 32 ± 2 (100) | 33 ± 2 (103) | 30 ± 3 (94) |
| Males—recovery period | | | | | |
| No. of cages | | 6 | 0 | 0 | 6 |
| Food consumption (g) | Week 0 | 33 ± 5 | NE | NE | 30 ± 3 (91) |
| | Week 1 | 34 ± 4 | NE | NE | 34 ± 2 (100) |
| | Week 2 | 35 ± 5 | NE | NE | 35 ± 2 (100) |
| Females—treatment period | | | | | |
| No. of cages | | 12 | 6 | 6 | 12 |
| Food consumption (g) | Week 1 | 19 ± 1 | 19 ± 1 (100) | 19 ± 2 (100) | 12 ± 3 ^c (63) |
| | Week 2 | 19 ± 2 | 20 ± 1 (105) | 20 ± 2 (105) | 19 ± 1 (100) |
| | Week 3 | 21 ± 2 | 21 ± 2 (100) | 22 ± 3 (105) | 20 ± 1 (95) |
| | Week 4 | 21 ± 2 | 19 ± 2 (90) | 21 ± 3 (100) | 21 ± 2 (100) |
| Females—recovery period | | | | | |
| No. of cages | | 6 | 0 | 0 | 6 |
| Food consumption (g) | Week 0 | 21 ± 2 | NE | NE | 21 ± 2 (100) |
| | Week 1 | 21 ± 2 | NE | NE | 26 ± 1 ^c (124) |
| | Week 2 | 22 ± 4 | NE | NE | 23 ± 3 (105) |

^aMinistry of Health and Welfare Japan (1996a).

^bFood consumption expressed as mean ± SD (% of control).

^cSignificantly different from control ($p = 0.01$); test was not reported.

NE = not examined.

| Table B.8. Incidences of Clinical Signs in Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days^a | | | | |
|---|---------------------------------|-----------|------------|------------|
| Weight | Exposure Group (mg/kg-d) | | | |
| | 0 | 60 | 200 | 700 |
| Treatment period | | | | |
| No. of animals | 12 | 6 | 6 | 12 |
| Decreased locomotor activity ^b | 0 | 0 | 0 | 3 |
| Recovery period | | | | |
| No. of animals | 6 | 0 | 0 | 6 |
| Decreased locomotor activity | 0 | NE | NE | 0 |

^aMinistry of Health and Welfare Japan (1996a).

^bParameter expressed as number of animals affected.

NE = not examined.

Table B.9. Selected Hematological Parameters of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | Exposure Group (mg/kg-d) | | | |
|--|--------------------------|------------------------------|------------------------------|------------------------------|
| | 0 | 60 | 200 | 700 |
| Males—after treatment | | | | |
| No. of animals | 12 | 6 | 6 | 12 |
| RBCs ($10^4/\mu\text{L}$) ^b | 765 ± 32 | 763 ± 43 (100) | 763 ± 29 (100) | 772 ± 22 (101) |
| MCV (fL) | 59 ± 3 | 60 ± 3 (102) | 59 ± 2 (100) | 61 ± 2 (103) |
| MCHC (%) | 34.6 ± 0.8 | 33.8 ± 0.4 ^c (98) | 33.5 ± 0.2 ^d (97) | 33.6 ± 0.4 ^d (97) |
| WBCs ($10^2/\mu\text{L}$) | 60 ± 16 | 58 ± 19 (97) | 58 ± 13 (97) | 64 ± 7 (107) |
| Males—after recovery period | | | | |
| No. of animals | 6 | 0 | 0 | 6 |
| RBCs ($10^4/\mu\text{L}$) | 784 ± 58 | NE | NE | 800 ± 49 (102) |
| MCV (fL) | 58 ± 2 | NE | NE | 58 ± 2 (100) |
| MCHC (%) | 34.3 ± 0.5 | NE | NE | 34.5 ± 0.8 (101) |
| WBCs ($10^2/\mu\text{L}$) | 76 ± 19 | NE | NE | 104 ± 22 ^c (137) |
| Females—after treatment | | | | |
| No. of animals | 12 | 6 | 6 | 12 |
| RBCs ($10^4/\mu\text{L}$) | 773 ± 21 | 778 ± 32 (101) | 752 ± 23 (97) | 778 ± 42 (101) |
| MCV (fL) | 57 ± 2 | 57 ± 2 (100) | 57 ± 1 (100) | 58 ± 1 (102) |
| MCHC (%) | 34.4 ± 0.4 | 34.9 ± 0.4 (101) | 34.4 ± 0.7 (100) | 33.9 ± 0.6 (99) |
| WBCs ($10^2/\mu\text{L}$) | 49 ± 12 | 41 ± 12 (84) | 38 ± 12 (78) | 36 ± 15 (73) |
| Females—after recovery period | | | | |
| No. of animals | 6 | 0 | 0 | 6 |
| RBCs ($10^4/\mu\text{L}$) | 817 ± 16 | NE | NE | 781 ± 21 ^d (96) |
| MCV (fL) | 55 ± 1 | NE | NE | 57 ± 1 ^d (104) |
| MCHC (%) | 34.6 ± 0.7 | NE | NE | 34.5 ± 0.3 (100) |
| WBCs ($10^2/\mu\text{L}$) | 49 ± 14 | NE | NE | 69 ± 22 (141) |

^aMinistry of Health and Welfare Japan (1996a) .

^bParameters expressed as mean ± SD (% of control).

^cSignificantly different from control ($p = 0.05$); test was not reported.

^dSignificantly different from control ($p = 0.01$); test was not reported.

RBCs = red blood cells; MCV = mean corpuscular volume; MCHC = mean cell hemoglobin concentration; WBCs = white blood cells; NE = not examined.

Table B.10. Selected Clinical Chemistry Parameters of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | Exposure Group (mg/kg-d) | | | |
|---|--------------------------|-------------------|-------------------------------|--------------------------------|
| | 0 | 60 | 200 | 700 |
| Males—after treatment | | | | |
| No. of animals | 6 | 6 | 6 | 6 |
| Alanine aminotransferase (ALT; IU/L) ^b | 28 ± 5 | 28 ± 6 (100) | 27 ± 3 (96) | 33 ± 5 ^c (118) |
| Total protein (g/dL) | 6.33 ± 0.22 | 6.12 ± 0.12 (97) | 6.07 ± 0.13 ^c (96) | 6.35 ± 0.13 (100) |
| Thromboglobulin (mg/dL) | 80 ± 25 | 71 ± 13 (89) | 86 ± 17 (108) | 110 ± 32 (138) |
| Glucose (mg/dL) | 134 ± 11 | 142 ± 24 (106) | 138 ± 9 (103) | 130 ± 18 (97) |
| Total bilirubin (mg/dL) | 0.35 ± 0.05 | 0.35 ± 0.05 (100) | 0.40 ± 0.05 (114) | 0.45 ± 0.03 ^d (129) |
| ChE (IU/L) | 25 ± 9 | 20 ± 6 (80) | 26 ± 4 (104) | 40 ± 12 ^c (160) |
| Cl (mEq/L) | 104 ± 0 | 104 ± 1 (100) | 104 ± 1 (100) | 102 ± 1 ^d (98) |
| Creatinine (mg/dL) | 0.51 ± 0.07 | 0.47 ± 0.06 (92) | 0.50 ± 0.05 (98) | 0.49 ± 0.04 (96) |
| Males—after recovery period | | | | |
| No. of animals | 6 | 0 | 0 | 6 |
| Alanine aminotransferase (ALT; IU/L) | 31 ± 6 | NE | NE | 36 ± 9 (116) |
| Total protein (g/dL) | 6.29 ± 0.34 | NE | NE | 6.09 ± 0.14 (97) |
| Thromboglobulin (mg/dL) | 90 ± 32 | NE | NE | 63 ± 16 (70) |
| Glucose (mg/dL) | 157 ± 12 | NE | NE | 143 ± 8 ^c (91) |
| Total bilirubin (mg/dL) | 0.28 ± 0.02 | NE | NE | 0.30 ± 0.05 (107) |
| ChE (IU/L) | 51 ± 22 | NE | NE | 45 ± 23 (88) |
| Cl (mEq/L) | 103 ± 2 | NE | NE | 103 ± 1 (100) |
| Creatinine (mg/dL) | 0.63 ± 0.03 | NE | NE | 0.57 ± 0.04 ^c (90) |
| Females—after treatment | | | | |
| No. of animals | 6 | 6 | 6 | 6 |
| Alanine aminotransferase (ALT; IU/L) | 24 ± 5 | 24 ± 4 (100) | 23 ± 4 (96) | 35 ± 6 ^d (146) |
| Total protein (g/dL) | 6.26 ± 0.36 | 6.49 ± 0.26 (104) | 6.41 ± 0.16 (102) | 6.36 ± 0.15 (102) |
| Thromboglobulin (mg/dL) | 26 ± 4 | 38 ± 12 (146) | 44 ± 12 ^d (169) | 32 ± 12 (123) |
| Glucose (mg/dL) | 130 ± 15 | 117 ± 13 (90) | 124 ± 10 (95) | 110 ± 4 ^c (85) |
| Total bilirubin (mg/dL) | 0.21 ± 0.01 | 0.22 ± 0.02 (105) | 0.22 ± 0.2 (105) | 0.24 ± 0.03 (114) |
| ChE (IU/L) | 304 ± 175 | 296 ± 106 (97) | 281 ± 60 (92) | 294 ± 41 (97) |
| Cl (mEq/L) | 106 ± 1 | 106 ± 1 (100) | 106 ± 2 (100) | 106 ± 1 (100) |
| Creatinine (mg/dL) | 0.54 ± 0.05 | 0.55 ± 0.04 (102) | 0.53 ± 0.02 (98) | 0.53 ± 0.04 (98) |

Table B.10. Selected Clinical Chemistry Parameters of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | Exposure Group (mg/kg-d) | | | |
|--------------------------------------|--------------------------|----|-----|-------------------|
| | 0 | 60 | 200 | 700 |
| Females—after recovery period | | | | |
| No. of animals | 6 | 0 | 0 | 6 |
| Alanine aminotransferase (ALT; IU/L) | 27 ± 6 | NE | NE | 29 ± 6 (107) |
| Total protein (g/dL) | 6.60 ± 0.29 | NE | NE | 6.62 ± 0.12 (100) |
| Thromboglobulin (mg/dL) | 46 ± 15 | NE | NE | 61 ± 19 (133) |
| Glucose (mg/dL) | 139 ± 13 | NE | NE | 125 ± 10 (90) |
| Total bilirubin (mg/dL) | 0.29 ± 0.05 | NE | NE | 0.28 ± 0.02 (97) |
| ChE (IU/L) | 292 ± 89 | NE | NE | 263 ± 47 (90) |
| Cl (mEq/L) | 105 ± 2 | NE | NE | 105 ± 1 (100) |
| Creatinine (mg/dL) | 0.65 ± 0.10 | NE | NE | 0.61 ± 0.05 (94) |

^aMinistry of Health and Welfare Japan (1996a).

^bParameters expressed as mean ± SD (% of control).

^cSignificantly different from control ($p = 0.05$); test was not reported.

^dSignificantly different from control ($p = 0.01$); test was not reported.

ChE = cholinesterase, Cl = chlorine, NE = not examined.

Table B.11. Selected Organ Weights of Male and Female Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | | Exposure Group (mg/kg-d) | | | |
|------------------------------------|-------------|--------------------------|-------------------|-------------------|--------------------------------|
| | | 0 | 60 | 200 | 700 |
| Males—after treatment | | | | | |
| No. of animals | | 6 | 6 | 6 | 6 |
| Weight ^b | Abs. spleen | 0.68 ± 0.05 | 0.62 ± 0.07 (91) | 0.62 ± 0.02 (91) | 0.58 ± 0.10 (85) |
| | Rel. spleen | 0.21 ± 0.02 | 0.20 ± 0.02 (95) | 0.20 ± 0.01 (95) | 0.20 ± 0.03 (95) |
| | Abs. liver | 9.77 ± 0.72 | 9.70 ± 0.88 (99) | 9.76 ± 0.37 (100) | 9.23 ± 0.65 (94) |
| | Rel. liver | 3.04 ± 0.22 | 3.05 ± 0.15 (100) | 3.11 ± 0.10 (102) | 3.22 ± 0.15 (106) |
| | Abs. brain | 1.99 ± 0.10 | 2.03 ± 0.07 (102) | 2.00 ± 0.08 (101) | 1.95 ± 0.04 (98) |
| | Rel. brain | 0.62 ± 0.03 | 0.64 ± 0.03 (103) | 0.64 ± 0.03 (103) | 0.68 ± 0.05 ^c (110) |
| | Abs. kidney | 2.47 ± 0.22 | 2.53 ± 0.14 (102) | 2.48 ± 0.11 (100) | 2.70 ± 0.30 (109) |
| | Rel. kidney | 0.77 ± 0.04 | 0.80 ± 0.05 (104) | 0.79 ± 0.05 (103) | 0.94 ± 0.06 ^d (122) |
| | Abs. heart | 1.10 ± 0.11 | 1.11 ± 0.13 (101) | 1.09 ± 0.05 (99) | 1.10 ± 0.09 (100) |
| | Rel. heart | 0.34 ± 0.03 | 0.35 ± 0.03 (103) | 0.35 ± 0.01 (103) | 0.39 ± 0.03 ^d (115) |
| Males—after recovery period | | | | | |
| No. of animals | | 6 | 0 | 0 | 6 |
| Weight | Abs. spleen | 0.77 ± 0.15 | NE | NE | 0.68 ± 0.09 (88) |
| | Rel. spleen | 0.19 ± 0.03 | NE | NE | 0.18 ± 0.02 (95) |
| | Abs. liver | 11.98 ± 1.62 | NE | NE | 10.56 ± 0.49 (88) |
| | Rel. liver | 2.96 ± 0.23 | NE | NE | 2.86 ± 0.11 (97) |
| | Abs. brain | 2.08 ± 0.09 | NE | NE | 2.00 ± 0.06 (96) |
| | Rel. brain | 0.52 ± 0.04 | NE | NE | 0.54 ± 0.04 (104) |
| | Abs. kidney | 2.69 ± 0.21 | NE | NE | 2.60 ± 0.27 (97) |
| | Rel. kidney | 0.67 ± 0.05 | NE | NE | 0.71 ± 0.08 (106) |
| | Abs. heart | 1.28 ± 0.12 | NE | NE | 1.25 ± 0.11 (98) |
| | Rel. heart | 0.32 ± 0.02 | NE | NE | 0.34 ± 0.03 (106) |

Table B.11. Selected Organ Weights of Male and Female Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | | Exposure Group (mg/kg-d) | | | |
|--------------------------------------|-------------|--------------------------|-------------------|-------------------|--------------------------------|
| | | 0 | 60 | 200 | 700 |
| Females—after treatment | | | | | |
| Sample size | | 6 | 6 | 6 | 6 |
| Weight | Abs. spleen | 0.48 ± 0.06 | 0.43 ± 0.05 (90) | 0.44 ± 0.08 (92) | 0.37 ± 0.03 ^c (77) |
| | Rel. spleen | 0.24 ± 0.03 | 0.22 ± 0.03 (92) | 0.23 ± 0.05 (96) | 0.20 ± 0.01 (83) |
| | Abs. liver | 5.95 ± 0.32 | 5.81 ± 0.31 (98) | 6.29 ± 0.96 (106) | 5.64 ± 0.38 (95) |
| | Rel. liver | 3.00 ± 0.18 | 2.97 ± 0.08 (99) | 3.19 ± 0.27 (106) | 3.01 ± 0.15 (100) |
| | Abs. brain | 1.82 ± 0.05 | 1.87 ± 0.04 (103) | 1.83 ± 0.03 (101) | 1.81 ± 0.05 (99) |
| | Rel. brain | 0.92 ± 0.05 | 0.96 ± 0.06 (104) | 0.94 ± 0.07 (102) | 0.97 ± 0.05 (105) |
| | Abs. kidney | 1.61 ± 0.11 | 1.58 ± 0.12 (98) | 1.63 ± 0.12 (101) | 1.60 ± 0.13 (99) |
| | Rel. kidney | 0.82 ± 0.07 | 0.81 ± 0.07 (99) | 0.83 ± 0.03 (101) | 0.85 ± 0.07 (104) |
| | Abs. heart | 0.77 ± 0.03 | 0.74 ± 0.04 (96) | 0.76 ± 0.07 (99) | 0.73 ± 0.06 (95) |
| | Rel. heart | 0.39 ± 0.02 | 0.38 ± 0.03 (97) | 0.39 ± 0.02 (100) | 0.39 ± 0.02 (100) |
| Females—after recovery period | | | | | |
| Sample size | | 6 | 0 | 0 | 6 |
| Weight | Abs. spleen | 0.44 ± 0.06 | NE | NE | 0.53 ± 0.05 ^c (120) |
| | Rel. spleen | 0.20 ± 0.02 | NE | NE | 0.24 ± 0.02 ^c (120) |
| | Abs. liver | 6.00 ± 0.84 | NE | NE | 6.69 ± 0.60 (112) |
| | Rel. liver | 2.74 ± 0.15 | NE | NE | 2.98 ± 0.09 ^d (109) |
| | Abs. brain | 1.84 ± 0.09 | NE | NE | 1.85 ± 0.05 (101) |
| | Rel. brain | 0.85 ± 0.08 | NE | NE | 0.83 ± 0.06 (98) |
| | Abs. kidney | 1.58 ± 0.23 | NE | NE | 1.58 ± 0.08 (100) |
| | Rel. kidney | 0.72 ± 0.05 | NE | NE | 0.71 ± 0.04 (99) |
| | Abs. heart | 0.79 ± 0.09 | NE | NE | 0.84 ± 0.06 (106) |
| | Rel. heart | 0.36 ± 0.02 | NE | NE | 0.38 ± 0.03 (106) |

^aMinistry of Health and Welfare Japan (1996a).

^bAbsolute weights expressed as mean ± SD (% of control); relative weights expressed as percentage of body weight.

^cSignificantly different from control ($p = 0.05$); test was not reported.

^dSignificantly different from control ($p = 0.01$); test was not reported.

NE = not examined.

Table B.12. Incidence of Selected Histopathological Findings in the Kidneys of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | Grade ^b | Exposure Group (mg/kg-d) | | | |
|--|--------------------|--------------------------|----|----------------|----------------|
| | | 0 | 60 | 200 | 700 |
| Males—after treatment | | | | | |
| No. of animals | | 6 | 6 | 6 | 6 |
| Hyaline droplets in prox. tubule epithelium | + | 1 | 0 | 5 | 1 |
| | ++ | 0 | 0 | 1 | 4 |
| | +++ | 0 | 0 | 0 | 1 |
| Total incidence | | 1 | 0 | 6 ^d | 6 ^d |
| Eosinophilic bodies in proximal tubule | + | 0 | 0 | 5 ^d | 4 ^c |
| Tubular basophilic change | + | 2 | 1 | 2 | 5 |
| Focul tubular dilatation with or without hyaline casts | + | 1 | 1 | 0 | 0 |
| Distal tubular dilatation | + | 0 | 0 | 1 | 1 |
| Males—after recovery period | | | | | |
| No. of animals | | 6 | 0 | 0 | 6 |
| Hyaline droplets in prox. tubule epithelium | + | 1 | NE | NE | 3 |
| | ++ | 0 | NE | NE | 0 |
| | +++ | 0 | NE | NE | 0 |
| Total incidence | | 1 | NE | NE | 3 |
| Eosinophilic bodies in proximal tubule | + | 1 | NE | NE | 0 |
| Tubular basophilic change | + | 4 | NE | NE | 5 |
| Focul tubular dilatation with or without hyaline casts | + | 0 | NE | NE | 0 |
| Distal tubular dilatation | + | 0 | NE | NE | 0 |
| Females—after treatment | | | | | |
| No. of animals | | 6 | 6 | 6 | 6 |
| Tubular basophilic change | + | 2 | NE | NE | 1 |
| Fibrotic focus | + | 0 | NE | NE | 1 |

Table B.12. Incidence of Selected Histopathological Findings in the Kidneys of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days^a

| Parameter | Grade ^b | Exposure Group (mg/kg-d) | | | |
|-------------------------------|--------------------|--------------------------|----|-----|-----|
| | | 0 | 60 | 200 | 700 |
| Females—after recovery | | | | | |
| No. of animals | + | 6 | NE | NE | 6 |
| Tubular basophilic change | + | NE | NE | NE | NE |
| Fibrotic focus | + | NE | NE | NE | NE |

^aMinistry of Health and Welfare Japan (1996a).

^bSeverity grades: + = slight, ++ = moderate, +++ = marked.

^cSignificantly different from control ($p = 0.05$); test was not reported.

^dSignificantly different from control ($p = 0.01$); test was not reported.

NE = not examined.

Table B.13. Clinical Chemistry and Pathology Data of Guinea Pigs Orally Exposed to Sulfolane for 3 or 6 Months^a

| Parameter | Exposure Group (mg/kg-d) | | | | |
|--|--------------------------|------|-------|-------|-------|
| | 0 | 0.25 | 2.5 | 25 | 250 |
| At 3 months | | | | | |
| ALT (IU/100mL) ^b | 59.4 | ND | ND | 40.8 | 45.8 |
| AST (IU/100mL) | 106 | ND | ND | ND | 71 |
| Marrow cell count ($\times 10^4/\text{mm}^3$) | 16.43 | ND | 10.99 | 12.25 | 10.56 |
| Spleen—dispersion of white pulp ^c | 0/14 | 0/14 | 1/14 | 2/14 | 6/14 |
| At 6 months | | | | | |
| Spleen—dispersion of white pulp ^c | 0/25 | 0/22 | 2/26 | 2/25 | 7/22 |
| Liver fatty degeneration ^c | 0/25 | 0/22 | 2/26 | 4/25 | 7/22 |
| Liver-significant fatty degeneration ^d | 0/25 | 0/22 | 1/26 | 2/25 | 5/22 |

^aZhu et al. (1987c).

^bData are assumed to be group mean. No standard deviation or standard error was provided.

^cData are provided as incidence (No. of animals with effect/No. of animals in test group).

^dMore severe fatty degeneration than noted in the line above.

ND = no data

Table B.14. Mean Body Weight and Survival of Male and Female Rats After Oral Exposure to Sulfolane for 41–50 Days^a

| Parameter | | Exposure Group (mg/kg-d) | | | |
|--------------------------------------|--------------|--------------------------|-----------------------------|-----------------------------------|--------------------------------|
| | | 0 | 60 | 200 | 700 |
| Male | | | | | |
| Sample size | | 12 | 12 | 12 | 12 (Days 1–4; 11 thereafter) |
| Weight ^b (g) | Day 1 | 367.2 ± 6.7 | 366.6 ± 5.8 (100) | 367.1 ± 6.2 (100) | 366.8 ± 5.5 (100) |
| | Day 4 | 382.0 ± 10.5 | 379.7 ± 7.0 (99) | 372.3 ± 8.9 ^d (97) | 322.5 ± 9.8 ^c (84) |
| | Day 8 | 393.5 ± 11.7 | 391.8 ± 8.4 (100) | 386.5 ± 10.1 (98) | 322.0 ± 18.6 ^c (82) |
| | Day 11 | 403.5 ± 14.1 | 403.0 ± 13.0 (100) | 399.6 ± 13.1 (99) | 341.6 ± 14.6 ^c (85) |
| | Day 15 | 419.3 ± 15.7 | 416.8 ± 16.6 (99) | 417.5 ± 14.1 (100) | 370.5 ± 14.1 ^c (88) |
| | Day 18 | 428.3 ± 16.9 | 427.3 ± 16.4 (100) | 420.5 ± 11.5 (98) | 373.1 ± 14.6 ^c (87) |
| | Day 22 | 445.9 ± 15.4 | 442.4 ± 16.1 (99) | 439.0 ± 12.9 (98) | 399.7 ± 18.2 ^c (90) |
| | Day 25 | 452.3 ± 18.2 | 453.2 ± 17.7 (100) | 450.2 ± 13.6 (100) | 411.7 ± 21.8 ^c (91) |
| | Day 29 | 469.9 ± 19.7 | 473.3 ± 23.7 (101) | 467.5 ± 13.6 (99) | 426.8 ± 20.6 ^c (91) |
| | Day 32 | 474.5 ± 21.0 | 474.5 ± 22.2 (100) | 473.2 ± 15.1 (100) | 432.9 ± 21.1 ^c (91) |
| | Day 36 | 479.8 ± 23.3 | 479.0 ± 20.6 (100) | 479.6 ± 15.4 (100) | 436.4 ± 20.4 ^c (91) |
| | Day 39 | 486.4 ± 23.7 | 485.7 ± 24.9 (100) | 485.9 ± 14.3 (100) | 440.1 ± 20.1 ^c (90) |
| | Day 43 | 493.1 ± 25.6 | 492.2 ± 26.7 (100) | 494.2 ± 12.1 (100) | 442.8 ± 19.7 ^c (90) |
| | Day 46 | 495.9 ± 24.2 | 496.5 ± 27.1 (100) | 496.7 ± 13.9 (100) | 448.2 ± 17.8 ^c (90) |
| Day 49 | 500.9 ± 25.6 | 503.3 ± 25.8 (100) | 501.7 ± 13.2 (100) | 449.4 ± 21.9 ^c (90) | |
| Survival ^c | | 12/12 | 12/12 | 12/12 | 11/12 |
| Female | | | | | |
| Sample size (except where indicated) | | 12 | 12 | 12 | 12 |
| Weight (g) | Day 1 | 218.3 ± 6.5 | 218.3 ± 6.1 (100) | 218.8 ± 6.0 (100) | 218.6 ± 5.8 (100) |
| | Day 4 | 218.4 ± 6.5 | 216.1 ± 7.9 (99) | 213.3 ± 6.8 (98) | 195.1 ± 6.6 ^c (89) |
| | Day 8 | 224.2 ± 9.0 | 219.8 ± 7.1 (98) | 217.9 ± 7.4 (97) | 201.3 ± 6.8 ^c (90) |
| | Day 11 | 229.4 ± 6.5 | 225.1 ± 8.6 (98) | 222.8 ± 7.9 (97) | 216.3 ± 9.1 ^c (94) |
| | Day 15 | 234.3 ± 7.9 | 231.0 ± 10.9 (99) | 230.7 ± 8.7 (98) | 226.7 ± 11.2 (97) |
| | Day 18 | 250.0 (<i>n</i> = 2) | 253.5 (<i>n</i> = 2) (101) | 243.3 ± 11.7 (<i>n</i> = 4) (97) | 258.0 (<i>n</i> = 5) (103) |
| | Day 22 | NR | NR | NR | 258.0 (<i>n</i> = 2) |
| | Day 25 | NR | NR | NR | 272.5 (<i>n</i> = 2) |
| | Day 29 | NR | NR | NR | 270.0 (<i>n</i> = 1) |

Table B.14. Mean Body Weight and Survival of Male and Female Rats After Oral Exposure to Sulfolane for 41–50 Days^a

| Parameter | | Exposure Group (mg/kg-d) | | | |
|--|--------|--------------------------|-------------------|-------------------|------------------------------|
| | | 0 | 60 | 200 | 700 |
| Pregnancy and Lactation Weights | | | | | |
| Sample size | | 11 | 12 | 10 | 10 |
| Pregnancy | Day 0 | 240.4 ± 9.9 | 236.8 ± 11.9 (99) | 236.9 ± 8.9 (99) | 235.5 ± 23.1 (98) |
| | Day 7 | 272.8 ± 8.1 | 269.2 ± 14.0 (99) | 267.8 ± 9.7 (98) | 262.8 ± 16.0 (96) |
| | Day 14 | 305.9 ± 11.6 | 300.3 ± 16.1 (98) | 295.0 ± 12.2 (96) | 291.9 ± 15.1 (95) |
| | Day 21 | 388.8 ± 18.0 | 383.1 ± 22.1 (99) | 375.5 ± 14.4 (97) | 369.1 ± 29.8 (95) |
| Lactation | Day 0 | 274.1 ± 14.3 | 269.9 ± 17.7 (98) | 265.0 ± 9.2 (97) | 269.4 ± 8.9 (98) |
| | Day 4 | 292.9 ± 17.2 | 290.3 ± 19.2 (99) | 284.3 ± 16.5 (97) | 272.2 ± 12.7 (n = 5) (93) |
| Survival | | 12/12 | 12/12 | 12/12 | 11/12 |

^aMinistry of Health and Welfare Japan (1999).

^bWeights expressed as mean ± SD (% of control).

^cSurvival expressed as number surviving/total number (% survival); % is calculated.

^dSignificantly different from control ($p < 0.05$); test was not reported.

^eSignificantly different from control ($p < 0.01$); test was not reported.

NR = not reported.

Table B.15. Food Consumption of Male and Female Rats During Oral Exposure to Sulfolane for 41–50 Days^a

| Parameter | Exposure Group (mg/kg-d) | | | | |
|---|--------------------------|------------|-------------------------------|------------------------------|------------------------------|
| | 0 | 60 | 200 | 700 | |
| Male | | | | | |
| No. of animals | 12 | 12 | 12 | 12 (Days 1–4; 11 thereafter) | |
| Consumption ^b (g/day) | Day 3 | 26.9 ± 1.9 | 27.1 ± 1.3 (101) | 24.0 ± 2.3 ^d (89) | 13.1 ± 2.8 ^d (49) |
| | Day 6 | 27.6 ± 1.8 | 28.9 ± 1.7 (105) | 26.9 ± 1.4 (97) | 12.4 ± 4.9 ^d (45) |
| | Day 10 | 27.6 ± 2.2 | 28.9 ± 2.3 (105) | 28.1 ± 2.0 (102) | 28.1 ± 2.2 (102) |
| | Day 13 | 27.7 ± 1.6 | 28.1 ± 1.4 (101) | 28.0 ± 2.0 (101) | 27.2 ± 1.9 (98) |
| | Day 31 | 25.2 ± 1.6 | 25.7 ± 1.8 (102) | 26.1 ± 1.4 (104) | 26.3 ± 2.5 (104) |
| | Day 34 | 25.5 ± 1.5 | 26.7 ± 2.7 (105) | 26.8 ± 1.8 (105) | 26.4 ± 2.2 (104) |
| | Day 38 | 25.3 ± 1.1 | 26.2 ± 2.4 (104) | 25.5 ± 2.0 (101) | 26.0 ± 1.8 (103) |
| | Day 41 | 25.5 ± 1.2 | 26.7 ± 3.5 (105) | 25.6 ± 2.0 (100) | 24.9 ± 2.1 (98) |
| | Day 45 | 25.3 ± 3.2 | 27.6 ± 3.1 (109) | 25.3 ± 2.2 (100) | 24.8 ± 2.4 (98) |
| | Day 48 | 24.5 ± 1.6 | 27.4 ± 3.1 ^c (112) | 23.6 ± 2.1 (96) | 24.0 ± 3.1 (98) |
| Female | | | | | |
| No. of animals (except where indicated) | 12 | 12 | 12 | 12 | |
| Consumption ^b (g/day) | Day 3 | 16.3 ± 1.7 | 15.0 ± 2.0 (92) | 14.7 ± 1.7 (90) | 9.1 ± 1.1 ^d (56) |
| | Day 6 | 18.0 ± 1.4 | 17.5 ± 2.2 (97) | 17.4 ± 2.0 (97) | 10.4 ± 2.4 ^d (58) |
| | Day 10 | 18.8 ± 1.4 | 18.7 ± 2.2 (99) | 19.0 ± 2.6 (101) | 20.7 ± 1.7 (110) |
| | Day 13 | 17.9 ± 2.3 | 17.8 ± 2.3 (99) | 18.6 ± 2.1 (104) | 19.5 ± 3.3 (109) |
| Pregnancy and Lactation | | | | | |
| No. of animals | 11 | 12 | 10 | 10 | |
| Pregnancy | Day 2 | 21.0 ± 1.7 | 20.9 ± 3.1 (100) | 21.0 ± 2.1 (100) | 18.7 ± 2.2 (89) |
| | Day 9 | 23.0 ± 1.8 | 22.9 ± 1.8 (100) | 22.9 ± 2.0 (100) | 21.2 ± 1.1 (92) |
| | Day 16 | 22.5 ± 0.9 | 22.3 ± 2.3 (99) | 21.4 ± 1.7 (95) | 22.6 ± 2.2 (100) |
| | Day 21 | 20.2 ± 2.6 | 19.4 ± 2.2 (96) | 20.3 ± 1.4 (100) | 21.5 ± 2.7 (106) |
| Lactation | Day 4 | 30.3 ± 5.1 | 30.2 ± 4.1 (100) | 29.8 ± 4.9 (98) | 18.4 ± 9.8 ^d (61) |

^aMinistry of Health and Welfare Japan (1999).

^bConsumption expressed as mean g/day ± SD (% of control).

^cSignificantly different from control ($p < 0.05$); test was not reported.

^dSignificantly different from control ($p < 0.01$); test was not reported.

Table B.16. Ovary Weight of Female Rats After Oral Exposure to Sulfolane for 41–50 Days^a

| Weight | Exposure Group (mg/kg-d) | | | |
|------------------------------------|--------------------------|---------------------|---------------------|---------------------------------|
| | 0 | 60 | 200 | 700 |
| Sample size | 12 | 12 | 12 | 12 |
| Final Body Weight ^b (g) | 289.0 ± 21.3 | 290.3 ± 19.2 (100) | 284.0 ± 15.0 (98) | 268.3 ± 14.2 ^c (93) |
| Ovaries (mg) | 94.79 ± 11.71 | 95.51 ± 11.57 (101) | 98.39 ± 10.42 (104) | 108.63 ± 17.99 (115) |
| Ovaries (mg %) | 32.90 ± 4.36 | 33.04 ± 4.62 (100) | 34.66 ± 3.33 (105) | 40.45 ± 5.92 ^d (123) |

^aMinistry of Health and Welfare Japan (1999).

^bWeights expressed as mean ± SD (% of control).

^cSignificantly different from control ($p < 0.05$); test was not reported.

^dSignificantly different from control ($p < 0.01$); test was not reported.

Table B.17. Selected Reproductive Parameters of Female Rats After Oral Exposure to Sulfolane for 41–50 Days^a

| Parameter | Exposure Group (mg/kg-d) | | | |
|---|--------------------------|----------------|----------------|-----------------------------|
| | 0 | 60 | 200 | 700 |
| Number of females | 12 | 12 | 12 | 12 |
| Number of estrous cases before mating (14 d) ^b | 3.5 ± 0.5 | 3.3 ± 0.5 (94) | 3.2 ± 0.4 (91) | 2.2 ± 0.9 ^c (63) |
| Number of pregnant females | 11 | 12 | 10 | 10 |
| Fertility index ^c | 91.7 | 100.0 | 83.3 | 90.9 |
| Number of pregnant females with live pups | 11 | 12 | 10 | 10 |
| Number of males | 12 | 12 | 12 | 11 |
| Number of males with successful copulation | 12 | 12 | 12 | 10 |
| Copulation index ^d | 100.0 | 100.0 | 100.0 | 91.7 |

^aMinistry of Health and Welfare Japan (1999).

^bPresented as mean ± SD (% of control).

^cExpress as %; calculated using the equation: (number of females with successful copulation/number of females) × 100.

^dExpressed as %; calculated using the equation: (number of males with successful copulation/number of males) × 100.

^eSignificantly different from control ($p < 0.01$); test was not reported.

Table B.18. Selected Pup Observations of Female Rats Exposed to Sulfolane for 41–50 Days^a

| Parameter | Exposure Group (mg/kg-d) | | | |
|-------------------------------|--------------------------|-------------------|------------------------------|-------------------------------|
| | 0 | 60 | 200 | 700 |
| Number of dams | 11 | 12 | 10 | 10 |
| Birth index ^b | 96.3 ± 6.5 | 95.8 ± 4.8 (99) | 90.5 ± 5.1 ^f (94) | 71.6 ± 26.2 ^g (74) |
| Dead pups on Lactation Day 0 | 0.3 ± 0.5 | 0.2 ± 0.4 (67) | 0.2 ± 0.4 (67) | 3.6 ± 4.4 ^g (1200) |
| Delivery index ^c | 98.1 ± 4.5 | 96.9 ± 4.0 (99) | 91.8 ± 4.1 ^f (94) | 94.0 ± 6.7 (96) |
| Live birth index ^d | 98.1 ± 3.3 | 98.8 ± 2.8 (101) | 98.7 ± 2.8 (101) | 75.9 ± 26.2 ^g (77) |
| Live pups on Lactation Day 4 | 14.8 ± 1.8 | 15.0 ± 1.9 (101) | 13.7 ± 1.3 (93) | 4.0 ± 5.6 ^g (27) |
| Viability index ^e | 99.5 ± 1.8 | 100.0 ± 0.0 (101) | 97.3 ± 3.5 (98) | 29.2 ± 40.4 ^g (29) |

^aMinistry of Health and Welfare Japan (1999).

^b(Number of live pups born/number of implantation scars) × 100.

^c(Number of pups born/number of implantation scars) × 100 (%).

^d(Number of live pups born/number of pups born) × 100.

^e(Number of live pups on day 4/number of live pups born) × 100.

^fSignificantly different from control ($p < 0.05$); test was not reported.

^gSignificantly different from control ($p < 0.01$); test was not reported.

Table B.19. Body Weights of Pups Born to Female Rats Exposed to Sulfolane for 41–50 Days^a

| Parameter | Exposure Group (mg/kg-day) | | | | |
|---|----------------------------|----------------|---------------------|---------------------------------|---|
| | 0 | 60 | 200 | 700 | |
| Number of dams (except where indicated otherwise) | 11 | 12 | 10 | 10 | |
| Mean pup weight ^b | Lactational Day 0 | 6.41 ± 0.33 | 6.03 ± 0.35 (94) | 6.05 ± 0.35 (94) | 5.16 ± 0.51 ^d (80) |
| | Lactational Day 4 | 9.57 ± 0.81 | 9.41 ± 0.99 (98) | 9.43 ± 1.13 (99) | 5.96 ± 1.52 ^d ($n = 5$) (62) |
| Litter weight | Lactational Day 0 | 95.27 ± 11.58 | 89.83 ± 7.64 (94) | 85.11 ± 5.60 ^c (89) | 59.22 ± 27.00 ^d (62) |
| | Lactational Day 4 | 141.07 ± 16.51 | 139.77 ± 10.53 (99) | 128.00 ± 8.19 ^c (91) | 48.94 ± 46.11 ^d ($n = 5$) (35) |

^aMinistry of Health and Welfare Japan (1999).

^bWeights expressed as mean ± SD (% of control).

^cSignificantly different from control ($p < 0.05$); test was not reported.

^dSignificantly different from control ($p < 0.01$); test was not reported.

Table B.20. Hematological Parameters of Male and Female Hartley-Derived Guinea Pigs After Inhalation Exposure to Sulfolane for 27 Days^a

| Parameter ^c | | Exposure Group, mg/m ³ (Adjusted Daily Concentration, mg/m ³) ^b | |
|--|----------------------|---|------------|
| | | 0 ^d | 495 (120) |
| Number of animals ^c | | DNP | 15 |
| White blood cell count (10 ³ /mL) | Preexposure | ND | 5.9 ± 0.5 |
| | Postexposure (~30 d) | 5.8 ± 0.8 | 4.9 ± 0.3 |
| Hematocrit count (% by volume) | Preexposure | ND | 46 ± 0.4 |
| | Postexposure (~30 d) | 39 ± 4.8 | 48 ± 0.5 |
| Hemoglobin count (g/100 mL) | Preexposure | ND | 13.9 ± 0.1 |
| | Postexposure (~30 d) | 12.4 ± 1.5 | 15.2 ± 0.1 |

^aAndersen et al. (1977c).

^bConcentration is adjusted for continuous exposure 24 hours/day, 7 days/week.

^cValues expressed as mean ± SE (% of control); % is calculated; male and female data were not reported separately.

^dThough data for a “control” group is reported in Table 3 of the study, a control group is not mentioned in the methods explanation; it is unclear what this “control” group represents.

^eSample sizes reflect those at the origin of study; hematological data were taken from 9–15 subjects.

DNP = data not provided by study authors.

ND = not determined.

Table B.21. Hematological Parameters of Male and Female Hartley-Derived Guinea Pigs After Inhalation Exposure to Sulfolane for 85–110 Days^a

| Parameter ^c | | Exposure Group, mg/m ³ (Adjusted Daily Concentration, mg/m ³) ^b | | | | | |
|--|------------------------------|---|-----------|-----------|-----------|------------------|-----------------------------|
| | | 0 ^d | 2.8 (2.7) | 4.0 (3.8) | 20 (19.2) | 159 (152) | 200 (192) |
| Exposure duration (d) | | DNP | 90 | 110 | 95 | 85 | 90 |
| Number of animals ^e | | DNP | DNP | DNP | DNP | 15 | 15 |
| White blood cell count (10 ³ /mL) | Preexposure | ND | DNP | DNP | DNP | 6.8 ± 0.3 (NA) | 5.9 ± 0.6 (NA) |
| | Exposure Day 20 | ND | DNP | DNP | DNP | ND | 3.1 ± 0.4 (NA) ^g |
| | Exposure Day 30 | 5.8 ± 0.8 | DNP | DNP | DNP | 6.9 ± 0.2 (119) | 3.8 ± 0.4 (66) ^g |
| | Exposure Day 60 | 4.6 ± 0.8 | DNP | DNP | DNP | 6.7 ± 0.3 (146) | 5.2 ± 0.3 (113) |
| | Exposure Day 90 ^f | 6.2 ± 1.1 | DNP | DNP | DNP | 6.8 ± 0.3 (110) | 4.4 ± 0.2 ^g (71) |
| Hematocrit count (% by volume) | Preexposure | ND | DNP | DNP | DNP | 46 ± 0.3 (NA) | 44 ± 0.4 (NA) |
| | Exposure Day 20 | ND | DNP | DNP | DNP | ND | 49 ± 0.9 (NA) |
| | Exposure Day 30 | 39 ± 4.8 | DNP | DNP | DNP | 46 ± 0.3 (118) | 51 ± 0.4 (131) |
| | Exposure Day 60 | 46 ± 0.5 | DNP | DNP | DNP | 47 ± 0.3 (102) | 47 ± 0.6 (102) |
| | Exposure Day 90 | 46 ± 0.8 | DNP | DNP | DNP | 46 ± 6.3 (100) | 47 ± 1.1 (102) |
| Hemoglobin count (g/100 mL) | Preexposure | ND | DNP | DNP | DNP | 16.0 ± 0.1 (NA) | 14.4 ± 0.1 (NA) |
| | Exposure Day 20 | ND | DNP | DNP | DNP | ND | 14.9 ± 0.2 (NA) |
| | Exposure Day 30 | 12.4 ± 1.5 | DNP | DNP | DNP | 16.8 ± 0.1 (135) | 15.5 ± 0.2 (125) |
| | Exposure Day 60 | 14.6 ± 0.2 | DNP | DNP | DNP | 16.9 ± 0.1 (116) | 15.1 ± 0.1 (103) |
| | Exposure Day 90 | 14.8 ± 0.2 | DNP | DNP | DNP | 16.6 ± 0.1 (112) | 14.6 ± 0.2 (99) |

^aAndersen et al. (1977d).

^bConcentration is adjusted for continuous exposure 24 hours/day, 7 days/week.

^cValues expressed as mean ± SE (% of control); % is calculated; male and female data were not reported separately.

^dThough data for a “control” group are reported in Table 3 of the study, a control group is not mentioned in the methods explanation; it is unclear what this “control” group represents.

^eSample sizes reflect those at the origin of study; hematological data were taken from 9–15 subjects at each dose level.

^fExcept for the 159 mg/m³ exposure-level, which only lasted for a duration of 85 days; observations were made at 85 days for this group.

^gSignificantly different from control ($p < 0.05$); Student’s *t*-test.

DNP = data not provided by study authors.

ND = no data.

NA = not applicable.

APPENDIX C. BMD OUTPUTS

A benchmark dose (BMD) analysis of the male renal effects (hyaline droplet) was not attempted because the dose response was nonmonotonic, and statistical analysis performed for this review indicates that incidence of hyaline droplet in cortical tubules at the highest dose was not statistically significantly different from control by Fisher's exact test (4/10 vs. 9/10, $p = 0.0573$). Finally, the endpoint based on leukocyte findings is more sensitive than the kidney effects.

BMD modeling of total WBC count in female rats was attempted using the available continuous models (polynomial, power, Hill, linear) in EPA's BMD software (Version 2.1.2) consistent with EPA's BMD technical guidance (U.S. EPA, 2000). A benchmark response (BMR) of one standard deviation change from the control mean is selected in the absence of a biological rationale for using an alternative BMR. The BMD analysis resulted in significant lack of fit (goodness-of-fit $p < 0.10$) for all continuous models employing nonconstant (modeled) variance (see Table C.1). The homogeneity variance p -value of less than <0.1 indicates that nonconstant variance is the appropriate variance model (and therefore it is inappropriate to assume constant variance for these data). Because all nonconstant variance models exhibited poor global fit to the data, a BMDL is not used as the POD.

| Model | Homogeneity Variance p-Value | Goodness-of-Fit p-Value^b | AIC for Fitted Model | BMD_{1SD} (mg/kg-d) | BMDL_{1SD} (mg/kg-d) | Conclusions |
|-----------------------------------|--|---|-----------------------------|------------------------------------|-------------------------------------|---|
| Hill (nonconstant variance) | 0.036 | 0.027 | 112.41 | 9.26 | -999.00 | Invalid BMDL p -score 4 < 0.1 |
| Linear (nonconstant variance) | 0.036 | 0.008 | 115.30 | 190.43 | 131.06 | Lowest AIC p -score 4 < 0.1 |
| Polynomial (nonconstant variance) | 0.036 | 0.008 | 115.30 | 190.43 | 131.06 | Lowest AIC p -score 4 < 0.1 Maximum order beta = 0 $\beta_2 = 0$ $\beta_3 = 0$ $\beta_4 = 0$ |
| Power (nonconstant variance) | 0.036 | 0.008 | 115.30 | 190.43 | 131.06 | Lowest AIC p -score 4 < 0.1 hit bound (power = 1) |

^aHuntingdon Life Sciences (2001).

^bValues <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

APPENDIX D. REFERENCES

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