Brit. J. industr. Med., 1966, 23, 302

Acute Toxicity and Skin Irritant Properties of Sulfolane

V. K. H. BROWN, L. W. FERRIGAN, and D. E. STEVENSON

From 'Shell' Research Ltd., Tunstall Laboratory, Sittingbourne, Kent

Sulfolane is a useful industrial solvent. The oral LD_{50} values were: rats, 1·7 to 2·7 g./kg.; mice, 1·9 to 2·5 g./kg., all deaths taking place within 24 hours. Rats showed no effects after 3·8 g./kg. had been applied to the skin. The compound did not irritate or sensitize the skins of guinea-pigs or rabbits and, undiluted, was almost without action on the eyes of rabbits.

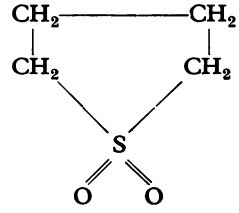
Because of its solvent properties, chemical inertness, and cheapness, sulfolane is a useful selective solvent in liquid-liquid and liquid-vapour extraction processes used for the separation of compounds with different degrees of saturation and polarity, *e.g.*, for the extraction of aromatic compounds from petroleum. It is also a good solvent for quaternary ammonium salts, nitrocellulose, polyvinylchloride, polystyrene, and for protein or amide-type fibres.

Very little information is available on the toxicity and possible irritancy of sulfolane, and, because of the importance of this material in industry, it was decided to investigate these properties.

The spelling 'sulfolane' may surprise readers more used to the spelling of sulphur in Britain. Sulfolane has been accepted as the generic name for hydrogenated sulphones of butadiene (Goldstein, 1958; Waddams, 1962).

Materials and Methods

Sulfolane Sulfolane has the structure:—



and the following alternative names: 2,3,4,5-tetrahydrothiophene-1,1-dioxide; thiocyclopentane-1,1-dioxide; (cyclo) tetramethylene sulphone; dihydrobutadiene sulphone; thiolane-1,1-dioxide; and sulphoxaline.

It is an unusually inert chemical and under normal conditions does not react with acids or bases. Substitution in the 3,4-position is relatively easy, and sulfolane can be reduced to 3,4-sulfolene (Reid, 1960). Sulfolane is almost odourless but at 220°C. it decomposes slowly with the formation of sulphur dioxide. Sulfolane is completely miscible with a wide range of different liquids, *e.g.*, water, acetone, glycerol, toluene, and many oils. Some of its other more important physical properties are given in Table I.

TABLE I

SOME PHYSICAL PROPERTIES OF TECHNICAL SULFOLANE

Physical Property	
Molecular weight	120·16
Freezing point	27·4-27·8°C.
Boiling point	285°C. (decomp.)
Specific gravity (30/20°C.)	1·265
Refractive index (30°C.)	1·47
Vapour pressure (150°C.)	14·53 mm. Hg
(250°C.)	333·70 mm. Hg
Viscosity (30°C.)	10·3 Centipoises
Dipole moment (in benzene)	4·69 Debye
Dielectric constant (30°C.)	44

All experiments described in this paper were carried out in rooms with an ambient temperature between 20° and 23°C. To facilitate handling, the sulfolane was warmed to 30°C. except when used diluted. Anhydrous sulfolane supplied by Shell Chemical Company was used for the whole investigation.

Animals The animals used are shown in Table II.

TABLE II

ANIMALS USED IN THIS INVESTIGATION

Species	*Strain or Breed*	*Breeding Unit*
Rat	Porton-derived Wistar	Tunstall Laboratory S.P.F. Breeding Unit
Mouse	Carworth Farm No. 1	Tunstall Laboratory S.P.F. Breeding Unit
Guinea-pig	Pirbright 'P' strain	Tunstall Laboratory Breeding Unit
Rabbit	New Zealand White	Tunstall Laboratory Breeding Unit

Received for publication April 13, 1966.

Acute Toxicity Tests

Oral The rats and mice were fasted overnight before being weighed and dosed with a syringe fitted with a ball-point needle. Water was allowed *ad libitum* throughout the experiment and food was freely available after dosing. Four rats of each sex and two mice of each sex were used at each dose level investigated.

Percutaneous Four rats of each sex were used for the acute percutaneous toxicity test; these were housed in individual cages before and during the 24 hours exposure period. Water was allowed to these rats *ad libitum* throughout the experiment but food was removed during the 24 hours exposure period. Undiluted sulfolane was placed on the shorn dorsolumbar skin and bandaged into contact using an impermeable dressing of aluminium foil and water-proof plaster. The dressing was left in position for 24 hours and then removed, and the treated site was washed with tepid dilute detergent solution.

All animals in the acute toxicity tests were observed for 10 days after exposure. At the end of that time all survivors were weighed and examined for general health.

Skin Irritation Studies The tests were of two types, those in which the skin was exposed to the sulfolane inside an impermeable covering, and those in which the skin was treated with free access to the atmosphere.

In the covered test, four male and four female rabbits were used. The dorsal hair between the shoulders and the hindquarters was cleanly shorn by means of fine electric clippers. On the first, second, and third days of the test the rabbits were immobilized for periods of six hours in a special holding device. Patches of lint, about 2 cm. × 2 cm., were cut, and 1 ml. of sulfolane was applied to each. Two patches were laid on each rabbit's back and covered with a sheet of thin polythene; these were bandaged into position by means of a 5-cm. open-weave bandage.

A visual assessment of the degree of erythema and oedema was made using the scoring system described by Hunter, Brown, and Ferrigan (1966) and intravenous sulphan blue in the method of Brown and Clarke (1965). Seven days after the first application the final visual assessment was made, and specimens of the animals' skins were taken for histopathological examination.

Rabbits (one male and one female) and guinea-pigs (five of each sex) were shorn from between the shoulders to the level of the hips on the Monday of each week of the test. Daily, five days per week for four and one-half weeks, 1 ml. for rabbits and 0·5 ml. for guinea-pigs of undiluted sulfolane was dropped onto the shorn area near the mid-line. A daily visual assessment was made of the gross skin damage, and on the day after the twenty-third application of test material the skin was removed for histopathological examination.

Skin Sensitization Studies The 'P' strain of guinea-pig was used in this investigation. This has been shown to be sensitized by a number of different organic compounds of low molecular weight injected intradermally or applied to the skin surface in a non-sensitizing solvent at a concentration of 0·1% w/v. The test was carried out by injecting or applying the solution to the shorn skin on the back of the guinea-pig on three days (Monday, Wednesday, and Friday) in each of three successive weeks. The animals received no treatment for the next 10 days, and a 'challenge' dose of the same solution was applied on the right flank and of solvent on the left flank on the eleventh day. After the 'challenge' the animals were examined at one hour, 24 hours, and 48 hours for signs of a sensitization-type reaction, *i.e.*, intense redness, wealing, or both. Subjective assessments were made of the reaction. Because of the negative result, the whole test was repeated using the same guinea-pigs.

Tests on Rabbit Eyes The method used was that described in the United States Federal Register (1964), and the assessment of irritancy was based on the recommendations of the United States Department of Health, Education, and Welfare.

Results

Acute Oral Toxicities

Rats The single dose acute oral LD_{50} was found to be 2·1 g./kg. (1·7 to 2·7 g./kg., 95% confidence limits).

All animals that died did so within 24 hours and mostly in less than three hours. In each case death was preceded by convulsions and gasping for breath. Necropsies on animals that died revealed no specific pathological lesion and it is believed from the character of the convulsions that anoxia was the cause of death.

Mice The single dose acute oral LD_{50} was found to be between 1·9 g./kg. and 2·5 g./kg. All animals that died did so within 24 hours. The general appearance was identical to that seen in rats.

Acute Percutaneous Toxicity Sulfolane does not wet skin very satisfactorily and the maximum dose investigated was 3 ml./kg. (3·8 g./kg.). No apparent effects were observed in any of the rats, and the percutaneous LD_{50} must therefore be greater than 3·8 g./kg.

Skin Irritation Studies In the covered test in rabbits no signs of skin irritation were observed in any of the rabbits used, and the total erythema score was less than 10 and can be ignored. The use of sulphan blue showed the skin to be unchanged, and histopathological examination of skins taken from the rabbits *post mortem* revealed no evidence of skin damage.

Undiluted sulfolane applied daily to the dorsal, shorn skin of rabbits and guinea-pigs produced no

gross appearance of skin irritation. Histopathological studies of the skin after the last application revealed no microscopic changes.

Skin Sensitization Studies Sulfolane did not produce signs of sensitization in either topical or intradermal tests. Both tests were repeated in the same guinea-pigs for a further course of injections; this also did not promote a sensitization response.

Tests on Rabbit Eyes Undiluted sulfolane, 0·2 ml., instilled into the right eyes of rabbits produced only a mild conjunctivitis which cleared within a few hours.

Discussion and Conclusions

Sulfolane has been shown to have an acute oral toxicity of 2·1 g./kg. (1·7 to 2·7 g./kg. at 95% probability level) in rats of the Porton strain. In mice of the CF No. 1 strain, the toxicity was found to lie between 1·9 and 2·5 g./kg. On the skin of rats, a single dose of 3·8 g./kg. produced no apparent systemic effects although the exposure was maintained for 24 hours under cover of an impermeable dressing. These results are in general agreement with the unpublished results of the Stanford Research Institute of California, U.S.A. (Stanford Research Institute, 1958) who found the acute oral toxicity for rats to be between 500 and 5,000 mg./kg. with death occurring up to 15 hours after exposure. Similarly, they found no ill effects in rabbits exposed to 2·8 g./kg. by the percutaneous route.

The convulsions observed in rats and mice were typical of those observed in anoxia, with gasping for breath and clonic spasms. The published work (Alexander, Abreu, Weaver, Faith, and Newberne, 1959) on monohalogenated sulfolanes shows that they have an analeptic action which may be followed by respiratory arrest.

Post-mortem examination of animals killed by sulfolane in our laboratory did not reveal any specific lesion.

The intravenous toxicity of sulfolane has not been investigated here but a single dose intravenous LD_{50} of 1,080 $\pm$ 56 mg./kg. has been quoted for mice (Alexander *et al.*, 1959).

Sulfolane appeared to be completely free from skin irritating and sensitizing properties and was only very mildly irritating to the eyes. Stanford Research Institute (1958) found sulfolane non-irritant to the skin but did not test for sensitization or eye irritancy.

There is now a substantial list of publications on the use of sulfolane in various industrial and laboratory applications and these suggest that the material will become of increasing importance. On the basis of the present evidence, on acute toxicity only, sulfolane may be judged to be reasonably safe to handle.

References

Alexander, W. M., Abreu, B. E., Weaver, L. C., Faith, H. E., and Newberne, J. W. (1959). *Arch. int. Pharmacodyn.*, **119**, 423.

Brown, V. K., and Clarke, R. A. (1965). *J. invest. Derm.*, **45**, 173.

Federal Register: Sept. 17, 1964: 29 F.R. 13009, 'Hazardous Substances'.

Goldstein, R. F. (1958). *The Petroleum Chemicals Industry*, 2nd ed. E. and F. N. Spon, London.

Hunter, C. G., Brown, V. K., and Ferrigan, L. W. (1966). *Brit. J. industr. Med.*, **23**, 137.

Reid, E. E. (1960). *Organic Chemistry of Bivalent Sulfur*, Vol. 3. Chemical Publishing Co., New York.

Stanford Research Institute (1958). Private Communication to Shell Development Co., Emeryville, California.

U.S. Dept. of Health, Education and Welfare (Food and Drug Administration)—Illustrated Guide for Grading Eye Irritation by Hazardous Substances.

Waddams, A. L. (1962). *Chemicals from Petroleum.* John Murray, London.