



**Recommendation from the Scientific Expert  
Group on Occupational Exposure Limits  
for sulfotep**  
SEG/SUM/69  
July 1997





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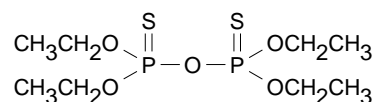


## Recommendation from the Scientific Expert Group on Occupational Exposure Limits for sulfotep

8 hour TWA	:	0.1 mg/m <sup>3</sup>
STEL (15 mins)	:	-
Notation	:	"skin"

### Substance:

Sulfotep



Synonyms : tetraethyl dithionopyrophosphate (TEDP); thiophosphoric acid, tetraethyl ester; ethylthiopyrophosphate; E393.

EINECS N° : 222-995-2

EEC N° : 015-027-00-3

Classification : T+; R27/28

CAS N° : 3689-24-5

MWt : 322.3

Conversion factor (20°C, 101 kPa) : 13.4 mg/m<sup>3</sup> = 1 ppm



## 1. Occurrence/use

Sulfotep is a pale yellow liquid with a garlic odour and BpT of 136-139 °C under 2 mm of Hg, and a vapour pressure of 22.3 kPa at 20°C.

Sulfotep is an anticholinesterase pesticide and has been used in smoke-generating systems for greenhouse fumigation. It may arise as a trace contaminant during manufacture of other pesticides. The production rate in the EU is in excess of 1000 tonnes per annum.

## 2. Health Significance

The main effect of sulfotep is its highly species specific cholinesterase inhibiting activity.

Single exposure toxicity studies indicate that sulfotep is well absorbed following inhalation, oral or dermal exposure (Kimmerle and Klimmer, 1974; Ben-Dyke *et al.*, 1970). After oral application of <sup>32</sup>P-labelled sulfotep, more than 90% was absorbed from the gastrointestinal tract. The majority of the administered radioactivity was excreted within 3 hours, 85 to 90 % by 24 h and 90 to 97% by 48 h after administration. 85 to 91 % of the administered radioactivity was excreted renally and 5 to 6 % by the faecal route. The highest concentrations were found in the liver, the lowest in the brain. No parent compound could be detected in the urine. 88 to 96 % of the radioactivity could be assigned to diethylthiophosphoric acid diester and 4 to 12 % to diethylphosphoric acid diester (Bayer, 1980b). Comparisons of anticholinesterase activity *in vivo* and *in vitro* have led to the assumption that once absorbed, sulfotep is metabolised to tetraethyl pyrophosphate, a more potent cholinesterase inhibitor (Kimmerle and Klimmer, 1974).

The acute toxicity of sulfotep is high, with 4h LC50 values in rats and mice of 40 - 60 mg/m<sup>3</sup> (rat, mouse), oral LD50 values of about 1 - 5 mg/kg bw (cat, dog), 5 - 15 mg/kg bw (rat), about 25 mg/kg bw (mouse, rabbit) and dermal LD50 values of 250 - 262 mg/kg bw (rat, 4h), about 25 - 70 mg/kg bw (rat, substance not removed) and about 5 mg/kg bw (rabbit, 24h) (Bayer, 1993b; Kimmerle and Klimmer, 1974). Signs of toxicity are those typically associated with cholinesterase inhibition.

The critical effect of sulfotep after single and chronic exposure is depression of cholinesterase enzymes with consequent peripheral and central nervous system effects. *In vitro*, inhibition of cholinesterase activity was higher in brain than in plasma or erythrocytes, whereas *in vivo*, no inhibition in brain cholinesterase could be detected in concentrations without excessive toxic effects (Kimmerle and Klimmer, 1974).

A repeated inhalation study is available in which rats were exposed to sulfotep at 0, 0.9, 1.9 or 2.8 mg/m<sup>3</sup>, 6h/d, 5d/week for 12 weeks. In the highest exposure group, the lung weights of females were significantly increased and plasma cholinesterase activity was decreased (Kimmerle and Klimmer, 1974). The NOAEL was 1.9 mg/m<sup>3</sup>. No histopathological examinations were carried out.

Administration of sulfotep to Wistar rats in diet at 0, 5, 10, 20 and 50 ppm for 3 months (Bayer, 1968) or at 0, 2, 10 and 50 ppm of a 50% pre-mix for 2 years (Bayer, 1983b) produced no significant effects on behaviour, body weight gain, food consumption, haematological parameters, gross and histopathological examination or tumour formation. The only clinical chemistry change observed was a dose-related decrease in both plasma and erythrocyte cholinesterase activity at 20 and 50 ppm. The NOAEL in both



experiments was 10 ppm (about 0.5 mg/kg bw/day). In a two-generation study, Sprague-Dawley rats were administered 0, 2, 10 or 50 ppm sulfotep in the diet. Female animals were shown to be more sensitive than male animals with reduction of body weight gain and decreased cholinesterase activity in erythrocytes and plasma at 10 ppm and above. At 50 ppm, cholinesterase activity in plasma was also decreased. For females, the NOAEL was 2 ppm (0.22 mg/kg bw/day). Male animals showed a decrease in plasma and erythrocyte cholinesterase activity at 50 ppm. The NOAEL for males was 10 ppm in the diet (0.93 mg/kg bw/day) (Bayer, 1991b).

Mice administered 0, 2, 10 or 50 ppm of a 50% pre-mix in the diet for 2 years did not show any relevant sign of toxicity (behaviour, body weight gain, food consumption, clinical-chemical or haematological parameters, gross and histopathological examination, tumour formation) or inhibition of cholinesterase activity). The NOAEL was therefore higher than 50 ppm pre-mix in the diet (corresponding to about 20 mg/kg bw/day) (Bayer, 1982).

In common with the response to other organophosphorus compounds, the dog seems to be more sensitive to sulfotep than rats or mice. In a subchronic study with administration of sulfotep in the diet at 0, 0.5, 3, 15 or 75 ppm for 13 weeks, a reduction of plasma cholinesterase activity was detectable at 3 ppm, reduction of erythrocyte cholinesterase at 3 ppm in females and 15 ppm in males, and 75 ppm was toxic to the animals producing overt signs such as frequent vomiting, glossless coat, loose, pultaceous faeces, anaemia (depressed haematocrit), reduced body weight gain and food consumption and slight thymus atrophy. The NOAEL was 0.5 ppm in the diet (0.0125 mg/kg bw/day) (Bayer, 1975).

Sulfotep did not show skin sensitising properties in a Buehler Test (OECD) with 12 male guinea pigs in the test group. The first induction was performed with 100% sulfotep, the second and third induction, and the challenge, with 50% sulfotep in Cremophor. Three animals died after the first or second induction as a result of the high level of test substance (Bayer, 1989a).

In all genotoxicity test systems performed *in vitro* as well as *in vivo*, sulfotep did not show relevant positive effects. *In vitro*, two Ames tests with *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 (Bayer, 1977 and 1989b) a mitotic recombination assay with *Saccharomyces cerevisiae* D7 (Bayer, 1989c) and a cytogenetic study with human lymphocytes (Bayer, 1990) were performed, all with and without metabolic activation. *In vivo*, a micronucleus test in the bone marrow of male and female NMRI mice (1-3 mg/kg bw; Bayer, 1978) and a dominant lethal test with male NMRI mice (10 mg/kg bw; Bayer, 1979) were carried out.

In two year studies with rats (Bayer, 1973b) and mice (Bayer, 1982) with sulfotep at up to 50 ppm in the diet, when the MTD was not achieved, no increased incidences of tumours were observed.

In developmental toxicity studies with rats (day 6-15 of gestation: 0, 0.1, 0.3, 1 mg/kg bw/day: Bayer, 1980; 0, 0.3, 0.8, 2.5 mg/kg bw/day: Bayer, 1991a; 0, 0.1, 1.4 mg/kg bw/day: Bayer, 1993a) or rabbits (day 6-18 of gestation: 0, 0.3, 1, 3 mg/kg bw/day; Bayer, 1984), no effects on fertility, embryotoxicity or teratogenicity were seen. As in the studies of subchronic and chronic toxicity, the inhibition of plasma and erythrocyte cholinesterase activity was the main effect. For rats, the NOAEL for maternal toxicity was 0.1 mg/kg bw/day and for developmental toxicity was 1.4 mg/kg bw/day (Bayer, 1993a). For rabbits, the NOAEL for maternal toxicity was 1 mg/kg bw and for developmental toxicity, 3 mg/kg bw/day. In lactating pups (rat), inhibition of plasma and erythrocyte cholinesterase activity was shown at, or, in the case of females, below concentrations which also led to inhibition in the parent animals (Coulston and Griffin, 1976).



No useful information is available on the effects of sulfotep in humans.

## Recommendation

The study of Kimmerle and Klimmer (1974), indicating a NOAEL of 1.9 mg/m<sup>3</sup> for effects on lung weight in rats, was considered to be the best available basis for proposing occupational exposure limits. An uncertainty factor of 20 was proposed because the basis is a rat study lasting only 12 weeks with no histopathology examination, which is therefore less sensitive than a full chronic study, and furthermore because the oral studies in different species conducted by Bayer indicate that the rat is relatively insensitive to the effects of sulfotep. The recommended 8-hour TWA is 0.1 mg/m<sup>3</sup>. This value is supported by analysis of results of a dietary study in dogs. In a subchronic study, a NOAEL of 0.5 ppm in the diet, corresponding to 0.0125 mg/kg bodyweight, was identified (Bayer, 1975). For a worker weighing 70 kg and breathing about 10 m<sup>3</sup> air during a work shift, a value of 0.09 mg/m<sup>3</sup> is derived. Since the dog is the most sensitive species, no further uncertainty factor is used.

No STEL was considered to be necessary.

Because skin absorption can be the major route of uptake of organophosphate pesticides, biological monitoring may be a more appropriate means of monitoring exposure. Such monitoring commonly involves measurement of urinary alkyl phosphate and/or blood cholinesterase activity (in red blood cells and/or plasma).

At the levels recommended, no measurement difficulties are foreseen.



## Key Bibliography

### Note

*Confidential data of "BAYER AG", which gave important contributions for hazard and risk evaluations of SULFOTEP are cited in the report. The original reports in an unabridged form were available to the Commission and to the Scientific Committee for Occupational Exposure Limits to evaluate the validity of the data. Information required by a third party about the company reports will be supplied by the company. The company is not obliged to supply copies, even of part of the reports, or to make the reports available for scrutiny by third parties.*

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