Health Consultation

Sulfolane

February 3, 2010

Prepared by

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Introduction and Background

The Alaska Department of Health and Social Services requested that the ATSDR Division of Toxicology and Environmental Medicine provide a chemical specific health consultation for the chemical sulfolane. Sulfolane has been detected in the groundwater under the city of North Pole, Alaska and a completed exposure pathway exists to residents through the groundwater. Alaska specifically requested that ATSDR develop a public health action level for sulfolane in the drinking water, as well as describing potential health effects of sulfolane exposure. The public health action level is a non-regulatory level set to identify if human exposure to that water needs to be evaluated further (a/k/a, a screening level). If exposure is occurring, then consideration should be given to reducing that exposure.

Chemical and Physical Properties of Sulfolane

Sulfolane is an industrial solvent used in liquid-liquid and liquid-vapor extraction of compounds such as aromatic hydrocarbons from petroleum (VKH Brown et al. 1966; Andersen 1976; HSDB 2006). Sulfolane has also been reportedly used in fractionalization of wood tars, a component of hydraulic fluid, textile finishing, and as a curing agent in epoxy resins (HSDB 2006). Sulfolane has reportedly no odor and is completely miscible in water, acetone, glycerol and many oils (VKH Brown et al. 1966). Figure 1 shows sulfolane's molecular structure. Important physical properties are summarized in Table 1. Sulfolane mixes well in water, is not very volatile, not highly viscous and is highly polar.

Figure 1: Sulfolane

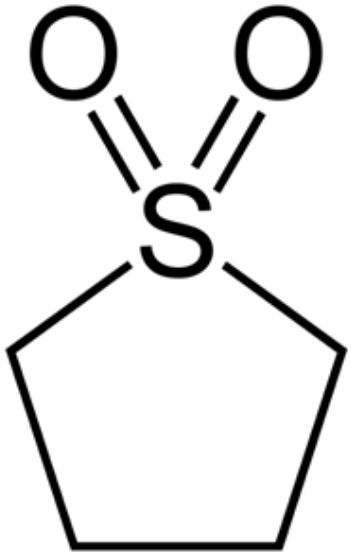

Table 1: Physical Properties of Sulfolane (VKH Brown et al. 1966; HSDB 2006; NIOSH 2006)

Physical Property	Value
CAS Number	126-33-0
Molecular Weight	120.18
Freezing Point	27.4 – 27.8 °C
Boiling Point	285 °C
Specific Gravity (30/20 °C)	1.265
Refractive Index	14.53 mm. Hg
Vapor Pressure (27.6 °C)	0.0062 mm. Hg
(116 °C)	5 mm. Hg
(150 °C)	14.53 mm. Hg
(250 °C)	333.70 mm. Hg
Henry's Law constant	4.6 X 10^{-6} atm-m^3/mole
Viscosity	10.3 Centipoises
Dipole moment (in benzene)	4.69 Debye
Dielectric constant (33 °C)	44

Absorption, Distribution, Metabolism and Excretion

Sulfolane is not well absorbed through human skin, with a reported permeability constant of 0.2 g/m^2/h (Ursin et al. 1995). Sulfolane is well absorbed through the oral route (Andersen 1976). Blood sulfolane decay curves were generated following intravenous injections of sulfolane in rabbits, dogs and squirrel monkeys (Andersen et al. 1977). Sulfolane distributed rapidly in test animals, with a reported volume of distribution that was near 1.0 l/kg (Andersen et al. 1977). Sulfolane was removed from plasma with a half life of 3.5 to 5.0 hours (Andersen et al. 1977).

The metabolite of sulfolane is 3-hydroxysulfolane (Roberts and Warwick 1961). As dosage of sulfolane increases in rats, the proportion of sulfolane that is excreted unchanged increases, suggesting a saturable metabolic pathway (Andersen et al. 1977). When 100 mg of sulfolane was administered intraperitoneal (i.p.) to rats, 85% of the sulfolane was excreted as a metabolite, 3-hydroxy sulfolane, in the first 24 hours (Roberts et al. 1960).

Acute Toxicity Data

Acute health effects arise from exposure to a substance that occurs once or for only a short time (up to 14 days). Acute lethal dose testing of sulfolane reported in the open literature is shown in Table 2. Non-lethal testing is shown in Table 3. Limited data on the dermal irritancy and sensitivity of sulfolane suggest a low potential for sulfolane to be a sensitizer or an acute irritant in drinking water.

Lethal Dose

In lethal dose studies, sulfolane produced signs consistent with central nervous system toxicity (Table 2) (Andersen et al. 1976). Mice and rats assumed a hunched, retreating posture with front limbs braced wide, and tail erect (Andersen et al. 1976). They were also hyperreactive, showed increased responsiveness to auditory stimulation, and respired rapidly (Andersen et al. 1976). At lethal doses, rats and mice exposed to sulfolane had clonic-tonic convulsions which could occur spontaneously or could be induced by sharp, loud noises (Andersen et al. 1976). Because sulfolane causes a regulated hypothermia, the lethality of sulfolane was directly related to ambient temperature, i.e. lower temperature resulted in lower mortality in mice (Gordon et al. 1986). This effect could be the result of the lower temperature itself, or the lowered metabolism induced by the regulated hypothermic response (Gordon et al. 1986).

Table 2: Acute Lethality Values for Sulfolane

Species	Type	Route	Value	Source
Rat	LD-50	Oral	2342 mg/kg	(Zhu et al. 1987)
	LD-50	Oral	2100 mg/kg	(VKH Brown et al. 1966)
	LD -50	Oral	1846 mg/kg	(Andersen et al. 1976)
	LD-50	Oral	1965 mg/kg	(Smyth et al. 1969)
	LD-50	Intraperitoneal	1600 mg/kg	RTECS (NIOSH 2006)
	LD-50	Intraperitoneal	1598 mg/kg	(Andersen et al. 1976)
	LD-50	Subcutaneus	1620 µl/kg (2049 mg/kg)	RTECS
	LD -50	Subcutaneus	1606 mg/kg	(Andersen et al. 1976)
	LD-50	Intravenous	1094 mg/kg	(Andersen et al. 1976)
	LD-50	Skin	>3800 mg/kg	RTECS
	LC-50	Inhalation	4-hour, >1200 mg/m^3	(Andersen et al. 1977)
	Other (lethal convulsions, pulmonary hemorrhage)	Inhalation	17.5-hour, 3600 mg/m^3	(Andersen et al. 1977)

Mouse	LD-50	Oral	1900 mg/kg	RTECS
	LD-50	Oral	2504 mg/kg	(Zhu et al. 1987)
	LD-50	Oral	(1900-2500 mg/kg) *	(VKH Brown et al. 1966)
	LD-50	Intraperitoneal	1250 mg/kg	RTECS
	LD-50	Intraperitoneal	1270 mg/kg	(Andersen et al. 1976)
	LD-50	Intravenous	1080 mg/kg	RTECS
	LD-50	Intravenous	632 mg/kg	(Andersen et al. 1976)
	LD -50	Subcutaneus	1360 mg/kg	(Andersen et al. 1976)
Rabbit	LD-50	Skin	3180 µl/kg (4023 mg/kg)	RTECS
	LD-50	Intravenous	(640– 850 mg/kg) †	(Andersen et al. 1976)
	LD-50	Subcutaneus	(1900-3500 mg/kg) †	(Andersen et al. 1976)
Guinea pig	LD-50	Oral	1815 mg/kg	(Andersen et al. 1976)
	LD-50	Oral	1445mg/kg	(Zhu et al. 1987)
	LD-50	Intraperitoneal	1331mg/kg	(Andersen et al. 1976)
Monkey	Other (lethality-convulsions >25% reduction in white blood count >15% reduction in HGB and HCT	Inhalation	4850 mg/m^3	(Andersen et al. 1977)

* Authors provided only a range value of LD-50 without explanation

† Not enough animals were used to calculate an LD50, so only a range is given – all animals survived at the lower dose and all animals died at the higher dose.

Acute Toxicity

The acute effects of sulfolane have been studied by several researchers (Table 3). The effects of sulfolane noted have been changes in thermoregulation, changes in motor activity, and changes in brain-wave patterns in rats. As noted above, lethal doses of sulfolane result in neurotoxicity as demonstrated by clonic-tonic convulsions.

Neurotoxicity

Single intraperitoneal (i.p.) injections of 800 mg/kg and 400 mg/kg produced dose-dependent significant changes in flash evocated potentials (FEPs) and pattern-reversal evoked potentials (PREPs) (Dyer et al. 1986). These changes lasted over six hours after treatment, with effects diminishing with time. The 200 mg/kg dose did not produce a change in either FEPs or PREPs.

The 400 mg/kg and 800 mg/kg doses resulted in hypothermia in the rats. Changes in FEPs were not shown to be secondary to hypothermia in the rats. When hypothermia was prevented in the 800 mg/kg dose group of rats by keeping them in a warm ambient environment, sulfolane still resulted in changes in FEPs latencies. PREPs were not measured in the group in which hypothermia was prevented.

Burdette and Dyer (1986) conducted a series of experiments to identify sulfolane dosages that alter seizure susceptibility to confirm the results of previous studies that sulfolane-treated animals are hyper-reactive to sound. A second set of experiments was conducted to determine the potential interaction between hypothermia and the convulsant properties of sulfolane. I.p. doses of 800 mg/kg (one-half the lethal dose), 400 mg/kg, 200 mg/kg and 0 mg/kg (controls) were administered to young male Long Evans hooded rats. On stimulation, audiogenic seizures were observed in approximately half the animals treated with 800 mg/kg in both experiments. Rats administered 400 mg/kg demonstrated minimal seizure susceptibility in the first study, but not in the second. No seizure activity was seen in the 200 mg/kg or control animals. With respect to the susceptibility to audiogenic seizures, the authors reported that it was evident that hypothermia provided a significant protective influence, as inferred from the statistically significant decrease in seizure severity and duration. It was further concluded that sulfolane preferentially lowers seizure thresholds in select brain structures, rather than creating a general predisposition to seizures triggered by any mechanism.

Metabolic Changes and Thermoregulation

Gordon et al. (1985) measured effects in thermoregulatory responses in male Sprague-Dawley-rats that were injected (i.p.) with 800 milligrams per kilogram (mg/kg) sulfolane at ambient temperatures of 15 or 25 degrees-C. At ambient temperatures of either 15 or 25 degrees, sulfolane significantly inhibited metabolic rates and colonic temperatures. The metabolic rate was depressed for 4 hours post injection, gradually recovering thereafter. Colonic temperature was depressed for 8 hours after injection. Tail skin temperature was not affected by sulfolane at either ambient temperature. The authors suggest that recovery of the thermoregulatory function may parallel sulfolane clearance from the blood in rats.

Male rats were injected i.p with 0, 200, 400 or 800 mg/kg of sulfolane and placed in ambient temperatures of 15, 25 or 35 °C (Gordon et al. 1984). At 15 and 25 °C, 400 and 800 mg/kg of sulfolane resulted in statistically significant reduction in core body temperatures in the rats. Metabolism was statistically lower in the 800 mg/kg treatment groups at ambient temperatures of 15 and 25 °C. At 35 °C, no dose of sulfolane resulted in statistically significant reductions in core body temperature.

In a similar experiment, mice were treated with sulfolane (0, 200, 400, 600 and 800 mg/kg i.p.) and kept at ambient temperatures of 20, 30 and 35 °C (Gordon et al. 1986). Sulfolane caused a dose dependent and temperature dependent significant decrease in metabolism and colonic temperature at 400, 600 and 800 mg/kg in mice. At an ambient temperature of 35 °C, no statistically significant changes in metabolism or colonic temperature were measured. At 20 °C, statistically significant decreases in metabolism and colonic temperature were measured at 400, 600 and 800 mg/kg doses. At 30 °C, the statistically significant decreases in metabolism and colonic temperature occurred in the 600 and 800 mg/kg dose groups only.

Sulfolane can affect the preferred ambient temperature of mice (Gordon et al 1986). Mice treated with 400, 600, and 800 mg/kg (i.p.) preferred significantly lower ambient temperatures in a temperature gradient. After 1 hour, mice having received 600 and 800 mg/kg of sulfolane still preferred statistically lower temperatures. The authors also studied preferred ambient temperature in 800 mg/kg (i.p.) sulfolane treated rats (Gordon et al. 1985). Rats selected the same ambient temperature (20.7 degrees) as the controls 1 hour after injection. Over time, sulfolane treated rats preferred a statistically insignificant lower temperature than controls. At the end of 8 hours, the preferred ambient temperature of control and sulfolane treated animals had increased to 24.5 and 23.5 degrees, respectively.

Ruppert and Dyer (1985) investigated the effects of sulfolane on the behavior of rats at ambient temperatures which would either prevent (32.3 °C) or facilitate (20.8 °C) the development of hypothermia using figure-of-eight mazes. Behavior was assessed 1 hour after i.p. dosing of saline, 200, 400 or 800 mg/kg sulfolane. Sulfolane reduced activity in the rats in both temperature groups at 400 and 800 mg/kg doses. However, at the warmer temperature, the effects were produced without hypothermia. At 20.8°C , the decrease in behavior activity was more pronounced than the warmer temperature group.

Burdette and Dyer (1986) found that the affect of sulfolane on hypothermia was different in animals maintained at 29^{o}C (approx. 84^{o}F) compared with animals maintained at 23^{o}C (approx. 74^{o}F) during experimentation. At 29^{o}C, the housing temperature was sufficiently warm to control/prevent the dose-dependent hypothermia seen at 23^{o}C housing temperature in all groups. At the 23^{o}C housing temperature, colon temperatures decreased rapidly in the 800 mg/kg and 400 mg/kg groups by more than 3^{o}C during the first half hour following injection, after which the deep body temperature either stabilized or continued to decrease. The colonic temperatures remained significantly depressed for up to 8 hours in both of these high-dose groups. In the 200 mg/kg and control groups, there was a slow recovery after 3 hours, the deepest point of temperature depression.

Subcutaneous injections of sulfolane in rabbits at an ambient temperature of 10 °C caused a dose-dependent decrease in colonic temperature (Mohler and Gordon 1988). While the metabolic rate remained the same, a 1.5 °C transient increase in ear temperature and approximately 0.3 °C decrease in colon temperature were observed at 200 mg/kg (Mohler and Gordon 1988).The mechanism of toxicity in rabbits appears to be a result of changes in the vasomotor component of thermoregulation, whereas in rats and mice it appears that sulfolane induced hypothermia is caused by a reduction in metabolic rate (Gordon et al. 1985; Mohler and Gordon 1988).

Mohler and Gordon (1989) studied the thermoregulatory effects of sulfolane on the central nervous system of rabbits by microinjection of sulfolane into the region of the brain that controls thermoregulation. The rabbits were kept during treatment at an ambient temperature of 15 °C. Microinjection of saline, 100,300 or 1000 µg of sulfolane in saline into the preoptic/anterior hypothalamic area of the brains of rabbits did not result in regulated hypothermia. This suggests that the sulfolane is not directly acting on the center of thermoregulation in the brain. To evaluate whether changes in thermoregulation were the result of other centers of the brain being affected by sulfolane, Mohler and Gordon (1989) administered intracerebroventricular, (ICV) microinjection of sulfolane to rabbits. ICV microinjection of 300 and 1000 µg of sulfolane resulted in slight rise in the temperature of the preoptic/anterior hypothalamic area. An ICV injection 3000 µg of sulfolane caused a statistically significant hyperthermia in rabbits. At

10,000 µg ICV injection, sulfolane caused a slight decrease in the temperature of the preoptic/anterior hypothalamic area, followed by an increase in temperature. These data do not support the conclusion that sulfolane directly affects the centers of the brain involved in thermoregulation. However, the metabolite of sulfolane (3-hydroxy sulfolane) may act on these centers (Mohler and Gordon 1989).

Table 3: Acute Non-lethal Values for Sulfolane

Species	Type	Route	Value	Source
Rat	LOAEL (Thermoregulation)	Intraperitoneal (i.p.)	800 mg/kg	(Gordon et al. 1985)
	LOAEL (Thermoregulation)	i.p.	400 mg/kg	(Ruppert and Dyer 1985)
	NOAEL (Thermoregulation)	i.p.	200 mg/kg	(Ruppert and Dyer 1985)
	NOAEL (Thermoregulation)	i.p.	200 mg/kg	(Ruppert and Dyer 1985)
	NOAEL (Thermoregulation)	i.p.	200 mg/kg	(Burdette and Dyer 1986)
	NOAEL (Visual Evocated Potentials)	i.p.	200 mg/kg	(Dyer et al. 1986)
	LOAEL (Seizure susceptibility)	i.p.	400 mg/kg	(Dyer et al. 1986)
	NOAEL (Seizure susceptibility)	i.p.	200 mg/kg	(Dyer et al. 1986)
	LOAEL (Motor activity)	i.p.	400 mg/kg	(Ruppert and Dyer 1985)
Rabbit	LOAEL (Thermoregulation)	Subcutaneous (s.c.)	200 mg/kg	(Mohler and Gordon 1988)
Mouse	LOAEL (Thermoregulation)	i.p.	400 mg/kg	(Gordon et al. 1986)
	NOAEL (Thermoregulation)	i.p.	200 mg/kg	(Gordon et al. 1986)
	NOAEL (Developmental)	Oral	280 mg/kg	(Zhu et al. 1987)
	LOAEL (Developmental)	Oral	840 mg/kg	(Zhu et al. 1987)
	NOAEL (Genotoxicity)	Oral	62.5 mg/kg	(Zhu et al. 1987)
Dog	LOAEL – Neurological Convulsions Aggressive Behavior Effects	Inhalation (After 7 days)	200 mg/m^3	(Andersen et al. 1977)

Skin and Eye Irritation and Sensitivity

Limited information on skin and eye irritation has been reported in the literature. Smyth et al. (1969) report that sulfolane resulted in a "2" on a 10 point ordinal scale of irritation on

uncovered rabbit belly. The procedure for evaluation was observation of the severest reaction on the clipped skin of five albino rabbits within 24 hours of the uncovered application of 0.01 milliliters undiluted sample or solutions in water, propylene glycol, or acetone. Grade 1 indicated no irritation; grade 2 indicated the least visible capillary injection from the undiluted chemical. Grade 6 indicated necrosis when undiluted chemical was applied, and grade 10 indicated necrosis from a 0.01% solution. 1 milliliter of sulfolane per day applied and occluded did not produce irritation to bare rabbit skin (VKH Brown et al. 1966). 0.5 to 1 milliliter of sulfolane applied to bare skin of rabbits and guinea-pigs for five days per week for four and one half weeks did not result in gross or microscopic skin irritation (VKH Brown et al. 1966). Intradermal or topical application of sulfolane did not result in sensitivity (VKH Brown et al. 1966).

Smyth et al. (1969) rated eye injury in rabbits exposed to sulfolane as a "4" on a 10 point grading. The exact conditions or effects of the test were not reported, but a grade 1 indicated no irritation, and a grade of 5 indicated a severe burn with 0.005 ml (Smyth et al. 1962). We suspect that this means the substance was graded as moderately irritating to the eyes. However, Brown et al. (1966) reported that 0.2 ml of undiluted sulfolane applied to the right eyes of rabbits produced mild conjunctivitis which cleared within a few hours.

Due to the subjectivity of these tests and non-standardized laboratory practices at the time, moderate intra-laboratory reproducibility and low inter-laboratory reproducibility have been noted in these types of tests (Weil and Scala 1971). Therefore, some discrepancies in the results are not unexpected.

Developmental Effects

Sulfolane was orally administered to pregnant mice at doses of 93, 280, or 840 mg/kg (Zhu et al. 1987). Skeletal changes were found in the fetuses at the 840 mg/kg dose but not at the lower treatment dosages.

Genotoxicity

Mice were orally administered doses of 62.5, 125, 250, 500, or 1000 mg/kg. Using the mice marrow erythrocyte micronucleus test, sulfolane did not cause increases to the micronucleus counts in the mice marrow erythrocytes (Zhu et al. 1987).

Intermediate/Sub-Chronic Toxicity

Intermediate/sub-chronic toxic effects are a result of exposure to a substance that occurs for more than 14 days and less than a year. Sub-chronic studies are summarized in Table 4. Another study, published by Huntington Life Sciences was reported in other literature as a 13 week oral study (CCME 2006). This study reported a NOAEL of 2.9 mg/kg/day. This research, however, is not available due to proprietary agreements (Turner 2009).

Table 4: Sub- Chronic Studies of Sulfolane

Species	Effect	Route	Value	Source
Rat	NOAEL – Respiratory	Inhalation 23 hrs/day 5 days/week 90 DAYS	20 mg/m^3	(Andersen et al. 1977)

	LOAEL – Inflamed hemorrhagic lungs	Inhalation 23 hrs/day 5 days/week 90 DAYS	159 mg/m^3	(Andersen et al. 1977)
	LOAEL – Chronic inflammation	Inhalation 8 hrs/day 5 days/week 27 days	495 mg/m^3	(Andersen et al. 1977)
	NOAEL	Oral 90 days	167 mg/kg/day	(Zhu et al. 1987)
	LOAEL – Decreased ascorbic acid in adrenal glands	Oral 90 days	500 mg/kg/day	(Zhu et al. 1987)
	LOAEL – decreased birth index and number of pups (day 0 and 4 of lactation)	Oral 49 days (males) 41-50 days (females)	200 mg/kg/day	(OECD 2004)
	NOAEL – Reproductive Developmental	Oral 49 days (males) 41-50 days (females)	60 mg/kg/day	(OECD 2004)
Monkey	LOAEL – Death	Inhalation 8 hrs/day 5 days/week 27 days	495 mg/m^3	(Andersen et al. 1977)
Dog	NOAEL – Respiratory	Inhalation 23 hrs/day 5 days/week 90 DAYS	20 mg/m^3	(Andersen et al. 1977)
	LOAEL – Inflamed hemorrhagic lungs	Inhalation 23 hrs/day 5 days/week 90 DAYS	159 mg/m^3	(Andersen et al. 1977)
Guinea Pig	LOAEL - Hepatic Effects Changes in Serum ALP Changes in White Blood Cell count	Oral (6 months)	2.5 mg/kg/day	(Zhu et al. 1987)
	NOAEL	Oral (6 months)	0.25 mg/kg/day	(Zhu et al. 1987)

Death

Nine male monkeys were exposed to 495 mg/m^3 for 27 days (23 hrs/day, 5 days/week) (Andersen et al. 1977). Three died during the course of the exposure and 5 others were found to be at the point of death and were sacrificed. The monkeys were found to have blood tinged fluid around the eyes and very pale livers and hearts. Of the remaining six monkeys surviving, fatty metamorphosis of the liver was observed in five.

Respiratory Effects

Andersen et al. (1977) exposed rats, guinea pigs and dogs to inhalation concentrations of 2.8, 4.0, 20, 159 or 200 mg/m^3. Hemorrhagic, inflamed lungs were observed in all species at concentrations of 159 and 200 mg/m^3. Dogs and rats exposed to 495 mg/m^3 for 27 days had chronic lung inflammation (Andersen et al. 1977).

Skin Irritation

Repeated application of 1 ml sulfolane to the bare skin of rabbits and 0.5 ml for guinea pigs of undiluted sulfolane for 5 days/week for four and one-half weeks did not result in gross visible skin irritation or in microscopic findings (VK Brown et al. 1966).

Hematological Effects

At 500 mg/kg for 90 days in guinea pigs the ascorbic acid content in the adrenal glands decreased. No blood change parameters were noted in rats at doses of 55.6 and 167 milligrams/kilogram/day (mg/kg/d) (Zhu et al. 1987). Guinea pigs were exposed to sulfolane at oral dose levels of 0, 0.25, 2.5, 25, or 250 mg/kg/d for six months (Zhu et al. 1987). Marrow cell numbers were lower in the 2.5, 25 and 250 mg/kg/d dose groups than the control group.

Hepatic Effects

Guinea pigs exposed to 200 mg/m^3 for 90 days via inhalation showed fatty vacuolization in livers (Andersen et al. 1977). This was not observed at 2.8, 4, 20 or 159 mg/m^3. Nine male monkeys were exposed to 495 mg/m^3 for 27 days (23 hrs/day, 5 days/week) (Andersen et al. 1977). Between exposure days 7 and 17, eight of the monkeys died or were found to be at the point of death and sacrificed. Fatty metamorphosis of the liver was observed in 5/6 of the surviving monkeys.

Guinea pigs and rats were orally exposed to doses of 55.6, 167 or 500 mg/kg/d for 90 days. Serum ALP activity decreased in guinea pigs at 55.6 and 167 mg/kg/d (but not at 500 mg/kg/d) (Zhu et al. 1987). White blood cell counts decreased in all groups. Guinea pigs exposed to 159 or 200 mg/m^3 via inhalation showed leucopenia and increased plasma transaminase activity (Andersen et al. 1977). This was not observed at 2.8, 4 and 20 mg/m^3.

Guinea pigs were exposed to sulfolane at oral dose levels of 0, 0.25, 2.5, 25, or 250 mg/kg/d for six months (Zhu et al. 1987). Biochemical and pathological evaluations were conducted on a subset of each dose group following three months and six months of exposure. GPT (Glutamic-pyruvic transaminase), GOT (glutamic-oxaloacetic transaminase) and fatty deposits of the liver were observed in pathological examinations of the 2.5, 25 and 250 mg/kg/d dose groups. No pathological effects were noted at 0.25 mg/kg/d dose group.

Lymphoreticular Effects

In the Zhu et al. (1987) 6-month study, at three months and six months of exposure, shrinkage of the white pulp in the spleen was observed in the 2.5, 25 and 250 mg/kg/d guinea pig dose groups, but not in the control groups. In the 2.5 mg/kg/d, 25 mg/kg/d and 250 mg/kg/d dosage groups, a decrease in cell counts in spinal marrow was found.

Neurological Effects

In the inhalation toxicity study of dogs conducted by Andersen et al. (1977), four dogs were exposed to 200 mg/m^3 by inhalation. The dogs suffered intermittent convulsions after 7 days of exposure and displayed fiercely aggressive behavior towards each other and their handlers (Andersen et al. 1977). After 11 days, one dog in the exposure group was suffering generalized motor seizures. Another dog had to be removed due to extremely aggressive behavior. A third dog was removed from the experiment after 29 days because he had become too dangerous for his handlers. Exposure in this group was intended for 23 hr/day for 90 days.

Developmental/Reproductive Effects

A reproduction/developmental toxicity screening test [OECD 421]) was reported in an OECD report (OECD 2004). This study was conducted by Japanese Ministry of Health (MHW 1999) and the report was peer reviewed by OECD. Rats were dosed at 0, 60, 200, or 700 mg/kg/d by gavage for 41 to 50 days from 14 days prior to mating to day 3 of lactation. Some mortality occurred in the high-dose group. There was a decrease in body weight gain and food consumption for males and females during the pre-mating period at 700 mg/kg/d. The number of oestrus cycles was decreased in the 700 mg/kg/d group. Four dams lost all their pups during the lactation period in the 700 mg/kg/d group. Birth index, live index, number of pups on days 1 and 4 of lactation, viability index and body weights of pups of both sexes on days 0 and 4 of lactation decreased, and the number of still births increased in the 700 mg/kg/d group. Delivery and birth index were decreased in the 200 mg/kg/d group. The NOAEL for reproductive and developmental toxicity was 60 mg/kg/day. There were no treatment-related findings in the external appearance, general conditions and necropsy findings in offspring.

Chronic Toxicity

Chronic toxic effects arise from exposure that exceeds one year. No chronic toxicity studies have been identified by ATSDR. Only one open literature report of longer term sub-chronic toxicity was located by ATSDR (Zhu et al. 1987).

In Vitro Tests

In five bacterial strains (TA 1535, TA 1536, TA 1537, TA 98, and TA 100), sulfolane was not mutagenic in the presence or absence of S-9 activation at concentrations of 0, 2, 20, 200, or 2000 µg per plate (Zhu et al. 1987). Sulfolane did not have a significant effect on sister chromatid exchange in vitro in human peripheral blood lymphocytes (Zhu et al. 1987). OECD (2004) and CCME (2006) did not note that sulfolane was mutagenic in bacteria, nor did it induce chromosomal aberrations in mammalian cells in other unpublished tests they had obtained.

Quantitative Structure Toxicity Relationships

Quantitative Structure Toxicity Relationship (QSTR) has been used as a method for the estimation of sulfolane toxicity. QSTR utilizes a computer-based method to predict the toxicity of a chemical solely from its molecular attributes. TOPKAT/QSTR 6.2, a tool for structure-based toxicity assessment, correlates toxicity with a set of structural descriptors and gives a probability value between 0 and 1. A value between 0 - 0.3 is considered negative or of low probability; a value between 0.3 – 0.7 is considered indeterminate (i.e. (50/50 probability) for an assessment to be meaningful, and a value greater than 0.7 is considered positive.

TOPKAT automatically performs two analyses, the univariate analysis or coverage examination and the multivariate analysis or Optimum Prediction Space (OPS) examination to increase confidence in prediction. The univariate analysis checks whether all of the structural fragments of the query structure are represented in the data base compounds that were used in model development and that at least three compounds in the data-base have the same descriptors as that present in the query compound. In the event that structural attributes of these query compounds are not presented in the training set, the software warns the user of this fact and displays a message stating that the toxicity assessment may be unreliable. The multivariate analysis or OPS examination checks to see whether the submitted structure fits within or near the periphery of the OPS of the equation. If a query compound is determined to be outside the OPS, a warning about the acceptability of the assessment is displayed.

It is important to note that a query chemical being inside or near the periphery of the OPS does not necessarily mean that the predicted toxicity value for that chemical will have agreement with the experimental value. Rather, it implies that the model is applicable to that particular query compound and the probability of agreement between the experimental and predicted value is as high as that for the chemicals in the database.

QSTR models were used to evaluate the rodent oral carcinogenicity (female/male; rat/mouse), rat oral developmental toxicity and mutagenesis of sulfolane (Table 5).

Table 5: TOPKAT prediction of toxicity of sulfolane

Effect	Species	Result
Carcinogenicity	Rat (male)	Negative
	Rat (female)	Negative
	Mouse (male)	Negative
	Mouse (female)	Negative
Developmental Toxicity Potential		Positive
Mutagenesis Potential	Bacteria	Positive
LD50	Rat	1000 mg/kg (95% CI 202.2 mg/kg – 5100 mg/kg)

Skin Sensitization	Negative
Skin Irritation	Negative
Ocular Irritancy	Positive

Discussion

Sulfolane is acutely toxic at relatively high doses (over 200 mg/kg) in species tested. While the acute toxicity of sulfolane has been characterized in a number of species, a paucity of data exists on the longer term effects of sulfolane. Only one sub-chronic study, Zhu et al. 1987 was identified with effects noted in hepatic and lymphoreticular systems of rats (90 days) and guinea pigs (90 days and 6 months). An oral NOAEL for guinea pigs was identified as 0.25 mg/kg/day.

To assess the appropriate uncertainty and modifying factors, ATSDR considers the following facts:

- Guinea pigs were an order of magnitude (i.e., about 10-fold) more sensitive to sub-chronic effects than rats.
- QSTR methodology provides some assurance that sulfolane is probably not carcinogenic in either rats or mice. However, QSTR indicates that there is a potential for sulfolane to present developmental effects in animals. Developmental effects have been seen in two studies. Zhu et al. (1987) found developmental effects at a relatively high dose (½ the LD50) in mice. The Japanese Ministry of Health (JMH 1999) identified an oral developmental NOAEL of 60 mg/kg/day in rats and a LOAEL for developmental/reproductive effects at 200 mg/kg/day.
- No chronic toxicity studies could be identified for sulfolane.
- While the QSTR predicted a potential for there to be mutagenic effects, several tests both in vivo and in vitro have not noted mutagenicity.

Recommendations for Drinking Water at North Pole

A sub-chronic oral NOAEL of 0.25 mg/kg/day in guinea pigs was identified by Zhu et al. 1987. Utilizing an uncertainty of 10 for extrapolation from animals to humans is justified. To account for human variability, another uncertainty factor of 10 is applied. ATSDR therefore recommends that human exposures be limited to no more than 0.0025 mg/kg/day (2.5 µg/kg/day). Using standard water consumption assumptions (ATSDR 2005), this dose equates to the following action levels as protective of public health:

25 µg/l (ppb) for infant populations (Assumes 1 liter water per day at 10 kg bodyweight)

40 µg/l (ppb) for child populations (Assumes 1 liter water per day at 16 kg bodyweight)

87.5 µg/l (ppb) for adult populations (Assumes 2 liters water per day at 70 kg bodyweight)

Alternative Public Health Levels

The Canadian Council of Ministers of the Environment calculated a tolerable daily intake for sulfolane based on the Huntington Life Sciences NOAEL of 2.9 mg/kg/day in female rats

(CCME 2006, unpublished). Uncertainty factors of 10 for human to animal extrapolation, 10 for human variability, and 3 for extrapolation to chronic exposures as well as other database uncertainties was used. A total uncertainty factor of 300 was applied for a tolerable daily intake of 0.0097 mg/kg/day (9.7 µg/kg/day) Using default Canadian drinking water guidance, CCME derive a drinking water guidance value of 0.09 mg/l (90 µg/l or ppb) for adult receptors drinking 1.5 liters of water a day.

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