3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vivo Studies

Groups of 3 male rats were dosed intravenously at 500 or 1000 mg/kg with non-radiolabelled sulfolane and the amount of sulfolane excreted unchanged in the urine was measured for 7 days after administration using gas-liquid chromatography. At 500 mg/kg, 28%, 36% and 37% of the dose was excreted unchanged between days 0-2, 0-4 and 0-7, respectively. At 1000 mg/kg, 50% and 67.2% of the dose was excreted unchanged between days 0-2 and 0-4, respectively. The observation that the proportion of the dose recovered increased with dosage suggests that the metabolic pathway is saturable. In a follow up to this study, blood-sulfolane decay curves were obtained following intravenous injections of sulfolane to a single rabbit, dog and squirrel monkey. Sulfolane was rapidly distributed throughout the animals and being slowly removed from plasma with a half-life of 3.5-5 hours (Andersen, 1976). No information is given on which tissues sulfolane distributes to in this study.

In a second study 3 male Wistar rats were injected intraperitoneally with ^{35}S-sulfolane (100 mg/rat in 2 ml water) and the 24 hour urinary samples analysed. One major metabolite was found, constituting 85% of the urinary radioactivity. Subsequently, 3 rabbits were injected intraperitoneally with a mixture of unlabelled sulfolane (1g) and ^{35}S-sulfolane (100 mg) and the urine samples collected and extracted with chloroform. The metabolite was identified as 3-hydroxysulfolane (Roberts, 1961).

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

There is one reliable study reported. Andersen et al (1977) examined the acute inhalation toxicity of sulfolane. No rats died after 4 hours exposure to sulfolane at 12,000 mg/m^3 (the highest concentration that could be maintained as a stable aerosol) or during a subsequent 2-week observation period. Exposures at these high concentrations were continued until all all rats died. It was calculated that a mean survival time of 24 hours would be observed in atmospheres containing 4700 mg/m^3 of sulfolane. In a second experiment, nine rats were exposed to sulfolane at a concentration of 3600 mg/m^3 for 17.5 hours (when all the rats had convulsed and were *in extremis*). Significant decreases in white blood cell counts were observed, but haemocrit and haemoglobin were unchanged. At necropsy, all rats exhibited varying degrees of pulmonary haemorrhage. In a third experiment, two squirrel monkeys exposed to 4850 mg/m^3 vomited and convulsed during exposure and were sacrificed after 18.5 hours. Both had a greater than 25% decrease in white blood cells and a greater than 15% reduction in haemoglobin and haematocrit. Once again, pulmonary haemorrhage was evident. The LC_{50} (4h, rat) was > 12,000 mg/m^3.

Table 3 Acute inhalation toxicity to experimental animals

Species	Exposure time	Result	Reference
Rat	4 h	LC_{50} >12 000 mg/m^3 (combined)	(Andersen et al.,

Rat	17.5 h	Total mortality: LC_{50} <3600 mg/m^3 (males)	1977)
Monkey	18.5 h	Total mortality: LC_{50} <4850 mg/m^3 (males)	

Dermal

There are four acute dermal toxicity studies, one of which is considered reliable. In this study, conducted to GLP [Directive 84/449/EEC, B3], sulfolane was applied directly to the intact skin of 5 male and 5 female rats at a dose of 2000 mg/kg and covered with an occlusive dressing for 24 hours. There were no deaths or signs of systemic toxicity during the 14-day observation period and no macroscopic changes were apparent at necropsy (Gardner, 1993). The LD_{50} was > 2000 mg/kg.

Oral

There are 10 acute oral toxicity studies. In a reliable study [OECD TG 401, GLP] male and female rats (5 animals of each sex per dose) were dosed by gavage at doses of 0, 892, 1204, 1626, 2191, 2963 and 4000 mg/kg. Clinical signs of convulsion as well as decreased locomotion activity, ptosis, salivation, piloerection, chromodacryorrhea and perineal region soiling with urine were observed in the treated groups. Body weights of the treated animals were lower than those of the control group on the day after dosing. All deaths occurred on the day of dosing at doses of 2195 mg/kg and above. Dead animals showed haemorrhagic black spots in their glandular stomach mucosa. The LD_{50} was 2006 mg/kg (males) and 2130 mg/kg (females) (MHW Japan, 1996a).

In a second reliable study [Directive 84/449/EEC, B1, GLP] male and female rats (5 animals of each sex per dose) were dosed by gavage at 1600, 2240 and 3136 mg/kg. Deaths occurred from two hours after dosing until Day 2 among rats treated at the intermediate and high dose levels. Clinical signs included fasciculation, tremor, twitching, splayed gait, hunched posture, piloerection, unkempt appearance and yellow staining of the anogenital fur. Convulsions and salivation developed among the rats dosed at 2240 and 3136 mg/kg. Isolated cases of hypersensitivity to stimuli, hyperactivity, lethargy, hypothermia, diarrhoea, lachrymation, pallor of the eyes and blood around the mouth were also observed. Onset of the principal clinical signs was generally apparent within four hours of dosing. All surviving rats had gained weight relative to their Day 1 bodyweights by the end of the of the 14 day observation period. Necropsy findings amongst the decedents were lung congestion, exaggerated lobular pattern or dark patches on the liver, darkening of the spleen or kidneys and abnormal contents (colourless liquid or gaseous) of the gastrointestinal tract, especially the stomach and small intestine. Rats killed at completion of the observation period showed no macroscopic changes other than a single case of hepatic pallor. The LD_{50} was 2489 mg/kg (males), 2324 mg/kg (females) and 2473 mg/kg (combined) (Gardner, 1993).

In a third reliable study male and females rats (5 animals of each sex per dose) were dosed by gavage at 0, 1000, 1500, 2000, 3000 and 5000 mg/kg (males) and 0, 1000, 2000, 2500, 3000 and 5000 mg/kg (females). One male and five females dosed at 1000 mg/kg and four males dosed at 1500 mg/kg appeared normal from normal to termination. Clinical signs noted in the remaining animals included depression, slight depression, rough coat, salivation, hunched appearance, tremors, ataxia, urine stains, soft faeces and red stains on the nose and/or eyes. All surviving rats that showed clinical signs appeared normal by Day 3 through to termination of the study. All surviving rats gained weight relative to their Day 1 bodyweights. No gross pathological findings were observed in rats surviving to termination. Alterations of the stomach and/or intestines were the most common findings amongst animals that died. These alterations included compound like material, dark red material, reddish fluid or yellowish fluid in the stomach and/or intestines. Findings in the

lung and liver were noted at the 5000 mg dose only. The LD_{50} was 2739 mg/kg (males), 2108 mg/kg (females) and 2363 mg/kg (combined) (Phillips Petroleum Company, 1983a)

Table 4 Acute oral toxicity in experimental animals

Species	LD_{50}	Reference
Rat	2006 (males); 2130 mg/kg (females)	(MHW Japan, 1996a)
Rat	2489 (males); 2324 (females); 2473 mg/kg (combined)	(Gardner, 1993)
Rat	2739 (males); 2108 (females); 2363 mg/kg (combined)	(Phillips Petroleum Company, 1983a)

Other Routes of Exposure

Ruppert and Dyer (1985) studied the influence of hypothermia on the acute behavioural toxicity of sulfolane. Adult male rats (Long-Evans), 10 per group, received a single interperitoneal injection of saline, 200, 400 or 800 mg/kg sulfolane. Separate groups of rats at each dose were housed in rooms maintained at 32.3±0.7°C (warm ambient temperature) or 20.8±0.2°C (cool ambient temperature). Motor activity was assessed in figure of eight mazes one hour after dosing. Immediately after testing (one hour), body temperatures were recorded.

At the cool ambient temperature, the body temperature of rats receiving 400 and 800 mg/kg was lower than that of the controls. At the warm ambient temperature, hypothermia in the rats receiving 400 and 800 mg/kg was attenuated, if not prevented. One animal receiving 800 mg/kg at the warm ambient temperature died during testing. At both ambient temperatures, 400 and 800 mg/kg sulfolane produced a decrease in motor activity. At the cool ambient temperature, 800 mg/kg sulfolane produced a decrease in movement throughout the maze. It was concluded that a behavioural change could be detected at sublethal dosages of sulfolane in the absence of hypothermia.

Another similar study was conducted by Mohler and Gordon (1988) to investigate the thermoregulatory responses of the rabbit. Nine male rabbits were subcutaneously injected with 0, 100, 200, 400, 600 and 750 mg/kg sulfolane at an ambient temperature of 10°C. This caused a dose-dependent decrease in colonic temperature of the rabbits. Metabolic rate remained unchanged during the initial phase of the hypothermia for all dose groups; but peripheral vasodilation, as indicated by an increase in ear skin temperature, was seen at the higher dose levels. The highest doses of sulfolane caused behavioural deficits in the rabbits. Two to three hours after exposure to 600 mg/kg sulfolane, when the rabbits were removed from the environmental chamber and first observed, the animals exhibited a slight postural tremor similar to shivering. Both rabbits receiving 750 mg/kg sulfolane exhibited tonic seizures characterised by gross muscle contraction, forceful urination, and some vocalisation. These episodes were followed by exhaustion, panting, loss of postural control, and near catatonia. All rabbits in these experiments survived the sulfolane exposure, even at the highest dose levels. Seven male rats were subcutaneously injected with 600 mg/kg sulfolane at ambient temperatures of 10, 20 and 28°C. At ambient temperatures of 10 and 20°C there was a significant decrease in colonic temperature, however metabolic rate did not change significantly prior to or during peak hypothermia. At an ambient temperature of 28°C, there was a significant increase in colonic temperature and metabolic rate following administration of sulfolane.

Conclusion

The oral LD_{50} (rat) was 2006 mg/kg (males) and 2130 mg/kg (females) [OECD TG 401]. The dermal LD_{50} (rat) was > 2000 mg/kg [Directive 84/449/EEC, B3]. The inhalation LC_{50} (4h, rat) was > 12,000 mg/m^3.

Acute behavioural studies indicated hypothermia contributed to the behavioural effect of 800 mg/kg sulfolane in rats, however, the rabbits became hyperthermic, at 28°C, upon injection of 600 mg/kg sulfolane.

3.1.3 Irritation

Skin Irritation

Studies in Animals

In a reliable study (Brown et al., 1966) undiluted sulfolane (1 ml) was applied to the shaved backs of 4 male and 4 female rabbits on 3 consecutive days and covered with an occlusive bandage for 6 hours each day. The final visual assessment was made on day 7. No signs of skin irritation were observed in any of the rabbits used. Histopathological examination of the skins taken post mortem revealed no evidence of skin damage.

Brown et al. (1966) also applied undiluted sulfolane (0.5 ml) daily, five days per week for four and a half weeks to the shaved backs of 10 guinea pigs. Application areas were left uncovered during the test. In findings similar to those in the rabbit, no signs of skin irritation were observed. Histopathological examination of the skins taken post mortem revealed no evidence of skin damage.

Eye Irritation

Studies in Animals

In a reliable study [US Federal Register 29 FR 13009] undiluted sulfolane (0.2 ml) was instilled into the right eyes of rabbits. Only a mild conjunctivitis was produced, which cleared within a few hours (Brown et al., 1966).

Conclusion

Sulfolane is not considered to be a skin or eye irritant.

3.1.4 Sensitisation

Studies in Animals

Skin

There are 3 sensitisation studies, one of which is reliable. In a guinea pig maximisation test [Directive 84/449/EEC, B6, GLP] a group of 10 male and 10 female guinea pigs were induced intradermally using 2% m/v sulfolane in water/Freunds Complete Adjuvant followed a week later by topical induction using undiluted sulfolane (0.3 ml) which was applied over the sites of the intradermal injections and covered occlusively for 48 hours. Challenge was carried out 3 weeks after the intradermal induction. Undiluted sulfolane (0.1ml) was applied to the shaven backs of the test animals and covered with occlusive tape for 24 hours. Dermal reaction to the challenge was assessed after removal of the bandages and at 24 hours and 48 hours after challenge. None of the test animals showed any positive response at either 24 or 48 hours after removal of the challenge patches and therefore sulfolane is not considered to be a skin sensitiser in guinea pigs (Gardner, 1993).

Conclusion

Sulfolane is not considered to be a skin sensitiser in guinea pigs.

3.1.5 Repeated Dose Toxicity

There are 8 studies for repeat dose inhalation toxicity and one study for repeat dose oral toxicity. None of the inhalation studies are considered to be reliable due to the non-standard test methods used. The oral study is considered to be reliable.

Studies in Animals

Oral

In a 28 day repeat dose toxicity study [Japanese TG] conducted to GLP (MHW Japan, 1996b) male and female rats were administered doses of 0, 60, 200 and 700 mg/kg/day of the chemical by gavage. There were 12 animals per dose for the group at 60, 200 mg/kg/day and 24 per dose for the group at 0, 700 mg/kg/day. The recovery period was 14 days.

At 700 mg/kg some females showed transient reduction of locomotor activity at the early stage of the administration period. Bodyweight gain and food consumption at this dose were decreased in both males and females. Blood chemistry revealed increases in cholinesterase and total bilirubin in males and GPT in females and decreases of chloride in males and glucose in females. Pathological examination revealed increases of hyaline droplets and eosinophilic bodies in the renal tubules and an increase in the relative weight of the kidney in males. There was a decrease of splenic weight in females, but no histological abnormalities were detected.

At 200 mg/kg pathological examination revealed increases of hyaline droplets and eosinophilic bodies in the renal tubules of males.

No changes considered to be attributable to sulfolane were observed on urinary and haematological examinations at any dose. Kidney lesions tended to recover and the other changes related to the chemical disappeared after a 14 day recovery period. The NOAEL is considered to be 60 mg/kg/day for males and 200 mg/kg/day for females.

Conclusion

The oral NOAEL is 60 mg/kg/day (males) and 200 mg/kg/day (females).

3.1.6 Mutagenicity

There are 8 *in vitro* mutagenicity studies, seven of which are considered to be reliable. There are no *in vivo* studies available.

In vitro Studies

Sulfolane has been tested for reverse mutation in *Salmonella typhimurium* and *Escherichia coli* with and without exogenous metabolic activation by standard Japanese test methods in full compliance with OECD TG 471 and 472 (MHW, 1996c). No cytotoxicity was observed at 5000 µg/plate in any of the 5 strains. The tests were negative, in both the presence and absence of a metabolising system. An *in vitro* chromosome aberration study in CHL cells was conducted in accordance with Japanese guidelines similar to OECD TG 473 (MHW, 1996d). The highest dose level was cytotoxic. Structural chromosomal aberrations and polyploidy were not induced up to the maximum dose either in the presence or absence of a metabolising system.

Several other bacterial mutagenicity tests, a chromosome aberration study using rat liver RL4, a sister chromatid exchange study and a yeast gene mutation assay are also reported as negative.

In a mouse lymphoma assay (Phillips Petroleum Company, 1982b) exposure to sulfolane in the presence and absence of metabolic activation increased the induction of forward mutations in L5178Y mouse lymphoma cells at the T/K locus. Sulfolane was considered to be mutagenic in this test system by the authors. However, there was no dose response and the survival percentage was not affected by increasing doses, therefore it is considered that this interpretation of the data is incorrect.

Table 5 Genotoxicity studies of sulfolane

Type of test	Test system	Dose	Result	Reference
Bacterial test (reverse mutation)	*S. typhimurium* TA 98, TA100, TA 1535, TA 1537. *E. coli* WP2uvrA	5 doses between 313 to 5000 µg/plate	Negative, with and without metabolic activation	(MHW, 1996c)
Bacterial test (reverse mutation)	*S. typhimurium* TA 98, TA100, TA 1535, TA 1537, TA 1538. *E. coli* WP2, WP2uvrA	8 doses between 31.25 to 4000 µg/plate	Negative, with and without metabolic activation	(Thorpe, 1982)
Bacterial test (reverse mutation)	*S. typhimurium* TA 98, TA100, TA 1535, TA 1537, TA 1538	5 doses between 642 to 52000 µg/plate	Negative, with and without metabolic activation	(Phillips Petroleum Company, 1982a)
In vitro chromosome aberration assay	CHL/IU	-S9: (continuous exp.24 or 48 h) 0.3, 0.6, 1.2 mg/ml +/- S9: (6h exp.) 0.3, 0.6, 1.2 mg/ml	Negative with and without metabolic activation	(MHW, 1996d)
Sister chromatid exchange	CHO	70, 210, 700, 2100, 6400 µg/ml	Negative with and without metabolic activation	(Phillips Petroleum Company, 1983b)
Yeast gene mutation assay	*Saccharomyces cerevisiae*	0.01, 0.1, 0.5, 1.0, 5.0 mg/ml	Negative with and without metabolic activation	(Thorpe, 1982)
In vitro chromosome aberration assay	Rat liver RL4	250, 500, 1000 µg/ml	Negative without metabolic activation	(Thorpe, 1982)
Mouse lymphoma assay	L5178Y T/K locus	60, 90, 135, 202, 301, 449, 670, 1000 µg/mL	Positive*	(Phillips Petroleum Company, 1982b)

* There was no dose response and the survival percentage was not affected by increasing doses, therefore it is considered that this interpretation of the data is incorrect.

In vivo Studies

No data available

Conclusion

Sulfolane was not mutagenic in bacteria [OECD TG 471 and 472] and did not induce chromosomal aberrations in mammalian cells *in vitro* [OECD TG 473] either with or without metabolic activation.

3.1.7 Carcinogenicity

No data available.

3.1.8 Toxicity for Reproduction

There is one study available for reproductive/developmental toxicity.

Studies in Animals

Effects on Fertility

A reproduction/developmental toxicity screening test [OECD TG 421] was performed (MHW Japan, 1999). Twelve animals of each sex were dosed once daily by gavage (0, 60, 200, 700 mg/kg b.w./day). Males were dosed for 49 days (from 14 days prior to mating) and females for 41-50 days (from 14 days prior to mating to day 3 of lactation). One male and one female in the 700 mg/kg group died. There was a decrease in body weight gain and food consumption amongst males, and females during the pre-mating period, at 700 mg/kg. The number of oestrus cases was decreased in the 700 mg/kg group. Four dams lost all their pups during the lactation period in the 700 mg/kg 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 birth increased in the 700 mg/kg group. Birth index and the number of pups on day 0 and 4 of lactation decreased in the 200 mg/kg group. Parental NOAEL was 200 mg/kg/day. NOAEL for offspring was 60 mg/kg/day.

Developmental Toxicity

In the above study, there were no treatment-related findings in the external appearance, general conditions and necropsy findings of the offspring.

Conclusion

The reproductive toxic effects, such as decreased number of oestrus stages and an increased number of litters totally died, in female parents were found at 700 mg/kg bw/day. Developmental toxic effects, such as decreased birth index and number of pups were observed at 200 mg/kg bw/day and higher. 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.

3.2 Initial Assessment for Human Health

Groups of 3 male rats were dosed intravenously at 500 or 1000 mg/kg of non-radiolabelled sulfolane and the amount of sulfolane excreted unchanged in the urine was measured for 7 days after administration using gas-liquid chromatography. At 500 mg/kg, 28%, 36% and 37% of the dose was excreted unchanged between days 0-2, 0-4 and 0-7, respectively. At 1000 mg/kg, 50% and 67.2% of the dose was excreted unchanged between days 0-2 and 0-4, respectively. The observation that the proportion of the dose recovered increased with dosage suggests that the metabolic pathway is saturable. In a follow up to this study, blood-sulfolane decay curves were obtained following intravenous injections of sulfolane to a single rabbit, dog and squirrel monkey. Sulfolane was

rapidly distributed throughout the animals and was slowly removed from plasma with a half-life of 3.5-5 hours.

In a second study 3 male Wistar rats were injected intraperitoneally with ^{35}S-sulfolane (100 mg/rat in 2 ml water) and the 24 hour urinary samples analysed. One major metabolite was found, constituting 85% of the urinary radioactivity. Subsequently, 3 rabbits were injected intraperitoneally with a mixture of unlabelled sulfolane and 35S-sulfolane (1 g: 100 mg) and the urine samples collected and extracted with chloroform. The metabolite was identified as 3-hydroxysulfolane.

The Oral LD_{50} (rat) was 2006 mg/kg (males) and 2130 mg/kg (females) [OECD TG 401]. The dermal LD_{50} (rat) was > 2000 mg/kg [Directive 84/449/EEC, B3]. The inhalation LC_{50} (4h, rat) was > 12,000 mg/m^3. The chemical is not a skin irritant or eye irritant [US Federal Register 29 FR 13009] or a skin sensitiser in guinea pigs [Directive 84/449/EEC, B6]. The acute behavioural studies showed that hypothermia contributed to the behavioural effect of 800 mg/kg sulfolane in rats, however, the rabbits became hyperthermic, at 28°C, upon injection of 600 mg/kg sulfolane.

Based on the results of a valid repeat dose study [Japanese TG], the NOAEL for repeat dose toxicity (oral) is 60 mg/kg/day (males) and 200 mg/kg/day (females).

Sulfolane was not mutagenic in bacteria [OECD TG 471 and 472] and did not induce chromosomal aberrations in mammalian cells *in vitro* [OECD TG 473]. There is no information on carcinogenicity, however in the absence of significant mutagenic effects *in vitro* there is no immediate concern.

In a reproduction/developmental toxicity screening test [OECD TG 421] males were dosed for 49 days (from 14 days prior to mating) and females for 41-50 days (from 14 days prior to mating to day 3 of lactation) at 0, 60, 200 and 700 mg/kg. One male and one female in the 700 mg/kg group died. There was a decrease in body weight gain and food consumption amongst males, and females during the pre-mating period, at 700 mg/kg. The number of oestrus cases was decreased in the 700 mg/kg group. Four dams lost all their pups during the lactation period in the 700 mg/kg 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 group. Birth index and the number of pups on day 0 and 4 of lactation decreased in the 200 mg/kg group. Parental NOAEL was 200 mg/kg/day. 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 of the offspring.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute and Chronic Toxicity Test Results

There are a number of studies reported on determination of acute aquatic effects of sulfolane. However many of the study results are reported by a secondary source and have to be considered as unreliable.

Acute Toxicity Test Results

In a reliable acute fish toxicity study [OECD TG 203] *Oryzias latipes* were exposed under semi-static conditions to sulfolane at a nominal concentration of 0 and 100 mg/L for 96 hours. There were no mortalities or signs of toxicity during the study in either the control or test fish. The LC_{50} was > 100 mg/L. In a further reliable acute fish toxicity study (Stephenson, 1982), *Salmō gairdneri* were exposed under semi-static conditions to sulfolane at concentrations of 100-1000 mg/L for 96

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