Drinking Water Guidance Value for Sulfolane

A health-based Drinking Water Guidance Value of 0.04 mg/L (40 µg/L) is established for sulfolane, based on lifetime exposure. Occasional short-term exceedances above this value are not considered to be of concern. For more significant, long-term exceedances that cannot be addressed through treatment, it is suggested that a plan be developed and implemented to address these situations.

Health Canada can develop a Drinking Water Guidance Value (DWGV) at the request of a federal department, a province or a territory. This DWGV has been established for the Alberta Department of Environment and Sustainable Resource Development. It is based on limited scientific information available at the time of the request, and not on a thorough research of all existing studies.

DWGVs are not subject to a review as thorough as the *Guidelines for Canadian Drinking Water Quality*, which undergo internal peer review and public consultation before being approved by the Federal-Provincial-Territorial Committees on Drinking Water and on Health and the Environment. DWGVs apply to water intended for human consumption, and do not replace or supersede existing guidelines or regulations in place.

Background Information

Identity, use and sources

Sulfolane ($C_4H_8SO_2$; CAS 126-33-0) is a solvent used for gas treating in a variety of industrial processes. It is known under a variety of synonyms and trade names, including bondelane A, 2,3,4,5-tetrahydrothiophene-1,1-dioxide, and tetramethylene sulfone. It has a molecular weight of 120.17 g/mol, a density of 1.276 $g \cdot cm^{-3}$ at 15°C, an aqueous solubility of 1,266,000 mg/L at 20°C, a log Kow of -0.4, a vapour pressure at 20°C of 1.33 × 10-3 kPa, and a Henry's law constant of 4.6×10^{-6} $atm \cdot m^3 \cdot mol^{-1}$. Sulfolane is poorly adsorbed to soil, has a high aqueous solubility, low volatility and is highly mobile in the subsurface. Under typical groundwater conditions, sulfolane degradation may be slow or non-existent. However, under conditions of typical surface water, sulfolane degradation is relatively rapid, with complete removal occurring after 5 to 11 weeks (CCME, 2006).

Exposure

The total worldwide production of sulfolane is estimated at between 18,000 and 36,000 tons per year. Reports on the presence of anthropogenic sulfolane in the North American environment are limited to data collected in the vicinity of gas processing facilities in Alaska (U.S.) and in Western Canada; the maximum measured sulfolane concentrations in groundwater were 800 mg/L in shallow till and 88 mg/L in bedrock (CCME, 2006). Testing of 28 monitoring wells at a North Pole refinery reported sulfolane concentrations ranging from 21 to 6,520 µg/L (Arcadis U.S. Inc., 2013). Sulfolane concentrations in private wells near the refinery ranged from 40 to 415 µg/L (Barr Engineering Company, 2013).

Multi-route exposure assessment

To assess the overall exposure of sulfolane in drinking water, the relative contribution of each exposure route was assessed through a multi-route exposure assessment approach (Krishnan and Carrier, 2008). Both the dermal and inhalation routes of exposure during bathing or showering are considered significant if they contribute to at least 10% of the drinking water consumption level. On the basis of the estimated skin permeability coefficients and the air to water concentration values, it was found that dermal and inhalation exposures through showering or bathing were not significant.

Kinetics

Sulfolane is well absorbed through the oral route but not through human skin. Sulfolane rapidly distributes throughout the body and is removed from plasma with a half-life of 3.5 to 5.0 hours in test animals. When 100 mg of sulfolane was administered intraperitoneal to rats, 85% of the sulfolane was excreted in urine as a metabolite, 3-hydroxy sulfolane, in the first 24 hours (ATSDR, 2010).

Toxicological Information

No studies were identified on the effects of oral or inhalation exposures of sulfolane in humans. No carcinogenicity studies of animals orally exposed to sulfolane have been identified and there is no evidence to suggest that sulfolane is genotoxic (CCME, 2006; ATSDR, 2010; NCEA, 2012). In animals, studies have found decreased total white blood cell (WBC) count as well as kidney and spleen effects. These studies are described below.

In a single published study that was translated to English from Chinese, 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 (studies summarized below). Study authors also conducted a developmental study (discussed below) and several negative genotoxicity tests (Ames, bone marrow micronucleus test, and sister chromatid exchange test). The study authors did not state whether the experiment adhered to GLP guidelines and data tables were not provided in the translation. This report appears to be an extended abstract of the original study and its use is limited for risk assessment purposes. For example, there is no clear indication of histopathological examination of any tissues in any test described, except for the spleen and liver in the 6-month study. Exposure type (e.g., gavage, drinking water, diet) and frequency of oral administration were not reported. The study authors did not delineate the specific biochemical parameters examined, nor did they specify the meaning of "liver biochemical index." Further, statistical testing is poorly reported. However, since studies on sulfolane toxicity are limited, and based on the fact that this study was used by ATSDR as a key study it is summarized below.

Subchronic toxicity

Huntingdon Life Sciences (HLS, 2001): A good laboratory practice (GLP)-certified subchronic (90 day) drinking water study for sulfolane in CD rats was conducted. Although this study was funded by industry and it is not publicly available, ATSDR obtained the data and extensive summaries are available in several independent reports (CCME. 2006; ATSDR, 2010; NCEA, 2012). Rats (10/sex/group) were exposed to concentrations of 0, 25, 100, 400 or 1600 mg

sulfolane/L drinking water *ad libitum* (estimated daily doses of 2.1, 8.8, 35 and 132 mg/kg bw per day in male rats and 2.9, 10.6, 42 and 191 mg/kg bw per day in female rats). A thorough examination of effects included: food and water consumption, bodyweight, organ weights, functional observations (e.g., reflexes, grooming, motor activity), hematological evaluations, blood chemistry, gross pathology and histopathological examination of: adrenals, brain, femur, heart, ileum, kidneys, liver, lungs, mammary area, spinal cord, stomach, thyroid and uterus.

The exposure was described as well tolerated, and the study authors identified two primary effects of concern. First, male renal toxicity involving inhibition of α-2μ-globulin that is probably not relevant to humans for purposes of risk assessment (Dellarco and Baetcke, 2005). Secondly, the most relevant effect considered to be treatment-related by the HLS study authors was a decrease in lymphocyte, monocyte and large unstained cell counts, as well as a concomitant decrease in total leukocyte or WBC counts in female rats administered 100, 400 or 1600 mg/L (10.6, 42 and 191 mg/kg bw per day). Males did not experience similar decreases in these cell counts. Although there was no assay of functional manifestation of the white cell decreases such as compromised immune function, the decreases in WBC counts seen in female rats were 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; this effect was reported in other studies of sulfolane exposures (albeit at higher exposures) in a different rat strain (Crj:CD[S-D]) and other species (guinea pigs; Zhu et al., 1987). A lowest observed adverse effect level (LOAEL) of 10.6 mg/kg bw per day and a no observed adverse effect level (NOAEL) of 2.9 mg/kg bw per day were identified in female rats, based on statistically significant decreases in total WBCs, lymphocyte, monocyte and basophil counts.

Ministry of Health and Welfare Japan (1996): In a GLP-compliant, peer-reviewed study, sulfolane was administered by gavage to 5-week old male and female Crj:CD(S-D) rats at dose levels of 0, 60, 200, or 700 mg/kg bw per day for 28 days. While written in Japanese, the study was reviewed and reported by the Organisation for Economic Cooperation and Development (OECD, 2004). There were 6 animals/sex in the 60 and 200 mg/kg bw per day groups and 12 animals/sex for the groups dosed at 0 and 700 mg/kg bw per day. After 28 days of treatment, 6 animals in the control and 6 in the 700 mg/kg bw per 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 bw per day group experienced significantly ($p < 0.01$) lower absolute body weight compared with controls throughout treatment (12−14% bodyweight depression from days 3−28), while high-dose females only showed significant differences ($p < 0.01$) from controls for the first 14 days of treatment (11% absolute body-weight depression only on day 3). High-dose males experienced significant ($p = 0.01$) decreased food consumption for the first 3 weeks of treatment, while females had significant ($p < 0.01$) decreased food consumption the first week of treatment. High-dose females experienced decreased locomotor activity (3/12 animals) during the beginning of the treatment period. Hematology revealed that all dosed male groups had significant ($p = 0.05$) slightly decreased (2−3%) mean cell hemoglobin concentration after 28 days of treatment, but there was no decrease observed after the 14-day recovery period. Males of the high-dose group

had significant (p = 0.05) higher WBC counts 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 relationship could not be evaluated. Effects on WBCs in treated females were not observed. High-dose females had significant reduced mean red blood cell counts and significant increased mean cell volume compared with controls after recovery (p = 0.01). The high-dose females had elevated ALT (46% above control) and decreased glucose (15% below control). High-dose male rats experienced significant increased (p = 0.05) relative kidney, brain and heart weight, and increased incidence and severity of hyaline droplets and eosinophilic bodies in the renal tubules at both 200 and 700 mg/kg bw per day. Based on observed kidney effects in male rats, a LOAEL of 200 mg/kg bw per day and a NOAEL of 60 mg/kg bw per day were identified, however as noted above, this effect is likely related to α-2μ-globulin and likely not relevant for human risk assessment.

Subchronic study (Zhu et al., 1987): 80 white rats and 80 guinea pigs (sex, age, strain not specified) where given 0, 55.6, 167, or 500 mg/kg-day sulfolane for 90 days, after which the animals were sacrificed. 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 was described or given. 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 bw per day) including changes in urine volume, increased gamma glutamyl transferase activity in the urine, decreased serum alkaline phosphatase activity, decreased ICD (undefined in the study report) and decreased thrombin. The study authors stated that other examined parameters did not exhibit statistically significant changes. The authors concluded that sulfolane affects the blood system, liver and kidneys and that guinea pigs are more sensitive than rats.

Subchronic/chronic toxicity

Zhu et al. (1987): Guinea pigs (20/sex/dose) were orally dosed with sulfolane at dose levels of 0, 0.25, 2.5, 25, or 250 mg/kg bw per day for 6 months. Biochemical and pathological evaluations were conducted on a subset of animals during an interim sacrifice at 3 months (subchronic) and at the end of the study at 6 months (chronic). The translation did not state the specific biochemical parameters, organs examined, or whether the pathology mentioned was gross pathology or histopathological. At the 3-month interim sacrifice, levels of ALT, AST and marrow cell number were lower than controls but statistical significance was not reported. Incidence of shrinkage of white pulp in the spleen in the 0, 0.25, 2.5, 25, and 250 mg/kg bw per day groups were reported as 0/14, 0/14, 1/14, 2/14 and 6/14, respectively (no statistical analysis reported). At 6 months, a "liver biochemical index" for male guinea pig was 40.2 and significantly different from the control group, but this term was undefined. A dose-response relationship in the increased incidence of fatty deposits in the liver was reported as 0/25, 0/22, 2/26, 4/25, and 7/22 and then again as changes in fatty liver deposits at 2.5 mg/kg bw per day (1/26), 25 mg/kg bw per day (2/25) and 250 mg/kg bw per day (5/22). Likewise, shrinkage of splenic white pulp was reported: 2/26 at 2.5 mg/kg bw per day, 2/25 at 25 mg/kg bw per day, and 7/22 at 250 mg/kg-day. Based on these reported histopathological results, a no-effect of 0.25 mg/kg bw per day and a chronic threshold of 2.5 mg/kg bw per day were reported.

Reproduction and Development

Zhu et al. (1987): female Chinese Kunming mice (number not reported) were orally administered sulfolane in distilled water at dose levels of 0, 93, 280, or 840 mg/kg bw per 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 examined for abnormalities. The study authors provided no other experimental details or methods of statistical analysis. In the highest dose group (840 mg/kg bw per day) the incidence of skeletal abnormalities was significantly higher ($p < 0.01$) than the negative control and the number of fetal resorptions increased compared to negative control (30.16% versus 13.53%, respectively), but statistical significance was not specified. No skeletal abnormalities were observed in pups in the 280 mg/kg bw per day group. Data from the study indicate a developmental NOAEL of 280 mg/kg bw per day and corresponding LOAEL of 840 mg/kg bw per 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.

The Ministry of Health and Welfare Japan (1999): This Japanese one-generation reproductive/ developmental toxicity screening test was peer-reviewed by OECD (2004), who also provided an English summary and data tables. The study followed OECD 421 guidelines and was conducted under GLP standards. Study authors administered sulfolane 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 bw per day for 41−50 days. The dosing period extended from 14 days before mating to lactation day 3. Study authors recorded the following parameters: number of successful copulated pairs, copulation index, paring 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 did not include a detailed organ or skeletal examination. In females of the 700 mg/kg bw per day dose group, fewer estrous cycles, a significant ($p < 0.01$) increase in stillbirths, increased relative ovary weight at necropsy and a significant ($p < 0.01$) decrease in birth index, live birth index, and number of pups were reported. Females dosed with 200 mg/kg bw per day had a significant ($p < 0.05$) decrease in delivery and birth indices. Mean pup weight was significantly decreased on lactation day 0 and 4 in the 700 mg/kg bw per day group ($p < 0.01$). Mean litter weights were significantly decreased ($p < 0.05$) compared to control at ≥200 mg/kg bw per day. No external anomalies were observed in any of the treated pups at necropsy. Based on decreased delivery and birth indexes, a NOAEL of 60 mg/kg bw per day an a LOAEL of 200 mg/kg bw per day were identified for reproductive and developmental toxicity.

Treatment Technology

There is limited information available in the literature for the removal of sulfolane from water supplies. Available bench-scale and pilot-scale data reported that filtration with granular activated carbon was effective in reducing sulfolane at the residential scale and in small systems.

Municipal Scale

Based on the information and testing for residential scale systems described below, municipal scale treatment of sulfolane is expected to be achievable using granular activated carbon (GAC) technology. Following the studies conducted by the Barr Engineering Company (2013) described below, the Drinking Water Program within the Alaska Department of Environmental Conservation (DEC) has granted approval to operate GAC sulfolane treatment systems at two Public Water Systems (Alaska Department of Environmental Conservation, 2014).

Residential Scale

The Barr Engineering Company (2013) conducted a number of studies on sulfolane, as described below.

Screening-level testing of residential treatment technologies was conducted at a contaminated site in North Pole, Alaska to evaluate: potassium permanganate; calcium hypochlorite; ultraviolet radiation (UV oxidation); hydrogen peroxide (H_2O_2); H_2O_2 + UV oxidation; and activated carbon adsorption. Results indicated that activated carbon adsorption showed the most promise for a potential point-of-entry (POE) residential system and that H_2O_2 + UV oxidation showed limited removal capacity.

Follow-up feasibility studies were conducted at bench-scale for advanced oxidation processes (AOPs) using H_2O_2 + ozone and H_2O_2 + UV oxidation and at both bench- and pilot-scale for activated carbon. They found that AOPs using H_2O_2 + ozone and H_2O_2 + UV oxidation, regardless of configuration or combinations of technologies, were not effective at removing sulfolane in drinking water (less than 40% reduction). The bench-scale study for carbon adsorption was conducted using feed water supplied via a 500-gallon tank, containing sulfolane concentrations ranging from 310 to 350 µg/L (average of 320 µg/L); TOC concentrations ranging from 2 to 3 mg/L; iron concentrations below 50 µg/L; manganese concentrations of approximately 1 µg/L; alkalinity of approximately 200 mg/L as $CaCO_3$; pH values between 7 and 8; and water temperature was maintained between 4 and 7°C. Samples were collected at the influent and effluent sampling points of each of 3 columns (in parallel) every 60 minutes for the 150 hour-duration of the test. An Empty Bed Contact Time (EBCT) of 4 min resulted in a time to breakthrough 66 hours for the first column, at a loading rate of 0.3 gpm (approximately 7,000 gallons/ft^3 of activated carbon). The bench-scale data showed that carbon adsorption was very effective for the treatment of sulfolane in drinking water, achieving at least 97% removal prior to breakthrough.

Pilot testing was undertaken to ensure that the treatment design was adequate for use at full residential scale on a variety of water sources to the clean-up level of 14 µg/L established by the Alaska Department of Environmental Conservation (DEC). Both accelerated and in-home pilot testing were undertaken in the study. The accelerated pilot test trials were conducted on a full-scale POE treatment system design of two primary 2.5-cubic-foot GAC vessels operating in

series at a loading rate of 3 gpm through one vessel (equivalent to two vessels in parallel at 6 gpm) using two different flow regimes. The first trial consisted of a constant flow with no downtime, while the second trial used a "50:50" flow scenario (20 min on and 20 min off for 16 hours, followed by eight hours of completely off)

In the first trial (constant flow), the influent concentration varied between 156 and 235 µg/L and the first detectable level of sulfolane in the first vessel effluent was seen after treatment of 10,739 gallons. In the second trial (50:50 flow scenario), the influent sulfolane concentration varied from 231 to 290 µg/L and the first detectable level of sulfolane in the first vessel effluent was seen after treatment of 11,794 gallons. The sulfolane concentration in the first vessel effluent showed minimal increase following breakthrough as the trial continued. The testing results of the accelerated pilot testing confirmed successful sulfolane removal through a POE treatment system with GAC, achieving sulfolane concentrations below the reporting limit of 10 µg/L or the detection limit of 3.1 µg/L prior to breakthrough.

In-home pilot testing was also undertaken at five selected residences using one or two 2.5-cubic-foot GAC vessels for the purposes of evaluating sulfolane breakthrough. The test homes were selected to include both higher and lower sulfolane concentrations and to provide a range of anticipated water qualities for the residences where installation of the full-scale systems was planned. Average concentrations of sulfolane varied between 36.3 and 403 µg/L. Weekly sampling included measurement of the water usage rate, collection of sulfolane samples from the feed to and effluent from the first GAC vessels. Measurements of iron, manganese, TOC, oxidation-reduction potential (ORP) and fecal coliforms were conducted weekly. The study included two types of POE treatment systems: (1) a two-vessel design consisting of first and second vessels plumbed in series followed by a third vessel for redundancy, which was installed at 3 locations and tested between November 2010 and November 2011; and (2) a single-vessel design consisting of a first vessel followed by a second vessel for redundancy, which was installed at 2 locations and tested between November 2010 and June 2011. All sulfolane concentrations were below10 µg/L prior to breakthrough in the first vessel and there was no detection of sulfolane in any of the subsequent (redundant) vessels.

Further to this in-home pilot study, the Water Quality Association (WQA) certified the single unit (simplex) 2.5-cubic-foot GAC vessel as capable of treating sulfolane to levels below 10 µg/L at a flow rate of 3 gpm. The certification treatment conditions are as follows: 25,000 gallons of water at an influent sulfolane concentration of 55 µg/L; 14,900 gallons at an influent sulfolane concentration of 155 µg/L; and 10,000 gallons at an influent sulfolane concentration of 350 µg/L. As such, any water with greater than 350 µg/L of sulfolane will require either remediation prior to treatment or pilot testing of other designs to ensure that they are capable of removing higher concentrations of sulfolane.

The report (Barr Engineering Company, 2013) concluded that the majority of homes where the POE treatment would be used have sulfolane concentrations below 100 µg/L, thus a standard 2.5-cubic-foot residential GAC vessel could last much longer than three months in those cases. It also found that the scale of the required GAC equipment provides sufficient capacity and redundancy for a residential setting.

Classification and Rationale

Currently, there are no epidemiological studies or other data that support the carcinogenicity of sulfolane in humans and no evidence of genotoxicity. The most acceptable study to use for deriving an oral reference value is a GLP compliant, peer-reviewed study (HLS, 2001) that identified statistically significant decreases in the total WBC and lymphocyte counts in female rats exposed to sulfolane in drinking water for 13 weeks. Although alternative studies are available (i.e., Zhu et al., 1987; Ministry of Health and Welfare Japan, 1996), they were originally published in a foreign language and the available translations do not contain detailed documentation of experimental methods and study design. By comparison, the HLS (2001) study authors conducted the drinking water study at a lower dose range and examined a wide array of endpoints.

Calculation of Health Canada's Drinking Water Guidance Value (DWGV)

The benchmark dose (BMD) approach is an alternative to the NOAEL/LOAEL approach that has been used for many years and by many international agencies (including the U.S. EPA and OECD) in dose-response assessment. The BMD approach is preferred in this assessment because of the recognized limitations in the NOAEL/LOAEL approach, and the key advantages BMD offers over the NOAEL approach, including using all experimental data (which reflects the dose-response relationship to a greater degree and is less dependent on study size), being independent of predefined dose levels and spacing of dose levels, and allowing the calculation of the magnitude of any effect within the observable range.

BMD modeling of total WBC and lymphocyte counts using historical and concurrent control HLS (2001) datasets from female rats resulted in the lowest $BMDL_{1SD}$ of 4.12 mg/kg bw per day (ATSDR, 2011) this value is used as our point of departure.

$$TDI = \frac{BMDL_{1SD}}{UF}$$

$$= \frac{4.12 \text{ mg/kg bw per day}}{1000}$$

$$= 0.00412 \text{ mg/kg bw per day}$$

where:

TDI = tolerable daily intake; the concentration of a chemical that is not expected to pose a risk to human health resulting from daily exposure over a lifetime;

$BMDL_{1SD}$ = For continuous datasets, the benchmark response was set to 1 standard deviation in order to obtain a benchmark dose 95% lower confidence limits ($BMDL_{1SD}$) value of 4.12 mg/kg bw per day for sulfolane which is comparable to a $BMDL_{10}$ (10 % additional risk) for dichotomous datasets; and

UF = uncertainty factor of 1000 is selected as follows: ×10 for interspecies variability, ×10 for intraspecies variability and ×10 for database deficiencies (including use of a subchronic study and lack of appropriate toxicity and epidemiological studies.

Based on the above TDI, a drinking water guidance value (DWGV) is calculated as follows:

$$\text{DWGV} = \frac{\text{TDI} \times \text{BW} \times \text{AF}}{\text{WC}}$$

$$= \frac{0.00412 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L}}$$

$$= 0.04 \text{ mg/L (rounded)}$$

where:

BW = body weight; the mean body weight estimated for an adult Canadian is 70 kg;
AF = allocation factor; the proportion of exposure to sulfolane from drinking water, as opposed to other environmental media (i.e., food, air, soil, consumer products). 20% is used as a "floor value" when drinking water is not a major source of exposure (Krishnan and Carrier, 2013);
WC = water consumption; the estimated daily volume of tap water consumed by an adult is 1.5 L.

A DWGV of 0.04 mg/L (40 µg/L) for sulfolane is recommended by Health Canada.

Appendix - International Considerations

There are no regulatory limits for sulfolane in drinking water. The Agency for Toxic Substances and Disease Registry (ATSDR) did perform a Health Consultation on sulfolane for the Alaska Department of Health and Social Services. The ATSDR recommended an oral exposure limit of 70 µg/L (ATSDR, 2011). This limit was based on a provisional health guidance value of 0.002 mg/kg/day resulting from a 1.5 mg/kg bw per day BMDL (dispersion of spleen's white pulp in guinea pigs after subchronic oral exposure (Zhu et al., 1987)) and an uncertainty factor of 1000 (×10 for interspecies variation, ×10 for intraspecies variability and ×10 for using a subchronic study). The ATSDR document was criticized by peer reviewers for the use of the Zhu et. al. (1987) study as the basis for their provisional health value.

The U.S. EPA Superfund Technical Support Center recently released a provisional chronic RfD value for sulfolane of 0.001 mg/kg bw per day based on a NOAEL of 2.9 mg/kg bw per day (reduced WBC counts in female rats; HLS, 2001) and a 3000-fold composite uncertainty factor (× 10 interspecies variation, ×10 intraspecies variation, ×10 for using a subchronic study and ×3 for developmental uncertainty; U.S. EPA, 2012).

The CCME developed a source guidance value for groundwater for sulfolane of 0.09 mg/L. A TDI of 0.0097 mg/kg bw per day was based on a NOAEL of 2.9 mg/kg bw per day (reduced WBC counts in female rats (HLS, 2001)) and an uncertainty factor of 300 (×10 for interspecies variation, ×10 intraspecies variation and ×3 for adequate but not extensive dataset and subchronic extrapolation; CCME, 2006). The British Columbia Ministry of Water, Land and Air protection also developed an ambient water quality guideline for sulfolane that is the same as CCME's (British Columbia, 2003).

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