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Toxicokinetics and bioavailability of sulfolane, a ground water contaminant, following oral and intravenous administration in rodents: a dose, species, and sex comparison

Suramya Waidyanatha^{1,*}, Sherry R. Black², Timothy R. Fennell², Scott L. Watson², Purvi R. Patel², Stephen D. Cooper², James Blake², Veronica Godfrey Robinson¹, Reshan A. Fernando², Chad R. Blystone¹

¹Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC;

²RTI International, Discovery Sciences, Research Triangle Park, NC

Abstract

Sulfolane is a ground water contaminant near refinery sites. The objective of this work was to investigate the toxicokinetics and bioavailability of sulfolane in male and female Harlan Hsd:Sprague Dawley® SD® rats and B6C3F1/N mice following a single oral administration of 10, 30, or 100 mg/kg. Sulfolane was rapidly absorbed in rats with the maximum plasma concentration, C_{max} , reached at 1.47 h. Although C_{max} increased proportionally to the dose, the half-life of elimination increased with the dose and the area under the concentration versus time curve (AUC) increased more than proportionally to the dose. In male and female rats, plasma elimination half-life increased with the dose from 1.97 to 6.33 h. Absorption of sulfolane in mice following oral administration was more rapid than in rats with C_{max} reached at 0.55 h. In addition, mice had a shorter half-life (1.25 h) and a lower AUC than rats. In male and female mice, both C_{max} and AUC increased more than proportionally to the dose. Bioavailability of sulfolane was higher in rats (81–83%) than mice (59–63%) at 10 mg/kg; at 30 and 100 mg/kg, bioavailability > 100% in both species and sexes suggesting that the saturation of metabolism and clearance processes of sulfolane may begin at a single oral dose of ~30 mg/kg. There was no apparent sex difference in toxicokinetic parameters of sulfolane in rats and mice. These data demonstrate that sulfolane was well-absorbed following oral administration with high bioavailability in rats and mice with some species differences, but no sex difference.

Keywords

sulfolane; bioavailability; toxicokinetics; rodents

*Correspondence: Suramya Waidyanatha, Division of the National Toxicology Program, National Institutes of Environmental Health Sciences, P.O. Box 12233, Mail Drop K2-07, Research Triangle Park, North Carolina 27709, waidyanathas@niehs.nih.gov.

Declaration of Interest

The authors report no declarations of interest.

Introduction

Sulfolane (tetrahydrothiophene 1,1-dioxide) is a polar, organosulfur compound used as a solvent in a variety of industrial applications (Clark, 2012). For example, it is used in liquid-liquid and liquid-vapor extraction processes during the extraction of aromatic hydrocarbons from petroleum (Brown et al., 1966; Andersen et al., 1976; HSDB, 2006). The annual production of sulfolane in the United States is between 10–50 million pounds (U.S. EPA, 2012; ATSDR, 2010). Sulfolane has a low vapor pressure, no odor, and is water miscible (Brown et al., 1966).

Sulfolane is a groundwater contaminant near refining sites. In North Pole, Alaska, sulfolane has been detected in nearly 300 drinking water wells since 2009, with levels ranging between 4–7 parts per billion (ppb) (North Pole, AK Drinking Water Quality Report, 2015; Alaska Department of Environmental Conservation, 2010). Sulfolane has also been detected in ground water near other natural gas or petroleum refining areas in the United States and in Canada (ATSDR, 2010). Therefore, there is potential for human exposure to sulfolane via occupational or environmental sources.

Following acute inhalation, intraperitoneal, or oral exposure to sulfolane in animals, effects on the central nervous system, chronic lung inflammation, liver inflammation, decreased white blood cell counts, increased incidences of fatty liver, weight loss, decreased food consumption, and decreased white blood cell counts have been reported (Andersen et al., 1976; Ruppert and Dyer, 1985; Gordon et al., 1986; OECD, 2004; Huntingdon Life Sciences, 2001). In a reproductive screening study of Sprague Dawley rats exposed to sulfolane via gavage, dams had reduced estrous cycles, increased litter loss, decreased pup number, and low pup weight, decreases in birth index and pup numbers (OECD, 2004). In a prenatal developmental toxicity study in mice, fetal resorptions and a few skeletal abnormalities were reported (Zhu et al., 1987).

Due to limited toxicity data and potential for human exposure, sulfolane was nominated to the National Toxicology Program (NTP) by various citizens and agencies from Alaska and by the Agency for Toxic Substances and Disease Registry (ATSDR) for toxicity testing. Absorption, distribution, metabolism, excretion (ADME) and toxicokinetics (TK) data are imperative to inform on toxicology study designs and to interpret toxicology study data. In a previous investigation, we reported a comprehensive investigation of ADME of [^{14}C]sulfolane following oral, dermal, and intravenous (IV) administration in Hsd:Sprague Dawley® SD® (HSD) rats and B6C3F1/N mice, the two rodent models used in NTP studies (Waidyanatha et al., 2019). There are very limited TK data in the literature for sulfolane. Briefly, following IV administration of sulfolane (dose not provided) in male rat, rabbit, dog, and squirrel monkeys, in limited studies, the authors reported that it was rapidly distributed to tissues with a volume of distribution $\sim 1 \text{ L/kg}$ and a plasma half-life of 3.5 to 5 h (Andersen et al., 1976). In another study following oral administration of [^3H]sulfolane (2.5 mg/kg) in Sprague Dawley rats with analysis of total ^3H , the maximum concentration, C_{max} , was reached $\sim 1 \text{ h}$ with an elimination half-life of $\sim 27 \text{ h}$; radioactivity was distributed to tissues (Zhu et al., 1988). The authors also investigated the disposition of [^3H]sulfolane in

pregnant rats and reported that the radioactivity in the rat embryos was similar to blood concentration in dams.

We designed studies to generate comprehensive plasma TK data for sulfolane in male and female HSD rats and B6C3F1/N mice using multiple dose levels and different routes of exposure as outlined in Table 1. The doses selected were based on the reported oral LD₅₀ in rats (~2000 mg/kg) (Andersen et al., 1976; Brown et al., 1966), and those used in previous ADME (Waidyanatha et al., 2019) and toxicology studies (<https://ntp.niehs.nih.gov/testing/status/agents/ts-11054.html>). The dose-response, species, and sex difference in TK properties were investigated in male and female rats and mice following a single oral administration of 10, 30, and 100 mg/kg sulfolane. To aid in the interpretation of oral data and to generate oral bioavailability, limited studies were also conducted following IV administration of 10 mg/kg in male and female rats and mice. Sulfolane was quantitated using a validated gas chromatography mass spectrometry (GC-MS) method (Silinski et al., 2019).

Materials and Methods

Chemicals and reagents:

Sulfolane (lot # MKBN9784V) was obtained from Sigma-Aldrich (Saint Louis, MO). The chemical identity was confirmed by infrared spectroscopy, ¹H- and ¹³C- nuclear magnetic resonance spectroscopy, gas chromatography (GC) coupled with mass spectrometry (MS), and elemental analysis. The purity was determined to be 99.9% based on GC with flame ionization detection (FID). The lot was also analyzed by differential scanning calorimetry (purity > 99.9%) and by Karl-Fischer titrimetry for water content (< 0.1%). d8-Sulfolane (lot # Z369P10) (internal standard, IS) was obtained from C/D/N Isotopes (Pointe-Claire, Canada). All other chemicals and reagents were procured from commercial sources.

Animal studies.

Studies were conducted at Mispro Biotech Services (RTP, NC) by RTI International (RTP, NC) and were approved by Mispro Biotech Services' Institutional Animal Care and Use Committee. Animals were housed in facilities that are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. Animal procedures were in accordance with the "Guide for the Care and Use of Laboratory Animals" (National Research Council, 2011). Male and female Hsd:Sprague Dawley® SD® (HSD) rats were obtained from Harlan Laboratories (Indianapolis, IN). B6C3F1/N mice were obtained from Taconic Farms (Germantown, NY). The animals were quarantined for at least 7 days before they were randomized into dosing groups and used in a study. Mice and rats had *ad libitum* access to certified, irradiated NTP 2000 feed (Ziegler Bros, Inc., Gardners, PA). All animals had access to city (Durham, NC) tap water. Feed was used within 120 days of milling. Environmental conditions included: room temperature 72 ± 3 °F (22 ± 2 °C), relative humidity 50% and a 12-h light/dark cycle. Enviro Dri packs (100% virgin kraft paper shreds (Shepherd Specialty Papers, Watertown, TN) were provided for environmental enrichment. Male (276–318 g) and female (187–233 g) rats were 9–10 weeks old and male (24.13–34.46 g) and female (19.22–26.42 g) mice were 11–12 weeks old at the time of dosing.

Oral dose formulations of sulfolane (for mice, 1, 3, and 10 mg/mL; for rats, 2, 6, and 20 mg/mL) were prepared in water and analyzed using a validated GC-FID method (linear range, 0.01–12 mg/mL (formulation analysis range 0.01–200 mg/mL); $r = 0.99$; precision (determined as relative standard deviation, RSD) $\leq 5\%$; accuracy (determined as relative error, RE), $\pm 10\%$). IV dose formulations of sulfolane (2.5 mg/mL for mice and 5 mg/mL for rats) were prepared in 0.9% saline and analyzed using a validated GC-FID method (linear range, 0.01 to 12 mg/mL $r = 0.99$; RSD $\leq 5\%$; RE, $\pm 10\%$). All oral and IV formulations were within 10% of the target concentration. Prior to study initiation, stability (RE $\pm 10\%$ of day 0) of both oral and IV formulations was confirmed for up to 42 days (oral) or 14 days (IV) when stored in sealed clear bottles with Teflon-lined lids at ambient or refrigerated conditions.

Each animal was weighed prior to dosing and its weight was recorded to determine the dosing volume. Single oral doses were administered at 10, 30, or 100 mg/kg; each dose group contained up to 15 rats and 30 mice. Dose formulations were administered in a volume of 5 mL/kg for rat and 10 mL/kg for mouse by intragastric gavage using a syringe equipped with a ball-tipped gavage needle (16G for rats, 18G for mice). Single IV dose was administered at 10 mg/kg. Dose was administered in a volume of 2 mL/kg for rats and 4 mL/kg for mice into a lateral tail vein using a syringe equipped with a 27G needle for rats and 30G needle for mice.

Target times for blood collection following dose administration are given in Table 1; time points were selected based on a preliminary TK study (data not shown). Blood samples were obtained from 3 animals per time point. Two blood samples at different timepoints were obtained from each rat: the first sample ($\sim 250 \mu\text{L}$) was obtained from the tail vein using a 20–22G needle and the second sample (as much blood as possible) was obtained via cardiac puncture following euthanasia with CO_2 . For rats administered sulfolane via the IV route, the tail vein used for dosing was marked, and the interim blood sample was collected from the other lateral vein. The blood sampling times were separated by at least 2 h for each rat. For non-terminal collections the total volume collected did not exceed 2% of body weight. All blood samples from mice were obtained via cardiac puncture following euthanasia with CO_2 . The actual times for blood collection was recorded for each animal. Immediately following collection, blood was dispensed into tubes containing K_3EDTA , mixed by inversion and placed on ice. Plasma was prepared within 1 h of collection by centrifugation of blood. All samples were stored at -70°C within 2 h of collection.

A Debra™ data collection and reporting system (LabLogic Systems, Ltd., Sheffield, England) was used for collection of body weights, dose administered, dosing time, and blood sample collection times. The Debra system was used to calculate and report dose administered in each animal and the time between dosing and sample collection.

Study sample preparation and analysis.

Study samples were prepared and analyzed using a validated analytical method using GC-MS (Silinski et al., 2019) (Note: as has been demonstrated during method validation there was no interference from K_3EDTA for quantitation of sulfolane). Depending on the anticipated sulfolane concentration in study samples, calibration ranges were run at either

20–1000 ng/mL or 1–100 µg/mL; the corresponding lower limits of quantitation were 20 and 1 µg/mL, respectively. Briefly, to 100 µL of plasma, 10 µL of d8-sulfolane (IS) in deionized water (2 µg/mL or 200 µg/mL, depending on the anticipated sulfolane concentration) and 50 µL 1 N NaOH was added. Samples were extracted with 0.5 mL ethyl acetate and the supernatants were analyzed by GC-MS. Study samples that exceeded the matrix calibration range were diluted into the validated range using respective control matrix. Each sample set was bracketed by method blanks, matrix calibration standards, and quality control (QC) samples prepared at low and high ends of the calibration curve. A linear regression with $1/x^2$ weighing was used to relate GC-MS peak area response ratio of analyte to IS and concentration of sulfolane in plasma. The concentration of sulfolane in samples was calculated using response ratio, regression equation, initial sample volume, and dilution when applicable. The concentration of analytes was expressed as ng/mL of plasma. All concentrations above the LOD (0.516 ng/mL) of the assay were reported. Data from study samples were considered valid if: the matrix calibration curve was linear ($r = 0.99$); matrix standards were within 10% of nominal; at least 67% of the QC samples were within 15% of nominal values. All QCs were within 15% of nominal value.

Toxicokinetic analysis.

Individual animal data were evaluated for aberrant concentrations and time points. Where actual blood collection times varied more than 10% from nominal, the actual blood collection time was used in toxicokinetic modeling, otherwise nominal blood collection times were used. All concentrations were evaluated to identify outliers by performing Q-tests although the original sample size was 3. Based on these assessments, three values were eliminated from TK analysis: one male rat IV, 5 min; one female rat IV, 15 min; one female mouse oral, (30 mg/kg) 45 min.

WinNonlin (Phoenix Version 6.3, Certara, Princeton, NJ) was used for TK analysis. A variety of compartmental models were tested for sulfolane concentration versus time data sets for both oral and IV groups. For each compartmental model, data sets were analyzed with and without weighting. The model and the weighting factor that resulted in the best goodness of fit (evaluated using the Akaike Information Criterion [AIC] and Schwarz Bayesian Criterion [SBC]) was selected as the final model. Based on this, the one-compartment model (Model 3, equation 1) with first order input and output with $1/y^2$ weighting was found to provide the best model fit using individual animal data for oral groups. For IV groups, the one-compartment model (Model 1, equation 2), which assumes a bolus intravenous dose and first order output, was used with individual time point data. A glossary of TK parameters estimated are given in Table S1.

$$C_{(t)} = A(e^{-k_{01}t} + e^{-k_{10}t}) \quad (1)$$

$$C_{(t)} = Ae^{-k_{10}t} \quad (2)$$

Results

Toxicokinetics of sulfolane in male and female rat:

In male and female rats following oral administration of a 10 mg/kg dose, sulfolane was detectable from 5 min to 12 h following dose administration with concentrations below the LOD at 24 h for all rats except one female rat. In male and female rats following oral administration of 30 or 100 mg/kg, sulfolane was detectable at all time points. Mean plasma sulfolane concentration versus time data for oral groups were fitted using a one-compartment model with first-order input and output, and $1/y^2$ weighting. Model fits for male and female rats are shown in Figure 1 and TK parameters estimated are given in Table 2.

Sulfolane was absorbed rapidly in male and female rats with the C_{max} reached between 0.93 and 1.47 h (T_{max} , Table 2). C_{max} increased proportionally to the dose. The volume of distribution (V/F , > 757 mL/kg) was higher than the reported body water volume in rats (688 mL/kg) (Davies and Morris, 1993). Plasma elimination half-lives of sulfolane increased with increasing dose, with values of 2.33, 3.07, and 6.33 h for males and 1.97, 2.67, and 6.28 h for females for 10, 30, and 100 mg/kg dose groups, respectively. In both males and females, AUC increased more than proportionally to the dose, and clearance decreased with the dose. There was no apparent sex-related difference in plasma toxicokinetic parameters of sulfolane in rats.

In male and female rats following IV administration of a 10 mg/kg dose, sulfolane was detected at all time points. Plasma sulfolane concentration versus time data were fitted using a one-compartment model with bolus input and first order output and $1/y^2$ weighting. Model fits for male and female rats are shown in Figure 2 and TK parameters estimated are given in Table 3. The volume of distribution (631–664 mL/kg) was similar to the reported body water volume in rats (688 mL/kg) (Davies and Morris, 1993). Plasma half-lives (1.81–1.92 h) were similar for males and females and were also similar to those following administration of a 10 mg/kg oral dose (1.97–2.33 h). AUC following a single IV dose of 10 mg/kg (40810–41110 h*ng/mL) was slightly higher than that following a similar oral dose (33480–33830 h*ng/mL) in males and females.

Toxicokinetics of sulfolane in male and female mice:

In male and female mice following oral administration of a 10 mg/kg dose, sulfolane was detectable up to 3 h following dose administration with concentrations below the LOD at later timepoints. In male and female rats following oral administration of 30 or 100 mg/kg, sulfolane was detectable in plasma at all timepoints (up to 9 h). Plasma sulfolane concentration versus time data were fitted using one-compartment model with first-order input and output and $1/y^2$ weighting. Model fits for male and female mice are shown in Figure 3 and TK parameters estimated are given in Table 4.

Sulfolane was absorbed rapidly in male and female mice with C_{max} reached at 0.55 h (Table 4). C_{max} increased more than proportionally to the dose in male and female mice. The volume of distribution (619–1083 mL/kg) was similar or higher than the reported body water volume in mice (725 mL/kg) (Davies and Morris, 1993). Plasma elimination half-lives

increased with increasing dose, with values of 0.30, 0.47, and 1.25 h in males and 0.38, 0.52, and 1.11 h in females for 10, 30, and 100 mg/kg, respectively. In both males and females, AUC increased more than proportionally to the dose and clearance decreased with the increasing dose suggesting saturation of metabolism and clearance processes with increasing dose. There was no apparent sex-related difference in plasma toxicokinetic parameters of sulfolane in mice.

In male and female mice following IV administration of a 10 mg/kg dose, sulfolane was detectable in plasma at all timepoints measured (up to 4 h). Plasma sulfolane concentration versus time data were fitted using a one-compartment model with bolus input and first order output and $1/y^2$ weighting. Model fits for male and female mice are shown in Figure 4 and TK parameters estimated are given in Table 5. The volume of distribution (602–687 mL/kg) was similar to reported body water volume in mice (725 mL/kg) (Davies and Morris, 1993). Plasma half-lives were similar for males (0.30 h) and females (0.37 h) and was similar to that following administration of a 10 mg/kg oral dose (0.30–0.38 h). AUC following a single IV dose of 10 mg/kg (7204–8091 h*ng/mL) was higher than that following a similar oral dose (4265–5127 h*ng/mL) in both males and females.

Bioavailability of sulfolane in male and female rats and mice:

Absolute bioavailability of sulfolane following a single oral administration was estimated in male and female rats and mice using AUC following oral and IV administration. Since two of the 3 gavage doses are higher than the IV doses, AUC was normalized for dose administered before calculating bioavailability ($\text{bioavailability (\%F)} = \text{as AUC/dose (oral)} \div \text{AUC/dose (IV)} \times 100$). In general, absolute bioavailability was high in both species and sexes (Table 6). Following administration of a 10 mg/kg, absolute bioavailability was 81–83% in male and female rats; values were > 100% for 30 and 100 mg/kg. In mice, following administration of 10 mg/kg, absolute bioavailability was slightly lower than rats (59–63%); as in rats estimated values were > 100% for 30 and 100 mg/kg. These data suggest that saturation of metabolism and clearance processes of sulfolane in male and female rats and mice may begin at ~ 30 mg/kg.

Discussion

Sulfolane has been detected in ground water near areas of natural gas or petroleum refining suggesting potential for human exposure. Due to limited toxicity data, the NTP is testing the potential toxicity of sulfolane in HSD rats, B6C3F1/N mice, and guinea pigs (<https://ntp.niehs.nih.gov/testing/status/agents/ts-11054.html>). In support of these toxicology studies, and due to lack of sufficient TK data in the literature, we investigated the TK behavior of sulfolane in HSD rats and B6C3F1/N mice following a single oral and IV administration. The doses selected were based on the reported oral LD₅₀ in rats (~2000 mg/kg) (Andersen et al., 1976; Brown et al., 1966), and those used in previous ADME (Waidyanatha et al., 2019) and toxicology studies (<https://ntp.niehs.nih.gov/testing/status/agents/ts-11054.html>).

In a previous investigation using [¹⁴C]sulfolane, we reported that sulfolane was well-absorbed in rodents; based on total radioactivity, > 87% and > 92% of a single oral dose of

30, 100, or 300 mg/kg of [^{14}C]sulfolane was absorbed in male HSD and B6C3F1/N mice (Waidyanatha et al., 2019). The current TK data support the data from our [^{14}C]sulfolane studies. Sulfolane was rapidly absorbed in both rats and mice following a single oral dose of 10, 30, and 100 mg/kg. Sulfolane was detected in plasma at the first sampling time point of 5 min at all doses in both species and sexes; C_{max} was reached within 1.47 h in rats and 0.55 h in mice. Zhu et al. (1988) reported, using total radioactivity, that C_{max} in rats was reached in 1 h following oral administration of 2.5 mg/kg [^3H]sulfolane. In our studies, in rats of both sexes, C_{max} increased proportionally to the dose; the dose-normalized C_{max} (C_{max} for a unit dose administered) for 10, 30, and 100 mg/kg was similar with 756, 1019, and 984 (ng/mL)/(mg/kg) for male rats and 850, 947, and 1008 (ng/mL)/(mg/kg) for female rats, respectively. However, for mice dose-normalized C_{max} increased with the dose; the dose-normalized C_{max} values for 10, 30, and 100 mg/kg for male mice were 584, 758, and 973 (ng/mL)/(mg/kg) and for female mice were 605, 810, and 1147 (ng/mL)/(mg/kg), respectively. This greater than proportional increase in C_{max} in mice may explain the decreased survival in mice at higher doses compared to rats as observed in 28-day toxicity studies (unpublished data).

Although the data from the current study fit well with a one-compartment model, sulfolane was distributed to the peripheral compartment as evident by the volumes of distribution at or above the total body water volumes in rats (688 mL/kg) and mice (725 mL/kg). This observation is consistent with our ADME data where using [^{14}C]sulfolane, we demonstrated that sulfolane was distributed to all tissues examined in rats and mice following oral administration (Waidyanatha et al., 2019).

Unlike C_{max} , where a more than dose-proportional increase was observed only in mice, AUC increased more than proportionally to the dose in both rats and mice. The dose normalized AUC (AUC for a unit dose administered, AUC/D) values for male rats were 3383, 5853, and 10400 (h*ng/mL)/(mg/kg), for female rats was 3348, 4733, and 10730 (h*ng/mL)/(mg/kg), for male mice was 427, 785, and 2175 (h*ng/mL)/(mg/kg) and for female mice were 513, 1053, and 2582 (h*ng/mL)/(mg/kg), for 10, 30, and 100 mg/kg, respectively. In addition, the plasma elimination half-lives increased and clearance decreased with increasing dose in both rats and mice. We have previously demonstrated, using [^{14}C]sulfolane, that the major route clearance is via the kidneys. The estimated bioavailability of sulfolane for male and female rats was 81–83% and for male and female mice was 59–63%, at 10 mg/kg; however, at higher doses, estimated bioavailability was > 100% in both species and sexes. These data point to saturation of metabolism and elimination processes of sulfolane beginning at ~ 30 mg/kg in rats and mice following oral administration of sulfolane.

In our studies following IV administration of 10 mg/kg sulfolane, volumes of distribution observed in rats (male, 631; female 664 mL/kg) and mice (male, 602; female 687 mL/kg) and plasma elimination half-lives (rat, 1.81–1.92 h; mice 0.30–0.37 h) were similar to those reported by Andersen et al. (1976) following IV administration of sulfolane in a rabbit, dog, and squirrel monkey (strains, sex or dose not provided) (volume of distribution, ~ 1 L/kg and a plasma half-life of 3.5 to 5 h).

There were species differences in TK parameters between rats and mice. For example, although $C_{\max}$ was similar between the two species, $C_{\max}$ was reached in male and female mice (0.55 h) faster than in male and female rats (1–2 h). In addition, plasma elimination half-lives in male and female mice (0.30–1.25 h) were much faster than rats (1.97–6.33 h). At a given dose, $AUC_{0-\infty}$ was lower for mice (Table 4) than rats (Table 3), per unit dose administered. Correspondingly, bioavailability in male and female mice (59–63%) was lower than male and female rats (81–83%). However, there was no apparent sex difference in the TK parameters of sulfolane in rats or mice following oral or IV administration. To our knowledge, this is the first comprehensive investigation of TK behavior of sulfolane in rats and mice following a single oral and IV administration of sulfolane.

The data from the current investigation could be used to interpret any potential species differences in toxicity. In addition, the systemic exposure data ($C_{\max}$ and AUC) generated here can be compared to human systemic exposures to determine the relevance of animal toxicity data to humans. However, at the present time, there are no data on human exposures to determine either the relevance of the animal doses or the systemic exposure to humans and hence subsequently the relevance of rodent toxicity data to humans.

Conclusion

Sulfolane was rapidly absorbed in rats and mice. Plasma elimination half-lives increased with the dose in both species and sexes with mice having shorter half-lives than rats. Although $C_{\max}$ increased proportionally to the dose in male and female rats, in male and female mice, $C_{\max}$ increased more than proportionally to the dose. In both species and sexes, AUC increased more than proportionally to the dose demonstrating saturation of elimination processes with increasing dose. Bioavailability of sulfolane in rats (81–83%) and mice (59–63%) was substantial at 10 mg/kg and at 30 and 100 mg/kg bioavailability was > 100% suggesting saturation of metabolism and clearance processes may begin at doses ~ 30 mg/kg. There was no sex difference in plasma toxicokinetic parameters of sulfolane in rats and mice. These data demonstrate that sulfolane was well-absorbed following gavage administration with high bioavailability in rats and mice, with no apparent sex difference but some species differences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Plasma concentration versus time profiles sulfolane following a single gavage administration of 10, 30, and 100 mg/kg sulfolane in male and female Hsd:Sprague Dawley® SD® rats. One-compartmental model with first order input, first order output and $1/y^2$ was used to fit the data.

Figure 2. Plasma concentration versus time profiles sulfolane following a single intravenous administration of 10 mg/kg sulfolane in male and female Hsd:Sprague Dawley® SD® rats. One-compartmental model with bolus input, first order output and $1/y^2$ was used to fit the data.

Figure 3.

Plasma concentration versus time profiles sulfone following a single gavage administration of 10, 30, and 100 mg/kg sulfone in male and female B6C3F1/N mice. One-compartmental model with first order input, first order output and $1/y^2$ was used to fit the data.

Figure 4. Plasma concentration versus time profiles sulfolane following a single intravenous administration of 10 mg/kg sulfolane in male and female B6C3F1/N mice. One-compartmental model with bolus input, first order output and $1/y^2$ was used to fit the data.

Table 1.

Study design Exposure to Bisphenol AF Disrupts Sex Hormone Levels and Vitellogenin Expression in Zebrafish

Species, Sex	Route	Dose (mg/kg)	Blood collection time points (h) ^a
Rat, Male	Oral	10, 30, 100	0 (predose), 0.083, 0.25, 0.50, 1, 2, 4, 8, 12, 24
Rat, Female	Oral	10, 30, 100	0 (predose), 0.083, 0.25, 0.50, 1, 2, 4, 8, 12, 24
Rat, Male	Intravenous	10	0 (predose), 0.083, 0.25, 0.50, 1, 2, 4, 8, 12
Rat, Female	Intravenous	10	0 (predose), 0.083, 0.25, 0.50, 1, 2, 4, 8, 12
Mouse, Male	Oral	10, 30, 100	10 mg/kg: 0 (predose), 0.083, 0.166, 0.25, 0.50, 0.75, 1.5, 2, 3, 4 30 and 100 mg/kg: 0 (predose), 0.083, 0.166, 0.25, 0.50, 0.75, 1.5, 3, 6, 9
Mouse, Female	Oral	10, 30, 100	10 mg/kg: 0 (predose), 0.083, 0.166, 0.25, 0.50, 0.75, 1.5, 2, 3, 4 30 and 100 mg/kg: 0 (predose), 0.083, 0.166, 0.25, 0.50, 0.75, 1.5, 3, 6, 9
Mouse, Male	Intravenous	10	0 (predose), 0.083, 0.166, 0.25, 0.50, 0.75, 1.5, 2, 3, 4
Mouse, Female	Intravenous	10	0 (predose), 0.083, 0.166, 0.25, 0.50, 0.75, 1.5, 2, 3, 4

^aTarget times for blood collection following the dose administration are given. Each dose group contained up to 15 rats and 30 mice. Each rat was bled up to 2 times. Each mouse was bled once. Number of animals used were 3 per timepoint.

Table 2.

Plasma toxicokinetic parameters of sulfolane following a single oral administration in male and female Hsd:Sprague Dawley® SD® rats^a

Parameters	Dose (mg/kg)		
<i>Male</i>	10	30	100
C _{max} (ng/mL)	7559 (525)	30580 (1276)	98360 (7153)
C _{max} /Dose (ng/mL)/(mg/kg)	756	1019	984
T _{max} (h)	0.968 (0.115)	1.15 (0.0863)	1.34 (0.197)
K01 Half-Life (h)	0.278 (0.0589)	0.314 (0.0403)	0.285 (0.0630)
K01 (1/h)	2.49 (0.528)	2.21 (0.284)	2.43 (0.538)
K10 (1/h)	0.298 (0.0390)	0.226 (0.0167)	0.110 (0.013)
K10 Half-Life (h)	2.33 (0.304)	3.07 (0.227)	6.33 (0.790)
Cl _F (mL/h/kg)	296 (25.5)	171 (8.69)	96.2 (9.22)
V _F ^a (mL/kg)	991 (112)	757 (49.4)	878 (83.6)
AUC (h*ng/mL)	33830 (2914)	175600 (8931)	1040000 (99600)
AUC/D (h*ng/mL)/(mg/kg)	3383	5853	10400
<i>Female</i>			
C _{max} (ng/mL)	8497 (529)	28720 (1597)	100800 (6999)
C _{max} /Dose (ng/mL)/(mg/kg)	850	947	1008
T _{max} (h)	0.934 (0.0954)	0.964 (0.105)	1.47 (0.200)
K01 Half-Life (h)	0.288 (0.0554)	0.259 (0.0456)	0.3256 (0.0680)
K01 (1/h)	2.41 (0.465)	2.68 (0.473)	2.13 (0.445)
K10 (1/h)	0.353 (0.0442)	0.260 (0.0221)	0.111 (0.0131)
K10 Half-Life (h)	1.97 (0.246)	2.67 (0.227)	6.28 (0.743)
Cl _F (mL/h/kg)	299 (23.1)	211 (14.5)	93.2 (8.41)
V _F (mL/kg)	847 (92.1)	813 (66.7)	844 (78.5)
AUC (h*ng/mL)	33480 (2586)	142000 (9714)	1073000 (96750)
AUC/D (h*ng/mL)/(mg/kg)	3348	4733	10730

^aBased on one-compartment model with first order input, first order output and 1/y weighting.

^bValues given are mean (standard error).

Table 3.

Plasma toxicokinetic parameters of sulfolane following a single intravenous administration of sulfolane in male and female Hsd:Sprague Dawley® SD® rats^a

Parameter ^b	Dose 10 mg/kg	
	Male	Female
C _{max} (ng/mL)	15670 (575)	14870 (514)
K ₁₀ (1/h)	0.384 (0.0225)	0.362 (0.0206)
K ₁₀ Half-Life (h)	1.81 (0.106)	1.92 (0.109)
Cl (mL/h/kg)	242 (11.5)	240 (11.0)
V (mL/kg)	631 (23.2)	664 (23.0)
AUC (h*ng/mL)	40810 (1930)	41110 (1877)

^aBased on one-compartment model with bolus dose and first order output.

^bParameter estimates and (standard error) are shown.

Table 4.

Plasma toxicokinetic parameters of sulfolane following a single oral administration in male and female B6C3F1/N mice^a

Parameter ^b	Dose (mg/kg)		
<i>Male</i>	10	30	100
C _{max} (ng/mL)	5837 (212)	22730 (1085)	97290 (6000)
C _{max} /Dose (ng/mL)/(mg/kg)	584	758	973
T _{max} (h)	0.227 (0.0160)	0.290 (0.0276)	0.369 (0.0553)
K01 Half-Life (h)	0.0929 (0.0153)	0.104 (0.0206)	0.0903 (0.0207)
K01 (1/h)	7.46 (1.23)	6.68 (1.32)	7.67 (1.76)
K10 (1/h)	2.32 (0.221)	1.48 (0.177)	0.553 (0.0546)
K10 Half-Life (h)	0.299 (0.0284)	0.467 (0.0557)	1.25 (0.124)
Cl _F (mL/h/kg)	2345 (99.5)	1274 (80.2)	464 (38.7)
V _F ^a (mL/kg)	1011 (93.8)	859 (90.0)	838 (72.8)
AUC (h*ng/mL)	4265 (181)	23550 (1481)	215700 (18000)
AUC/D (h*ng/mL)/(mg/kg)	427	785	2157
<i>Female</i>			
C _{max} (ng/mL)	6048 (173)	24300 (1837)	114700 (7299)
C _{max} /Dose (ng/mL)/(mg/kg)	605	810	1147
T _{max} (h)	0.235 (0.0140)	0.412 (0.0536)	0.548 (0.0691)
K01 Half-Life (h)	0.08345 (0.00975)	0.173 (0.0574)	0.172 (0.0376)
K01 (1/h)	8.31 (0.972)	4.00 (1.33)	4.02 (0.878)
K10 (1/h)	1.801 (0.105)	1.332 (0.298)	0.626 (0.0625)
K10 Half-Life (h)	0.385 (0.0223)	0.5206 (0.116)	1.11 (0.111)
Cl _F (mL/h/kg)	1950 (65.4)	949.5 (93.9)	387 (33.0)
V _F (mL/kg)	1083 (61.6)	713.1 (155)	619 (66.1)
AUC (h*ng/mL)	5127 (172)	31600 (3121)	258200 (22010)
AUC/D (h*ng/mL)/(mg/kg)	513	1053	2582

^aBased on one-compartment with first-order input and output, no lag time, and 1/y weighing

^bParameter estimates of mean and (standard error) are shown.

Table 5.

Plasma toxicokinetic parameters of sulfolane following a single intravenous administration of sulfolane in male and female B6C3F1/N mice^a

	Dose 10 mg/kg	
Parameter ^b	Male	Female
C _{max} (ng/mL)	16780 (293)	15290 (492)
K ₁₀ (1/h)	2.33 (0.0474)	1.889 (0.0721)
K ₁₀ Half-Life (h)	0.298 (0.00605)	0.3669 (0.0140)
Cl (mL/h/kg)	1402 (20.6)	1298 (37.9)
V (mL/kg)	602 (10.5)	686.8 (22.1)
AUC (h*ng/mL)	7204 (106)	8091 (236)

^aBased on one-compartment model with bolus dose and first order output

^bParameter estimates and (standard error) are shown.

Table 6.

Bioavailability of sulfolane following a single oral administration in Hsd:Sprague Dawley® SD® rats and B6C3F1/N mice

Dose (mg/kg)	Bioavailability (%) ^a			
	Male Rats	Female Rats	Male Mice	Female Mice
10	83	81	59	63
30	143	115	109	130
100	254	261	299	319

^a Bioavailability (%F) was calculated as $\text{AUC/Dose (oral)} \div \text{AUC/Dose (IV)} \times 100$.