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# **Sulphuryl difluoride**

(CAS No: 2699-79-8)

Health-based Reassessment of Administrative Occupational Exposure Limits

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Committee on Updating of Occupational Exposure Limits,  
a committee of the Health Council of the Netherlands

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No. 2000/15OSH/141 The Hague, November 9, 2004

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## 1 Introduction

The present document contains the assessment of the health hazard of sulphuryl difluoride by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by I Gubbels-van Hal, M.Sc. (NOTOX BV, 's-Hertogenbosch, the Netherlands).

The evaluation of the toxicity of sulphuryl difluoride has been based on reviews published by the American Conference of Industrial Hygienists (ACG99), the US Environmental Protection Agency (EPA92), and Nitschke and Eisenbrandt in the 'Handbook of Pesticide Toxicology' (Nit01). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in September 1999, literature was searched in the databases Toxline, Medline, and Chemical Abstracts, covering the periods 1965 until September 1999, 1966 until September 1999, and 1967 until September 1999, respectively, and using the following key words: 2699-79-8. The final literature search was carried out in Toxline and Medline in October 2003.

In October 2003, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: R Billington (Dow AgroSciences, Abingdon, UK). These comments were taken into account in deciding on the final version of the document.

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## 2 Identity

name	:	sulphuryl difluoride
synonyms	:	sulphuryl fluoride; sulphuryl difluoride; sulfuryl fluoride; sulfur difluoride dioxide; sulfonyl fluoride; sulfuric oxyfluoride vikane, vikane fumigant
molecular formula	:	F <sub>2</sub> O <sub>2</sub> S
structural formula	:	-
CAS number	:	2699-79-8

Data from ACG99, NLM01.

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### 3 Physical and chemical properties

molecular weight	:	102.06
melting point	:	-136°C
boiling point	:	-55°C
flash point	:	not available
vapour pressure	:	at 21°C: 1700 kPa
solubility in water	:	750 mg/L
log P <sub>octanol/water</sub>	:	0.41 (estimated)
conversion factors	:	20°C, 101.3 kPa: 1 ppm = 4.25 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.24 ppm

Data from ACG99, NLM01, [http://www.syrres.com/esc/est\\_kowdemo.htm](http://www.syrres.com/esc/est_kowdemo.htm).

Sulphuryl difluoride is a colourless, odourless, non-flammable gas (ACG99).

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### 4 Uses

Sulphuryl difluoride is an inorganic gas fumigant used to control a wide variety of household pests, including cockroaches, rodents, clothes moths, bedbugs, drywood termites, and carpet beetles. Due to the fact that it has no odour, chlorpicrin, an irritant gas, is added as a warning material (ACG99, Nit01). For structural fumigation, the building to be fumigated is covered with large vinyl tarpaulins, sealing the building. The fumigant is introduced into the unoccupied house via a tube or hose, and fumigators leave the site. Documented air concentrations for sulphuryl difluoride during this operation varied from 16,150-161,500 mg/m<sup>3</sup> (3800-38,000 ppm) of house area, and concentrations within 0.6 m of the tarpaulins during the opening process in houses were up to 106 and 1063 mg/m<sup>3</sup> (25-250 ppm), respectively (Ang86).

According to the on-line database of the Dutch Pesticide Authorisation Board (CTB)\*, sulphuryl difluoride is at the present not permitted for its use as an active ingredient in pesticides in the Netherlands.

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### 5 Biotransformation and kinetics

In humans, the normal background levels for plasma fluoride range between 0.01 and 0.2 mg/L. Fluoride levels in the blood of 2 individuals exposed to unknown,

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\* at: <http://www.ctb-wageningen.nl>.

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but lethal concentrations of sulphuryl difluoride were 50 mg/L (24 to 36 hours post-mortem) and 20 mg/L (ante-mortem), respectively (Sch86).

Serum fluoride levels have been elevated compared to control values in several experimental species, including mice, rats, rabbits, and dogs, following acute or subchronic exposure to sulphuryl difluoride (Eis89, Nit86, Nit91, Nit93).

The biotransformation and kinetics of sulphuryl difluoride were studied in F344 rats exposed to concentrations of <sup>35</sup>S-labelled compound of 127.5 and 1275 mg/m<sup>3</sup> (30 and 300 ppm), for 4 hours, and reported in an abstract. Sulphuryl difluoride was rapidly absorbed. The pulmonary absorption was 11-14%\*. Maximum concentrations of radioactivity in plasma and red blood cells occurred near the end of the 4-hour exposure period. The radioactivity was cleared from the plasma and red blood cells with initial half-lives of 2.5 and 1-2.5 hours after exposure to 127.5 and 1275 mg/m<sup>3</sup> (30 and 300 ppm), respectively. The terminal half-life of radioactivity was 2.5-fold longer in red blood cells than in plasma. The radiolabel was rapidly excreted, mainly via the urine. Radiochemical profiles of blood and urine did not indicate presence of parent compound in the blood and suggested initial hydrolysis into fluorosulphate, with release of fluoride, and subsequent hydrolysis into sulphate, with release of another fluoride. Analysis of tissues 7 days post-exposure, the end of the experiment, showed an even distribution among tissue, which was ascribed to incorporation of radiolabelled S into amino acids. The lungs had the highest level of radioactivity and also the nasal turbinates had detectable levels. Red blood cell levels were still elevated. Of the non-respiratory tissues, highly perfused tissues such as spleen and kidneys had the higher <sup>35</sup>S concentrations (Men03).

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## 6 Effects and mechanism of action

### Human data

A 30-year-old male was hospitalised after exposure to sulphuryl difluoride containing 1% chloropicrin for about 4 hours under conditions of limited ventilation. Although not measured at the time of exposure, the concentration of sulphuryl difluoride was assumed to be at least 21 mg/m<sup>3</sup> (5 ppm). Effects experienced consisted of nausea, vomiting, crampy abdominal pain, and pruritis. He was found to have reddened conjunctivae and pharyngeal and nasal mucosa,

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\* R Billington, Dow AgroSciences, Abingdon, UK; personal communication.

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diffuse rhonchi, and paraesthesia of the lateral border of the right leg up to 4 days after exposure. On the day of hospitalisation, a low serum potassium concentration was measured, which was normalised after 2 days. One day after admission, qualitative analyses of serum fluoride was positive, serum lactate dehydrogenase was normal, but serum alkaline phosphatase and serum phosphorus levels were below their lower normal limits. After being released from hospital on the 4th day after admission, he remained complaining about scratching of the throat, flatulence, and difficulty in reading. Serum biochemistry results were within normal levels on day 9 after admission (Tax66).

Three cases of suicide by exposure to sulphuryl difluoride were reported. In one case, a 29-year-old man was found dead in his apartment, which had been fumigated with sulphuryl difluoride the previous day. In the second case, a 22-year-old man was found dead next to an open sulphuryl difluoride container in a warehouse. Both men were found dead with bloody froth covering their mouth, and both had faecal soiling suggestive of parasympathetic stimulation. Post-mortem examination revealed congestion of the mucosa of the respiratory tract and the lungs. In one of these cases, the serosa were dotted with petechiae. A third case concerned a 19-year-old Arabic woman who was found unconscious after re-entry in her residence on the afternoon of the fumigation. Upon arrival in the hospital, she was alert, responsive, coughing, and complaining of chest discomfort. She appeared to be hypotensive. After 6 hours, she became hyperexcitable, hyperventilated, and developed tachycardia. A few hours later, she died after developing carpopedal tetany and cardiac dysrhythmias. The main autopsy finding was pulmonary oedema, with congestion and petechiae of the visceral pleura. Blood fluoride concentrations were 50 mg/L (24 to 36 hours post-mortem) and 20 mg/L (ante-mortem) in cases 1 and 3, respectively (Sch86).

Two other fatalities have been reported for an elderly couple, who returned to their home approximately 5-8 hours after their house was ventilated to remove sulphuryl difluoride, remaining after a 24-hour fumigation of their home. The man died after one day. Symptoms included dyspnoea, restlessness, cough, and seizure followed by cardio-pulmonary arrest. The wife experienced weakness, nausea, vomiting, dyspnoea, intermittent chills, and anorexia. In hospital, severe hypoxaemia and diffuse pulmonary infiltrates were seen. Four days later, she died after ventricular fibrillation (Nuc87).

In an overview of 1065 cases of confirmed occupational illnesses and injuries, potentially related to pesticides, 5 cases of systemic poisoning were ascribed to due to exposure to sulphuryl difluoride in California in 1986. No further details were given (Edm87).

A retrospective investigation was carried out on 24 workers in soil and structure fumigation in California, using sulphuryl difluoride as a fumigant during 80% or more of the applications (mean: 92%; the other fumigant being methyl bromide). Personal air samples in the breathing zone of 6 fumigators after application of approximately 16,000 mg/m<sup>3</sup> (3800 ppm) of house area were on average 22 mg/m<sup>3</sup> (5 ppm) (2-hour TWA) with a maximum of 37 mg/m<sup>3</sup> (8.7 ppm). Workers were subjected to neurobehavioural testing, including tests on motor activity, nerve conduction velocity, grip strength, eye-hand coordination, sensory aspects (tactile sensitivity, eye-movements and vision, noise-stimulus effects), and cognition (memory, association and discrimination). Comparison with a reference group (n=29), which mostly has sedentary and less strenuous jobs and differed with respect to age, race, educational level, and use of alcohol, prescription drugs, and illegal drugs, did not show any statistically significant difference in results of any of about 70 tests (Ang86).

A cross-sectional study was conducted, in south Florida (USA), on 123 male structural fumigation workers, engaged in the application of sulphuryl difluoride and/or methyl bromide. A referent group, consisting of 120 males, was recruited by asking the fumigators to identify a male friend or neighbour who was of similar age and had never worked with or been poisoned by pesticides. Only 11 workers in this group had been working with sulphuryl difluoride only, the rest with both sulphuryl difluoride and methyl bromide. The mean application time was less than 2 hours/day. The median lifetime duration of employment in sulphuryl difluoride fumigation was 2.85 years (range: 0.11-20.5 years) and in methyl bromide fumigation 1.2 years (range: 0-22 years). Based on personal airborne sampling results of another cohort of fumigation workers conducted in 1991, it was expected that air concentrations to sulphuryl difluoride over the year preceding examination were far below 20 mg/m<sup>3</sup> (5 ppm) and in most cases even below the analytical limit of detection. Participants in the investigation were subjected to standardised questionnaires, tests of neurological function, and a physical examination. Sulphuryl difluoride employment was associated with a significantly reduced performance on the Pattern Memory test, while there was no impairment in the other memory-related tests (Pattern Memory recall time, Symbol Digit, Symbol Digit recall score, Serial Digit Learning score) and on olfactory testing compared to the reference group. In addition, fumigation workers had significantly reduced performance on tests in median nerve function (nerve motor conduction velocity; Santa Ana Dexterity Test of the dominant hand - a non-computerised test of psychomotor function), but these peripheral nerve effects were likely caused by ergonomic stresses rather than with sulphuryl exposure (Cal98). The committee notices methodological limitations of the study

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design and of some of the tests used. Also, no more statistically significant positive findings (less than 10%) were observed than would be expected given the large number comparisons made. Further, concomitant exposure to methyl bromide, a neurotoxic compound, cannot be excluded. Therefore, the committee is of the opinion that the results of this study are better explained by bias, confounding, or change than by exposure to sulphuryl chloride and that they are not indicative of any neurotoxic potential.

In another case-control study, no increased risk of developing brain tumours was found for workers working with vikane in termite treatment (Pog97).

## Animal data

### *Acute toxicity*

The 4-hour LC<sub>50</sub> values of sulphuryl difluoride were 4769 and 4212 mg/m<sup>3</sup> (1122 and 991 ppm) in male and female Fischer 344 rats, respectively. Macroscopic and microscopic examination revealed primarily changes in the upper and lower respiratory tract and, in addition, liver, kidney, heart, and spleen effects (Mil80). The 1-hour LC<sub>50</sub> values were 15,853 and 12,835 mg/m<sup>3</sup> (3730 and 3020 ppm) for male and female Sprague-Dawley rats, respectively (Ver77). In B6C3F<sub>1</sub> mice, the 4-hour inhalation LC<sub>50</sub> values were between 1700 and 2550 mg/m<sup>3</sup> (400 and 600 ppm) for both males and females, and in CD-1 mice, 2805 and 2729 mg/m<sup>3</sup> (660 and 642 ppm) for males and females, respectively (Nit89, Nit90). In an older study, it was reported that rabbits were less sensitive and mice more sensitive to acute effects of sulphuryl difluoride than rats. When rats (n=5-15) and rabbits (n=1-5) were exposed during 60 minutes to 8500-42,500 mg/m<sup>3</sup> (2000-10,000 ppm) and mice (n=10-20) to 4250-21,250 mg/m<sup>3</sup> (1000-5000 ppm), symptoms observed consisted of convulsions and flat body posture. Cause of death was blockage of the respiratory muscles. Macroscopic examinations showed congestion of the lungs and haemorrhageous alveolitis (Tru73).

The 4-hour dermal LC<sub>50</sub> of sulphuryl difluoride vapour in rats was greater than 40,800 mg/m<sup>3</sup> (9600 ppm). The only clinical effects were chromodacryorrhea and faecal soiling. There was no evidence of body tremors. Macroscopic or microscopic examination of skin and brain did not reveal treatment-related changes (Bra90).

The acute oral LD<sub>50</sub> of sulphuryl difluoride was 100 mg/kg bw in both rats and guinea pigs (Lew96).

In a study, designed to understand the mode of action of sulphuryl difluoride, male rats (n=5/group) were exposed to ca. 17,000, 42,500, 85,000, or 170,000

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mg/m<sup>3</sup> (4000-40,000 ppm) until incapacitation (i.e., not longer capable of walking on a rotating activity wheel), after which exposures were terminated. A dose-related decrease in the time to incapacitation was observed as the sulphuryl difluoride exposure increased. At the 2 highest concentrations, rats were incapacitated within 12 minutes and died within 10 minutes after terminating exposure. At 42,500 or 17,000 mg/m<sup>3</sup>, incapacitation was observed within 18 or 46 minutes, respectively, and the survival times were 61 or 150 minutes after incapacitation occurred, respectively. Symptoms observed consisted of clinging to the floor or side and ride the wheel rather than walk. The rats made postural adjustments, while clinging to the screen, to remain in an upward position. Rats exposed to the 3 highest concentrations developed cyanosis shortly after exposure occurred. Tonic convulsions were observed during exposure in 3 out of 5 animals in the lowest concentration group, but after exposure in most animals of the other groups. Pulmonary congestion appeared to contribute significantly to the death of the animals. According to Nitschke et al., the responses observed were probably related to fluoride toxicity. Pre-treatment with calcium gluconate (a known fluoride ion antagonist) increased the survival in rats at 17,000 mg/m<sup>3</sup>, but not at 42,500 mg/m<sup>3</sup>. However, there was no apparent protection against convulsions. At both exposure concentrations, rats had increased serum fluoride levels and decreased serum cholinesterase and magnesium levels, which were statistically significant in a dose-related fashion, either with or without pre-treatment with calcium gluconate. Administration of calcium gluconate resulted in about 10% increase in serum calcium levels, but did not affect fluoride or magnesium levels. Pre-treatment with phenobarbital was effective in decreasing the effects of exposure to the lowest exposure concentration. All 5 animals survived without any evidence of convulsions (Nit86).

Exposure of female rats to 0, 425, or 1275 mg/m<sup>3</sup> (0, 100, 300 ppm) sulphuryl difluoride for 2 consecutive days (6 hours/day) did not result in any changes in a functional observational test battery, grip performance, landing foot splay, motor activity, and a battery of electrodiagnostic tests, including flash evoked potentials, somatosensory evoked potentials, and auditory brainstem responses, when compared to pre-exposure performance (Alb93).

#### *Subacute and subchronic toxicity*

Fischer 344 rats (n=5/sex/group) were exposed to concentrations of sulphuryl difluoride of 0, 425, 1275, and 2550 mg/m<sup>3</sup> (0, 100, 300, 600 ppm), 6 hours/day, 5 days/week, for 2 weeks. At the high exposure, all male and 4 female rats died after a period of reduced activity and lethargy. These rats had severe kidney

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lesions, including papillary necrosis, dilation of collecting ducts, and reduced basophilic cytoplasm, and patchy segments in the epithelial cells of the descending proximal tubules. Respiratory effects observed in these animals consisted of pulmonary oedema and/or haemorrhage or fibrin within the alveoli (with thrombi in the capillaries). Other observations included visceral congestion, stomach erosion, metastatic mineralisation, hypertrophy of the adrenal cortex, and necrosis and depletion of the lymphoid tissue in thymus, spleen, and lymph nodes. The one surviving female animal had a significantly decreased body weight at the end of the study and kidney effects similar to those found in the animals that died, as well as debilitation and dehydration, significantly increased relative heart and kidney weights, significantly decreased thymus weight, elevated urea nitrogen levels, glucosuria, significant increase in mean total white blood cell counts, inflammation and multifocal ulceration of the nasal mucosa with bronchoalveolar inflammation and myeloid hyperplasia of the bone marrow. Among the male and female animals of 1275-mg/m<sup>3</sup> group, papillary hyperplasia and hyperplasia of the collecting ducts and a significant increase in the mean total white blood cell counts became apparent. In the females, significantly increased relative kidney and heart weights and significantly decreased thymus weights (both absolute and relative) were seen. In the low-exposure group, there was only a significant increase in the mean total white blood cell counts in females, which was not of toxicological significance. The NOAEL was 425 mg/m<sup>3</sup> (Eis89).

In a subsequent 13-week study, rats (n=10/sex/group) were exposed to sulphuryl difluoride concentrations of 0, 127.5, 425, and 1275 mg/m<sup>3</sup> (0, 30, 100, 300 ppm), 6 hours/day, 5 days/week. No treatment-related deaths were reported. In rats exposed to 1275 mg/m<sup>3</sup>, effects seen consisted of a significantly decreased body weight gain, vacuolisation of area of the caudate-putamen nuclei (no further specification), decrease in microscopic protein droplets ( $\alpha_{2\mu}$ -globulin) in the convoluted tubules of the kidney (males only), hyperplasia of the renal collecting ducts (females only), significantly decreased urinary gravity (males only), pale foci on the pleural surface of the lungs (subpleural histiocytosis), inflammation of the nasal, respiratory, and olfactory mucosa with mucopurulent exudate in the nasal passages, and mottled teeth (dental fluorosis). Serum fluoride levels were increased compared to control animals, but the difference was not statistically significant. Apart from mottled teeth (dental fluorosis) in rats exposed to 425 mg/m<sup>3</sup> (100 ppm), no effects were observed in the animals exposed to 425 and 127.5 mg/m<sup>3</sup> (100 and 30 ppm) (Eis89).

Because of the neurological effects seen in acute and 2-week studies, additional groups of rats (n=7/sex/group) were included in the above-discussed

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13-week study to evaluate the neurological function following exposure to sulphuryl difluoride (at concentrations of 127.5, 425 and 1275 mg/m<sup>3</sup>). After 8-9 weeks, epidural electrodes were implanted into the skull of the animals. A battery of neurological tests was conducted on all animals at 12 hours after the end of the 13-week exposure, except on 2 animals/sex of the high-exposure and control groups, which were allowed to recover for approximately 2 months for the assessment of an auditory brainstem response. Body weight gain was reduced in males and females of the high-exposure group. Dental fluorosis was seen in all animals in the mid- and high-exposure groups. No effects were seen in a functional observation test battery and hind limb grip strength testing in any of the exposure groups. In the high-exposure male and female groups, electrophysiological data collected 42 to 48 hours after the last exposure showed a significant increase in the latency time to flash and somatosensory evoked responses and to auditory brainstem response. Cortical flicker fusion was slightly altered in high-concentration males and females. No effect on caudal nerve action potentials was seen at any treatment. At 425 mg/m<sup>3</sup>, flash evoked potential and auditory brainstem response were slightly, but significantly altered (significance was attributed to females). At necropsy, pale foci on pleural surfaces, vacuolisation in the caudate putamen (not further specified), nasal tissue inflammation, mild multifocal inflammation of the lungs, hyperplasia of renal collecting ducts (females only), and a decrease in protein droplets in the cortical tubules of the kidney (males only) were seen in high-concentration animals. At 425 mg/m<sup>3</sup>, pale foci on pleural surfaces were reported for one male and one female. No brain lesions were found at this exposure level. Auditory brainstem responses and brain histology were within normal limits in the 2 animals/sex of the high-exposure group after an 8-week recovery period, indicating that the effects were, at least to a great extent, reversible. The NOAEL for neurological effects was 127.5 mg/m<sup>3</sup> (30 ppm) (Mat88).

In a 2-generation inhalation reproduction toxicity study (see also Section 'Reproduction toxicity'), parental (F0) rats (Sprague-Dawley; n=30/sex/group) were exposed to concentrations of sulphuryl difluoride of 0, 21, 85, or 637.5 mg/m<sup>3</sup> (0, 5, 20, 150 ppm), 6 hours/day, 5 days/week, prior to mating, i.e., 10 weeks, and 6 hours/day, 7 days/week during mating, gestation, and lactation, i.e., another 10 weeks. No treatment-related mortality or clinical signs of toxicity were observed in any of the exposure groups. Statistically significant decreases in body weight were seen in the high-concentration group only: in the male animals from day 14 through the end of the exposure period and in the females from day 14 to day 56 and during gestational days 7-14 and 1-21 and lactation days 1, 4, and 7. At post-mortem macroscopic examinations, there were dental

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fluorosis ('dark lower incisors') in 27/30 males and 29/30 females of the high-concentration group and multiple, round, pale or grey foci in the lungs in 30/30 males and 18/30 females of the high-concentration group and in 5/30 males of the mid-concentration group. Microscopically, lesions of the lungs and brain were observed. The lung lesions consisted of aggregates of alveolar macrophages, which showed a dose-related increase in incidence and severity and which were graded as 'very slight' (i.e., 1 to 3 small aggregates), 'slight' (3 to 6 usually larger aggregates), and 'moderate' (more than 6 large aggregates). These aggregates were observed in 3 (all 'very slight'), 5 (all 'very slight'), 11 (10 'very slight'; 1 'slight'), and 30 (6 'very slight'; 17 'slight'; 7 'moderate') males of the control, low-, mid-, and high-concentration group, respectively, and in 7 (all 'very slight'), 10 (9 'very slight'; 1 'slight'), 19 (all 'very slight'), and 30 (1 'very slight'; 16 'slight'; 13 'moderate') females of the control, low-, mid- and high-concentration group, respectively. Especially in the animals of the high-concentration group, the presence of these aggregates was accompanied by chronic inflammation (graded as 'very slight' in 9 males and 19 females and as 'slight' in 5 males and 6 females). The brain lesions were limited to the high-concentration group and consisted of bilaterally symmetrical vacuolation of the caudate putamen myelinated fiber tracts in 11 males (graded as 'very slight') and 14 females ('slight'). Based on the increased incidence of aggregates of alveolar macrophages, the (parental) NOAEL was placed at 21 mg/m<sup>3</sup> (5 ppm) (Bre92, Bre93).

When mice (CD-1; n=5/sex/group) were exposed to sulphuryl difluoride at concentrations of 0, 127.5, 425, or 1275 mg/m<sup>3</sup> (0, 30, 100, 300 ppm), 6 hours/day, 5 days/week, for 2 weeks, all males and 4 females of the high-exposure group died during the second week. Clinical signs were tremors and body weight loss. Microscopic examination revealed vacuolation in the cerebellum and/or medulla in the high- and mid-exposure groups. The NOAEL was 127.5 mg/m<sup>3</sup> (30 ppm) (Nit95).

In an unpublished 13-week study, CD-1 mice (n=14/sex/group) were exposed to 0, 4.25, 127.5, or 425 mg/m<sup>3</sup> (0, 10, 30, 100 ppm), 6 hours/day, 5 days/week. At the highest concentration, a 10% decrease in body weight was observed in both males and females. No treatment-related changes in haematology, clinical chemistry, organ weight, or gross pathology were observed. Serum fluoride levels were significantly increased in a dose-related fashion in the mid- and high-exposure groups (males and females). Microscopic examination revealed effects on the brain and the thyroid gland in males and females exposed to 425 mg/m<sup>3</sup>. Changes in the cerebrum consisted of slight vacuolation in the external capsule

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and the caudate putamen. Vacuolation was also observed in the thalamus/hypothalamus region of these animals. Microscopic changes in the thyroid gland were characterised by very slight hypertrophy of the follicular epithelial cells associated with a decrease in the amount of colloid present. The NOAEL was 127.5 mg/m<sup>3</sup> (30 ppm) (Nit93).

When New Zealand white rabbits (n=3/sex/group) were exposed to sulphuryl difluoride at concentrations of 0, 425, 1275, and 2550 mg/m<sup>3</sup> (0, 100, 300, 600 ppm), 6 hours/day, 5 days/week, for 2 weeks, 2 females of the high-exposure group were euthanised after they were found with fractures of the tibia and vertebra, respectively. For one of these females, this fracture resulted from a convulsion. The only other clinical sign observed in males and females of the high-exposure group consisted of hyperactivity. Slightly decreased body weights were observed in some rabbits. At necropsy, effects on the respiratory tract (moderate inflammation of nasal mucosa with mucopurulent exudate in the nasal cavities; inflammation of the trachea in a few animals; acute inflammation of bronchi and bronchioles in the female survivor), the nervous system (vacuolisation in globus pallidus and basal nuclei in the putamen; effects on myelinated tracts; malacia with gliosis and demyelination (no more detailed description provided), and the liver (decreased weight, - not specified - altered cytoplasmic homogeneity of liver cells) were seen, as well as decreased serum albumin and lymphoid hyperplasia in mediastinal lymph nodes and the spleen. The latter effects were considered to be a haematopoietic reaction on the inflammation of the respiratory tract. In the animals exposed to 1275 mg/m<sup>3</sup>, there were slightly decreased body and liver weights in some animals, moderate inflammation of nasal mucosa with mucopurulent exudate in the nasal cavities in most animals, and - probably - similar haematopoietic responses as found in the high-exposure group. No effects were seen in the animals exposed to 425 mg/m<sup>3</sup> (100 ppm), which was considered to be the NOAEL of the study (Eis89).

In a subsequent 13-week study, rabbits (n=7/sex/group) were exposed initially to 0, 127.5, 425 and 2550 mg/m<sup>3</sup> (0, 30, 100, 300 ppm), 5 days/week, 6 hours/day, but clinical effects seen in high-exposure animals (posterior paralysis attributing to a fractured vertebra in 1 female and convulsions in 1 male and 1 female) caused reduction of the concentration to 1275 mg/m<sup>3</sup> after 9 days, leading to a 90-day time-weighted average concentration of ca. 1432 mg/m<sup>3</sup> (337 ppm). The female with posterior paralysis was euthanised. After the decrease of the exposure level, no further clinical signs were observed. A dose-related decrease of body weight gain throughout the study period was seen in animals exposed to the high and mid concentrations, reaching statistical significance in

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high-exposure males only. Absolute and relative liver weights were significantly decreased in female rabbits of the high-exposure group, and absolute liver weight in male rabbits at 425 mg/m<sup>3</sup>. At the high concentration, brain lesions seen in both males and females consisted of microscopic changes in the area of the putamen, globus pallidus, and the internal and external capsule of the cerebrum, malacia, and slight vacuolisation accompanied by gliosis and endothelial cell hypertrophy. Moderate vacuolation of the cerebrum was seen in a single female at 425 mg/m<sup>3</sup>. Treatment-related inflammation of the nasal mucosa with mucopurulent exudate and hypertrophy and hyperplasia of respiratory epithelium were observed in the respiratory tract of all high-exposure rabbits. Degeneration of olfactory epithelium was associated with the inflammation in 2 males and 3 females of the high-exposure group. White blood cell counts for male rabbits exposed to 1432 mg/m<sup>3</sup> were significantly increased. Serum fluoride levels were significantly increased in a dose-related fashion in all treatment groups, compared with the controls. The NOAEL was 127.5 mg/m<sup>3</sup> (30 ppm) (Eis89).

In beagle dogs (n=1/sex/group) exposed to concentrations of 0, 127.5, 425, or 1275 mg/m<sup>3</sup> (0, 30, 100, 300 ppm), 6 hours/day, 5 days/week, for 2 weeks, clinical signs observed at the high concentration were infrequent intermittent episodes of tremors and tetany in both dogs, beginning with the 5th exposure. These effects were rapidly reversible when exposure was terminated and even during the exposure period. Body weight loss was observed in the female animal. Serum fluoride levels of dogs exposed to the 2 highest concentrations were increased 2- to 4-fold compared with the control values. No changes were observed in serum calcium levels. There were no exposure-related changes in haematology, organ weights, or gross pathology in any of the treated groups. Microscopic examination revealed inflammatory changes in the nasal turbinates of dogs exposed to the high concentration. No abnormalities were seen in tissues from the cerebral cortex, brainstem, cerebellum, and medulla oblongata. The NOAEL was 425 mg/m<sup>3</sup> (100 ppm) (Nit91).

In a subsequent unpublished study, groups of beagle dogs (n=4/sex/group) were exposed to concentrations of 0, 127.5, 425, or 850 mg/m<sup>3</sup> (0, 30, 100, 200 ppm), 6 hours/day, 5 days/week, for 13 weeks. On exposure day 19, one high-exposed dog showed tremors, tetany, salivation, and incoordination at 75 minutes after the beginning of exposure. These effects were reversible and were not observed during the remainder of the study. At the end of the study, the mean body weights of male and female dogs were slightly reduced at the highest concentration. There were no treatment-related changes in haematology, clinical chemistry, organ weight, or gross pathology. Microscopic examination revealed a

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single small bilaterally symmetrical focal change in the putamen of the midbrain of one male and one female dog, exposed to the highest concentration. This change was characterised by vacuolation, gliosis, perivascular cuffing, and hypertrophy of endothelial cells. No other treatment-related microscopic changes were observed. The NOAEL was 425 mg/m<sup>3</sup> (100 ppm) (Nit92).

An unpublished 1-year toxicity study was conducted with beagle dogs (n=4/sex/group) exposed to concentrations of 0, 85, 340, or 850 mg/m<sup>3</sup> (0, 20, 80, 200), 6 hours/day, 5 days/week. In the high-exposure group, a decrease in body weight was observed leading to morbidity and death (not further specified). At approximately 9 months of exposure, high-exposed animals started to show clinical signs, including laboured breathing, shallow and rapid respiration, and pale and blue mucous membranes, eventually leading to death. No treatment-related clinical signs were observed in the dogs exposed to 85 or 340 mg/m<sup>3</sup>. Gross examination of the high-exposure dogs revealed dark-coloured lungs that appeared to be consolidated. No macroscopic abnormalities were seen in any of the low- and mid-exposure groups. Microscopic changes in the high-exposure dogs were noted in the lungs, brain, thyroid, and canine teeth, and in the lungs and canine teeth of the dogs exposed to 340 mg/m<sup>3</sup>. The pulmonary changes were a chronic active inflammation that primarily involved the peripheral regions of the lung. An increased number of alveolar macrophages was observed in scattered alveoli. In the more advanced stages of inflammation, these foci apparently increased in size, and hypertrophied type II pneumocytes were observed. In the more severe cases, a focal thickening of the pleura and interalveolar septae was observed as well. In dogs exposed to 340 mg/m<sup>3</sup>, a very slight increase in the aggregate of alveolar macrophages was observed, with several dogs showing a very slight degree of chronic active inflammation. In the brain of 5 out of the 8 high-exposure dogs, a focus of malacia was noted. No other brain abnormalities were found in any of the treated groups compared with the controls. Effects found in the thyroid gland consisted of slight hypertrophy of the follicular epithelium in the high-exposure dogs. There were no exposure-related effects noted in dogs exposed to the lowest level, and consequently the NOAEL was 85 mg/m<sup>3</sup> (20 ppm) (Qua93a).

#### *Chronic toxicity and carcinogenicity*

Groups of Fischer 344 rats (n=50/sex/group) were exposed to sulphuryl difluoride at concentrations of 0, 21, 85, and 340 mg/m<sup>3</sup> (0, 5, 20, 80 ppm), 6 hours/day, 5 days/week, for 24 months. Simultaneously with this core study, satellite groups of 15 rats/sex/exposure level were included that were sacrificed after 12 months

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for the assessment of general toxicity (haematology, clinical chemistry, urinalysis, organ weights, and macroscopic and microscopic examination) and neurotoxicity (functional observation battery, motor activity, and microscopic examination of nervous system tissues in 5 animals/sex/group; see below: Spe94). In the core study, mortality of rats in the treated groups was similar to the control group during the first 16 months, but thereafter strongly increased in the high-exposure group. At the end of the 24 months, mortality amounted to 18, 22, and 50 males and 13, 12, and 50 females, in the low-, mid-, and high-exposure groups, respectively, vs. 21 males and 25 females in the control group. Causes of death included normal age-related diseases for the animals of the control and the low- and mid-exposure groups. For the high-exposure group, most deaths were related to chronic renal disease. In the high-exposure group, body weights were significantly decreased in males and females after 400 to 500 days exposure. Haematology parameters were considered to be within normal ranges at the different sampling times (at 19 and 21 months). Main changes in clinical chemistry parameters were significant increases in urinary specific gravity and in serum urea nitrogen, creatinine, and phosphorus, and significant decreases in total protein, albumin, and chloride in high-exposure rats. The committee considered these changes related to or secondary to the renal disease observed in these animals. In the satellite study, the only change was a decrease in serum albumin levels of rats exposed to the highest concentration for 12 months. Relative kidney and liver weights of male rats were significantly increased in this group. At necropsy (both in the satellite and the core groups), the target organs for sulphuryl difluoride toxicity in high-exposure animals appeared to be the kidney, the lungs, and the teeth (dental fluorosis). Microscopic examination revealed only a slight degree of chronic progressive glomerulonephropathy in high-exposure male and female animals after 12 months. However, kidney changes had progressed to severe or very severe chronic progressive glomerulonephropathy in rats exposed to the highest concentration for 24 months. Along with these kidney changes, secondary changes, such as hyperparathyroidism and mineralisation of many tissues were observed. In the lung, slight aggregates of alveolar macrophages were noted in the satellite group, but were not considered to significantly impair pulmonary function. These changes were not increased in severity after 24 months of exposure. Macroscopic and microscopic dental effects were seen in the upper incisor teeth of both males and females exposed to the high concentration for 12 or 24 months. In addition, after 24 months, a very slight fluorosis of the teeth of male rats exposed to 84 mg/m<sup>3</sup> was found. There was no increase in the incidence of any tumour in male or female rats in any of the treated groups compared with the control animals.

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Both in the 12-month and 24-month study, the NOAELs were 21 (5 ppm) (based on slight dental fluorosis) and 85 mg/m<sup>3</sup> (20 ppm) (based on lung and renal injury), for male and female rats, respectively (Qua93b).

In the separate 12-month neurotoxicity study, no treatment-related effects were found in the functional observation battery or motor activity, and no treatment-related abnormalities in the microscopic examination. The NOAEL for neurotoxic effects was 340 mg/m<sup>3</sup> (80 ppm) (Spe94).

Groups of CD-1 mice (n=50/sex/group) were exposed to concentrations of sulphuryl difluoride 0, 21, 85 and 340 mg/m<sup>3</sup> (0, 5, 20, 80 ppm), 6 hours/day, 5 days/week, for 18 months. A separate satellite group of 10 mice/sex/exposure level was included in the study for blood sampling and necropsy after 12 months. In the core study, mortality was comparable for exposed and control groups, except for the females of the high-exposure group (males: 23/50, 20/50, 25/50, and 32/50; females: 18/50, 12/50, 20/50, and 36/50 at 0, 21, 85, 340 mg/m<sup>3</sup>, respectively). Body weights were significantly decreased in high-exposure males and females. No treatment-related effects were reported on clinical observations, haematology, clinical chemistry and organ weights (changes related to the decreased body weights only), and macroscopic examination. Microscopically, the main findings in high-exposure animals were a minimal vacuolation of the external capsule of the brain, but only in 1 animal in the area of the caudate putamen, and not in the amygdaloid regions (no more details given), and slight hypertrophy of the thyroid follicular epithelial cells. These findings proved to be less severe in the core group animals than in the satellite animals. All other microscopic changes were considered to be unrelated to sulphuryl difluoride exposure. There was no increased incidence of any tumour in any of the treated groups compared with controls. The NOAEL for both the 12 and 18 months studies was 84 mg/m<sup>3</sup> (Qua93c).

A summary of the results of short- and long-term toxicity studies in rats, mice, rabbits, and dogs is shown in Table 1.

Table 1 Summary of short- and long-term inhalation toxicity studies for sulphuryl difluoride.

species <sup>a</sup> (strain)	dose levels (mg/m <sup>3</sup> )	exposure duration <sup>b</sup>	critical effect	NOAEL (mg/m <sup>3</sup> )	reference
rat (F344)	0, 425, 1275, 2550	2 weeks	lung, renal injury	425	Eis89
(F344)	0, 127.5, 425, 125	13 weeks	lung, nasal, renal injury; dental fluorosis	127.5	Eis89
(F344)	0, 127.5, 425, 1275	13 weeks	neurotoxicity study: electrophysiological effects in brain	127.5	Mat88
(Sprague-Dawley) (F344)	0, 21, 85, 637.5	20 weeks <sup>c</sup>	reproduction toxicity study: lung injury	21	Bre92, Bre93
(F344)	0, 21, 85, 340	12 months	dental fluorosis lung, renal injury	21 (male) 85 (female)	Qua93b
(F344)	0, 21, 85, 340	12 months	neurotoxicity study: no adverse effects reported	340	Spe94
(F344)	0, 21, 85, 340	24 months	dental fluorosis lung, renal injury	21 (male) 85 (female)	Qua93b
mouse (CD-1)	0, 127.5, 425, 1275	2 weeks	brain injury	127.5	Nit95
(CD-1)	0, 42.5, 127.5, 425	13 weeks	brain, thyroid injury	127.5	Nit93
(CD-1)	0, 21, 85, 340	12 months	brain, thyroid injury	85	Qua93c
(CD-1)	0, 21, 85, 340	18 months	brain, thyroid injury	85	Qua93c
rabbit (New Zealand)	0, 425, 1275, 2550	2 weeks	lung, nasal, brain injury	425	Eis89
(New Zealand)	0, 127.5, 425, 1432	13 weeks	lung, nasal, brain injury	127.5	Eis89
dog (beagle)	0, 127.5, 425, 1275	2 weeks	nasal injury	425	Nit91
(beagle)	0, 127.5, 425, 850	13 weeks	brain injury	425	Nit92
(beagle)	0, 85, 340, 850	12 months	lung, brain, thyroid injury; dental fluorosis	85	Qua93

<sup>a</sup> Studies were performed using Fischer 344 rats, CD-1 mice, New Zealand white rabbits, and beagle dogs.

<sup>b</sup> 6 hours/day, 5 days/week.

<sup>c</sup> 6 hours/day, 5 days/week, for 10 weeks, then 6 hours/day, 7 days/week, for another 10 weeks.

#### *Mutagenicity and genotoxicity*

- *In vitro* tests:

Sulphuryl difluoride did not induce reverse mutations in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without metabolic activation, at nominal concentrations of 1275, 4250, 12,750, 42,500, and 127,500 mg/m<sup>3</sup> (300-30,000 ppm) (4 hours, 37°C) (Gol90a).

Sulphuryl difluoride did not increase unscheduled DNA synthesis in rat primary hepatocytes at concentrations ranging from ca. 867 to 4335 mg/m<sup>3</sup> (204-1020 ppm) (Gol91).

- *In vivo* tests:

Cytogenetic assays. No increased frequency of micronucleated polychromatic erythrocytes was observed in the bone marrow of mice, exposed to air concentrations of sulphuryl difluoride of ca. 0, 212.5, 744 or 2210 mg/m<sup>3</sup> (0, 50, 175, 520 ppm) (Gol90b)

*Reproduction toxicity*

In a 2-generation reproduction study, groups of 30 male and 30 female Sprague-Dawley rats were exposed to concentrations of sulphuryl difluoride of 0, 21, 85, or 637.5 mg/m<sup>3</sup> (0, 5, 20, 150 ppm), 6 hours/day, 5 days/week, for 10 weeks for the F0 and 12 weeks for the F1 generation prior to mating, and 6 hours/day, 7 days/week during mating, gestation, and lactation through 2 generations. Male and female F0 and F1 rats had significantly decreased body weights at 637.5 mg/m<sup>3</sup> during most of the pre-mating period, and female rats during gestation. Body weights were also decreased in F1 females during the lactation period, but an increase was seen in F0 females. No exposure-related effects were found on the F0 and F1 male or female conception index, fertility indices, length of gestation, time to mating, pup survival indices, or pup sex ratio. The number of F1 or F2 pups born dead or alive or the litter size was not significantly different between any of the exposed groups and the control group. In the high-exposure group, decreased body weights were observed in F1 and F2 pups throughout most of the lactation period. This effect was considered to be secondary to the decreased growth of female F0 and F1 rats during the pre-mating and gestation periods. The effect on pup weight in the high-exposure group was less severe in the F2 litters. Microscopic examination revealed an increased incidence of very slight to slight, bilaterally symmetrical, vacuolation of the caudate putamen myelinated fiber tracts in the brain of F0 and F1 male and female parental rats in the high-exposure group. Dental fluorosis was also observed in high-exposure parental animals. At a concentration of 85 mg/m<sup>3</sup>, F0 and F1 parental effects were limited to an increased incidence of aggregates of alveolar macrophages in the lung. No treatment-related abnormalities were found in macroscopic or microscopic examination of the reproductive organs. The parental NOAEL was 21 mg/m<sup>3</sup> (5 ppm) for males and females, the NOAEL for neonatal growth was 85mg/m<sup>3</sup> (20 ppm), and the NOAEL for reproductive toxicity and fertility was 637.5 mg/m<sup>3</sup> (150 ppm) (Bre92, Bre93).

In a developmental toxicity, pregnant F344 rats (n=35-36/group) were exposed to sulphuryl difluoride concentrations of 106, 319, and 956 mg/m<sup>3</sup> (0, 25, 75, 225 ppm), 6 hours/day, on gestational days 6-15. No mortality was

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observed and maternal effects were limited to an increased water consumption in high-exposure rats. Pregnancy rate, numbers of implantations and litter sizes, and fetal sex ratio in the exposed groups were not statistically significantly different compared with the control group. In the high-exposure group, a statistically significant increase in fetal body weight and fetal crown-rump length was found, which was not considered of toxicological significance. Teratological examination revealed a statistically significant increased incidence of bilobed thoracic vertebral centra in fetuses of dams exposed to 106 or 956 mg/m<sup>3</sup> and of unfused thoracic vertebral centra at 319 mg/m<sup>3</sup>. However, no relationship with dose was apparent, and, therefore, the committee decided that these effects were of no toxicological significance. The NOAEL for maternal and developmental toxicity was 956 mg/m<sup>3</sup> (225 ppm), the highest level tested (Han89).

In another development study, groups of 28-29 inseminated New Zealand white rabbits were exposed to sulphuryl difluoride concentrations of 106, 319, and 956 mg/m<sup>3</sup> (0, 25, 75, 225 ppm), 6 hours per day, on gestational days 6-18. Mortality was observed in 2/29, 1/28, and 3/29 rabbits of the low-, mid- and high-exposure group, respectively; 4 of these deaths were attributed to pneumonia, most probably pasteurellosis. No overt signs of maternal toxicity were observed, but, in the high-exposure group, animals lost weight during gestational days 9-19 (decrease statistically significant during days 12-15) and did not gain weight in the post-exposure period (gestational days 19-29). No effects on number of corpora lutea, number of implantation sites, and number of resorptions were found. Apart from decreases in body weight (by 14%) and in crown-rump length in fetuses of the high-exposure group, no treatment-related fetal effects (morphology, skeletal ossification) were seen in any of the exposed groups. The NOAEL for maternal and developmental toxicity was 319 mg/m<sup>3</sup> (75 ppm) (Han89).

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## **7 Existing guidelines**

The current administrative occupational exposure limit (MAC) for sulphuryl difluoride in the Netherlands is 20 mg/m<sup>3</sup> (5 ppm), 8-hour TWA.

Existing occupational exposure limits in some European countries and the USA are summarised in the annex.

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## 8 Assessment of health hazard

The health hazard assessment of sulphuryl difluoride is based to a large extent on a toxicology review in 'The Handbook of Pesticide Toxicology' (Nit01), describing numerous unpublished toxicology studies.

The principal route of occupational exposure to sulphuryl difluoride is through inhalation. Increased fluoride concentrations found in the blood or urine of exposed humans indicated that at least part of the sulphuryl difluoride is metabolised into inorganic fluoride. In rats, exposed to concentrations of <sup>35</sup>S-labelled compound of 127,5 and 1275 mg/m<sup>3</sup> (30 and 300 ppm) for 4 hours, the pulmonary absorption was 11-14%. Radioactivity in plasma and red blood cells peaked near the end of the 4-hour exposure period and was rapidly cleared with initial half-lives of about 2.5 hours. The terminal half-life of radioactivity was 2.5-fold longer in red blood cells than in plasma. The radiolabel was rapidly excreted, mainly via the urine. Radiochemical profiles of blood and urine did not indicate presence of parent compound and suggested hydrolysis into fluorosulphate and subsequently into sulphate releasing fluoride in both steps. Analysis of tissues 7 days post-exposure showed a rather even distribution among tissue, which was ascribed to incorporation of radiolabelled sulphur into amino acids, with the highest levels of radioactivity in the lungs, still elevated levels in the red blood cell, and detectable levels in the nasal turbinates. Of the non-respiratory tissues, highly perfused tissues such as spleen and kidneys had the higher <sup>35</sup>S concentrations.

Several fatalities have been published in humans exposed to the compound after re-entry in their fumigated homes. Signs of toxicity were seizures, tetany, and cardiac rhythm disturbances. Post-mortem examination revealed visceral congestion and pulmonary oedema. Two studies on structural fumigation workers did not show evidence of neurotoxic effects due to occupational exposure to sulphuryl fluoride.

The committee did not find experimental animal data on skin or eye irritation, or on skin sensitisation. Based on the results of acute lethal toxicity studies in test animals, the committee considers the compound as harmful after inhalation, and as unlikely to present an acute health hazard after dermal exposure. Rats exposed to 17,000 mg/m<sup>3</sup> (4000 ppm) were incapacitated within 45 minutes; although exposure was terminated, they died about 2.5 hours later. Sulphuryl difluoride did not induce neurotoxicity in rats exposed 6 hours/day, for 2 consecutive days to concentrations up to 1275 mg/m<sup>3</sup> (300 ppm).

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In short- or long-term studies in rats, mice, rabbits, and dogs, the target organs after exposure to sulphuryl difluoride were the respiratory tract and the brain. In addition, renal effects were observed in Fischer 344 (but not in Sprague-Dawley) rats, effects on the thyroid in mice and dogs, and dental fluorosis - which the committee considers as a biomarker of fluoride exposure rather than a toxicological effect - in rats and dogs. The NOAELs were:

- 21 mg/m<sup>3</sup> (5 ppm) for (parental) rats, based on lung lesions of minor severity and incidence in a 2-generation reproduction toxicity study (6 hours/day, 5 days/week, for 10 weeks, then 6 hours/day, 7 days/week, for another 10 weeks);
- 85 mg/m<sup>3</sup> (20 ppm) for female rats, based on renal and lung injury and dental fluorosis in a 24-month study (6 hours/day, 5 days/week);
- 85 mg/m<sup>3</sup> (20 ppm) for mice, based on brain injury and effects on the thyroid in an 18-month study (6 hours/day, 5 days/week);
- 85 mg/m<sup>3</sup> (20 ppm) for dogs, based on lung and brain injury, thyroid effects, and dental fluorosis in a 12-month study (6 hours/day, 5 days/week);
- 127.5 mg/m<sup>3</sup> (30 ppm) in rabbits, based on effects on the brain and the respiratory tract in a 13-week study (6 hours/day, 5 days/week).

*In vitro* and *in vivo* tests for mutagenicity or genotoxicity were negative, and no evidence of carcinogenicity was found in 18- and 24-month studies in mice and rats, respectively.

In a 2-generation reproductive toxicity study in rats, the NOAELs for parental and reproduction toxicity were 21 and 85 mg/m<sup>3</sup> (5 and 20 ppm), respectively, on the basis of effects on the respiratory tract in parental males and females and reduced body weights of pups throughout most of the lactation period, respectively. In developmental toxicity studies, no effects indicative of maternal or developmental toxicity were seen in rats at concentrations up to 956 mg/m<sup>3</sup> (225 ppm), the highest level tested. In rabbits, slight fetotoxicity (decreased weight and crown-rump length) and maternal toxicity (weight loss) were seen at 956 mg/m<sup>3</sup> (225 ppm) but not at 319 mg/m<sup>3</sup> (75 ppm).

From the above-presented data, the committee concludes that, generally, the various toxicity studies do not show remarkable differences concerning effects and effect levels between the species (rat, mouse, rabbit, dog) tested, apart from 21 mg/m<sup>3</sup> (5 ppm) for the minor lung lesions. These lesions were seen in the 2-generation reproduction study in parental animals exposed to 85 mg/m<sup>3</sup> (20 ppm), 6 hours/day, 5 days/week for 10 weeks and 6 hours/day, 7 days/week for another 10 weeks, but not in rats, mice, and dogs exposed to 84 mg/m<sup>3</sup> (20 ppm) for 5 days/week for much longer exposure times of 12 to 24 months. The committee considers these lung lesions to be due to the continuous exposure of 7

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days/week in the second half of this study. Since workers are exposed 5 days/week, the committee prefers to use the animals studies with 5-days/week exposure schedules in deriving a health-based occupational exposure limit (HBROEL), and concludes that 85 mg/m<sup>3</sup> (20 ppm) is the overall NOAEL to be taken as a starting point. For the extrapolation to a HBROEL, an overall assessment factor of 9, covering intra- and interspecies variation, is established. Thus, applying this factor and the preferred value approach, a health-based occupational exposure limit of 10 mg/m<sup>3</sup> (2.4 ppm) is recommended for sulphuryl difluoride.

The committee recommends a health-based occupational exposure limit for sulphuryl difluoride of 10 mg/m<sup>3</sup> (2.4 ppm), as an 8-hour time-weighted average (TWA).

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## References

- ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). Sulphuryl fluoride. In: TLVs<sup>®</sup> and other occupational exposure values - 1999. [CD-ROM]. Cincinnati OH, USA; ACGIH<sup>®</sup>, 1999.
- ACG04a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2004. Cincinnati OH, USA: ACGIH<sup>®</sup>, 2004: 133.
- ACG04 American Conference of Governmental Industrial Hygienists (ACGIH). 2004 TLVs<sup>®</sup> and BEIs<sup>®</sup> based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH<sup>®</sup>, 2004: 52.
- Alb93 Albee RR, Spencer PJ, Bradley GJ. Sulphuryl fluoride: Electrodiagnostics, FOB, and motor activity evaluation of nervous effects from short-term exposure. Midland MI, USA: The Dow Chemical Company, 1993; unpublished report, cited in Nit01.
- Ang86 Anger WK, Moody L, Burg J, et al. Neurobehavioral evaluation of soil and structural fumigators using methyl bromide and sulphuryl fluoride. *Neurotoxicology* 1986; 7: 137-56.
- Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 37 (At-vejledning C.0.1).
- Bra90 Bradley GJ, Landry TD, Battjes JE, et al. Sulphuryl fluoride: four-hour dermal vapor exposure in Fischer 344 rats. Midland MI, USA: The Dow Chemical Company, 1990; unpublished report, cited in Nit01.
- Bre92 Breslin WJ, Liberacki AB, Kirk HD, et al. Sulphuryl fluoride: two-generation inhalation reproduction study in Sprague-Dawley rats. Midland MI, USA: The Dow Chemical Company, 1992.
- Bre93 Breslin WJ, Liberacki AB, Kirk HD, et al. Sulphuryl fluoride: two generation reproduction study in Sprague-Dawley rats. *Toxicologist* 1993; 13: 368.
- Cal98 Calvert G, Mueller C, Fajen J. Health effects associated with sulphuryl fluoride and methyl bromide exposure among structural fumigation workers. *Am J Publ Health* 1998; 88: 1774-80.
-

- DFG04 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2004. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH Verlag GmbH & Co. KGaA, 2004; rep no 40.
- EC04 European Commission: Directorate General of Employment and Social Affairs. Occupational exposure limits (OELs). [http://europe.eu.int/comm/employment\\_social/health\\_safety/areas/oels\\_en.htm](http://europe.eu.int/comm/employment_social/health_safety/areas/oels_en.htm).
- Edm87 Edmiston S, Maddy KT. Summary of illnesses and injuries reported in California USA by physicians in 1986 as potentially related to pesticides. *Vet Hum Toxicol* 1987; 29: 391-7.
- Eis89 Eisenbrandt DL, Nitschke KD. Inhalation toxicity of sulfuranyl fluoride in rats and rabbits. *Fundam Appl Toxicol* 1989; 12: 540-57.
- EPA92 US Environmental Protection Agency (EPA). Reregistration eligibility decision (RED). Sulfuryl fluoride. List A. Case 0176. Washington DC, USA: Environmental Protection Agency, Office of Pesticide Programs, Special Review and Reregistration Division, 1992; <http://www.epa.gov/pesticides/reregistration/status.htm>.
- Go190a Gollapudi BB, Samson YE, Zempel JA. Evaluation of sulfuranyl fluoride in the Ames Salmonella/mammalian microsomal bacterial mutagenicity assay. Midland MI, USA: The Dow Chemical Company, 1990; unpublished report, cited in Nit01.
- Go190b Gollapudi BB, McClintock ML, Nitschke KD. Evaluation of sulfuranyl fluoride in the mouse bone marrow micronucleus test. Midland MI, USA: The Dow Chemical Company, 1990; unpublished report, cited in Nit01.
- Go191 Gollapudi BB, McClintock ML, Zempel JA. Evaluation of sulfuranyl fluoride in the rat hepatocyte unscheduled DNA synthesis (UDS) assay. Midland MI, USA: The Dow Chemical Company, 1991; unpublished report, cited in Nit01.
- Han89 Hanley TR Jr, Calhoun LL, Kociba RJ, et al. The effects of inhalation exposure to sulfuranyl fluoride on fetal development in rats and rabbits. *Fundam Appl Toxicol* 1989; 13: 79-86.
- HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 26.
- Lew96 Lewis RJ Sr. Sax's Dangerous properties of industrial materials. 9th ed. New York, USA: Van Nostrand Reinhold, 1996: 3050-1.
- Mat88 Mattson JL, Albee RR, Eisenbrandt DL, et al. Subchronic neurotoxicity in rats of the structural fumigant sulfuranyl fluoride. *Neurotoxicol Teratol* 1988; 10: 127-33.
- Men03 Mendrala AL, Eisenbrandt DL, Markham DA, et al. Sulfuryl fluoride: pharmacokinetics and metabolism in F344 rats. *Toxicologist* 2003; 62: 147.
- Mil80 Miller RR, Calhoun LL, Keyes DG, et al. Sulfuryl fluoride (VIKANE gas fumigant): An LC50 determination. Midland MI, USA: The Dow Chemical Company, 1980; unpublished reported, cited in Nit01.
- Nit86 Nitschke KD, Albee RR, Mattison JL, et al. Incapacitation and treatment of rats exposed to a lethal dose of sulfuranyl fluoride. *Fundam Appl Toxicol* 1986; 7: 664-70.
-



- Nit89 Nitschke KD, Lomax LG. Sulfuryl fluoride: Acute LC50 study with B6C3F1 mice. Midland MI, USA: The Dow Chemical Company, 1989; unpublished report, cited in Nit01.
- Nit90 Nitschke KD, Quast JF. Sulfuryl fluoride: Acute LC50 study with CD-1 mice. Midland MI, USA: The Dow Chemical Company, 1990; unpublished report, cited in Nit01.
- Nit91 Nitschke KD, Quast JF. Sulfuryl fluoride: two-week inhalation toxicity study in beagle dogs. Midland MI, USA: The Dow Chemical Company, 1991; unpublished report, cited in Nit01.
- Nit92 Nitschke KD, Quast JF. Sulfuryl fluoride: thirteen-week inhalation toxicity study in beagle dogs. Midland MI, USA: The Dow Chemical Company, 1992; unpublished report, cited in Nit01.
- Nit93 Nitschke KD, Quast JF. Sulfuryl fluoride: thirteen-week inhalation toxicity study in CD-1 mice. Midland MI, USA: The Dow Chemical Company, 1993; unpublished report, cited in Nit01.
- Nit95 Nitschke KD, Quast JF. Sulfuryl fluoride: two-week inhalation toxicity study in CD-1 mice. Midland MI, USA: The Dow Chemical Company, 1995; unpublished report, cited in Nit01.
- Nit01 Nitschke KD, Eisenbrandt DL. Sulfuryl Fluoride. In: Krieger RI, ed. Agents. 2nd ed. San Diego CA, USA: Academic Press 2001: 1881-96 (Handbook of pesticide toxicology; Vol 2).
- NLM01 US National Library of Medicine (NLM). Sulfuryl fluoride. In: The Hazardous Substances Data Bank (HSDB) (last review date sulfuryl fluoride file: 31 January 1998); <http://toxnet.nlm.nih.gov>.
- Nuc87 Nuckolls JG, Smith DC, Walls WE, et al. Fatalities resulting from sulfuryl fluoride exposure after home fumigation – Virginia. JAMA 1987; 258: 2041- 4.
- Pog97 Pogoda JM, Preston-Martin S. Household pesticides and risk of pediatric brain tumours. Environ Health Perspect 1997; 105: 1214-20.
- Qua93a Quast JF, Beekman MJ, Nitschke KD. Sulfuryl fluoride: one-year inhalation toxicity study in beagle dogs. Midland MI, USA: The Dow Chemical Company, 1993; unpublished report, cited in Nit01.
- Qua93b Quast JF, Bradley GJ, Nitsche KD. Sulfuryl fluoride: 2-year inhalation chronic toxicity/oncogenicity study in Fischer 344 rats. Midland MI, USA: The Dow Chemical Company, 1993.
- Qua93c Quast JF, Bradley GJ, Nitsche KD. Sulfuryl fluoride: 18-months inhalation oncogenicity study in CD-1 mice. Midland MI, USA: The Dow Chemical Company, 1993.
- Sch86 Scheuerman EH. Suicide by exposure to sulfuryl fluoride. J Forens Sci 1986; 31: 1154-8.
- Spe94 Spencer PJ, Bradley GJ, Quast JF. Sulfuryl fluoride: Chronic neurotoxicity study in Fischer 344 rats-Final report. Midland MI, USA: The Dow Chemical Company, 1994; unpublished report, cited in Nit01.
- Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.
- SZW04 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2004. The Hague, the Netherlands: Sdu Uitgevers, 2004: 40.
- Tax66 Taxay EP. Vikane Inhalation. J Occup Med 1966; 8: 425-6.
- TRG04 TRGS 900. Technische Regeln für Gefahrstoffe. Grenzwerte in der Luft am Arbeitsplatz. BARbBl 2004; (7/8).
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- Tru73 Truhaut R, Boudene CI, Cluet JL. Toxicité de quelques dérivés gazeux fluores et oxyfluores du soufre. *Arch Mal Prof Med Trav Secur Soc* 1973; 34: 581-91.
- Ver77 Vernot EH, MacEwen JD, Hann CC, et al. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol Appl Pharmacol* 1971; 42: 417-23.

## Annex

### Occupational exposure limits for sulphuryl difluoride in various countries.

country - organisation	occupational exposure		time-weighted average	type of exposure limit	note <sup>a</sup>	reference <sup>b</sup>
	ppm	mg/m <sup>3</sup>				
the Netherlands						
- Ministry of Social Affairs and Employment	5	20	8 h	administrative		SZW04
Germany						
- AGS	-	21	8 h			TRG04
- DFG MAK-Kommission	-	-				DFG04
Great-Britain						
- HSE	5	21	8 h	OES		HSE02
	10	42	15 min			
Sweden	-	-	8 h			Swe00
Denmark	5	20	8 h			Arb02
USA						
- ACGIH	5	-	8 h	TLV		ACG04b
	10	-	15 min	STEL		
- OSHA	5	20	8 h	PEL		ACG04a
- NIOSH	5	20	10 h	REL		
	10	40	15 min	STEL		ACG04a
European Union						
- SCOEL	-	-				EC04

<sup>a</sup> S = skin notation; which mean that skin absorption may contribute considerably to body burden;  
sens = substance can cause sensitisation.

<sup>b</sup> Reference to the most recent official publication of occupational exposure limits.

