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127. Hydrogen sulphide

Kristin Svendsen

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Editor-in-chief: Staffan Marklund
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National Institute for Working Life
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Sweden

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Preface

An agreement has been signed by the Dutch Expert Committee on Occupational Standards (DECOS) of the Health Council of the Netherlands and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities in both the Netherlands and in the Nordic Countries.

The document on health effects of hydrogen sulphide was written by Dr. Kristin Svendsen at the University Hospital of Trondheim, Norway and has been reviewed by DECOS as well as by NEG.

Editorial work was performed by NEG's scientific secretary, Jill Järnberg, and technical editing by Karin Sundström, both at the National Institute for Working Life in Sweden.

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Chairman
DECOS

G. Johanson
Chairman
NEG

Abbreviations

EEG	electroencephalogram / electroencephalographic
GABA	gamma aminobutyric acid
IC_{50}	concentration at which 50 % inhibition of a certain function is found, compared with the control value
IDLH	immediately dangerous to life or health
LC_{50}	lethal concentration for 50% of the exposed animals
LD_{50}	lethal dose for 50% of the exposed animals
NOEL	no observed effect level
PAM	pulmonary alveolar macrophage
REL	recommended exposure limit
STEL	short term exposure limit
TWA	time weighted average

Contents

1. Introduction

Hydrogen sulphide is a gas found in the environment in volcanic gases, swamps, sulphur springs and as a product of bacterial processes during the decay of plant and animal protein. The generation of hydrogen sulphide can be expected whenever oxygen is depleted, and organic material containing sulphur is present. Therefore, this gas is a common environmental pollutant in sewage plants and agriculture. Another source of H_2S is crude oil and natural gas. The sulphur content of the oil and gas varies from field to field. Hydrogen sulphide can be formed whenever elemental sulphur or sulphur-containing compounds come into contact with organic materials at high temperatures (32). Several reviews on the toxicity of hydrogen sulphide to humans have been published during the last decades. A criteria document on dihydrogen sulphide was written for the Nordic Expert Group in 1982 (74). Since then, some new issues about the health effects of this gas have been raised (56).

2. Substance identification

IUPAC name:	Hydrogen sulfide
Common name:	Hydrogen sulphide
CAS number:	7783-06-4
Synonyms:	dihydrogen monosulphide, dihydrogen sulphide, hydrogen sulphuric acid, sewer gas, stink damp, sulphuretted hydrogen, sulphur hydride
Molecular formula:	H_2S
Molecular weight:	34.09

3. Physical and chemical properties

Freezing point at 101.3 kPa:	-85.5°C
Boiling point at 101.3 kPa:	-60.7°C
Vapour density (air=1):	1.19
Vapour pressure at 25.5°C:	2026 kPa
Explosive limits in air (vol/vol):	Lower limit: 4.3% Upper limit: 45.5%
Solubility w/w at 20°C:	0.4% in water 2.1% in ether
Odour threshold:	0.13 ppm (16)
Conversion factors at 25°C:	1 ppm = 1.394 mg/m^3 1 mg/m^3 = 0.717 ppm

Hydrogen sulphide is a colourless, irritant and asphyxiant gas. It is flammable and explosive at high concentrations in air and may even be ignited by static discharge (16).

An aqueous solution of H_2S exhibits two acid dissociation constants. The first dissociation yields a hydrosulphide anion (HS^-). A second proton may dissociate yielding sulphide anion (S^{2-}). The pKa values for the first and second dissociation step of hydrogen sulphide are 7.0 and 12.0, respectively. Therefore, approximately one third of the H_2S will exist in the undissociated form (H_2S) at physiologic pH (7.4), and the remaining part will largely be the HS^- anion. Very small amounts of S^{2-} are present (5).

4. Occurrence, production and use

Hydrogen sulphide is one of the principal compounds involved in the natural cycle of sulphur in the environment. The substance is often present in volcanic gases. It is also produced by bacterial processes during the decay of both plant and animal protein (e.g. in sewage water) or through the direct reduction of sulphate (32). Hydrogen sulphide also occurs in most petroleum and natural gas deposits and in mines where sulphur is present. Occupational exposure to hydrogen sulphide is primarily a problem in the "sour gas" segment of the natural gas industry, where natural gas with a high concentration of sulphur is processed. There have been several reports of accidental deaths and injuries at a number of work situations and work places such as flat fish farming (44), asphalt roofing (30), liquid manure pits in farming (85), oil fields (42), oil refineries (43), and sewage handling (85). Large quantities of H_2S are used in the production of deuterated water (16). Hydrogen sulphide is formed in manufacturing processes whenever elemental sulphur or sulphur compounds are present with organic chemicals at high temperatures. Examples of industries where H_2S can be generated include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, viscose rayon manufacture, sulphur production, iron smelters, food processing plants, and tanneries (16, 32).

5. Occupational exposure data

Concentrations varying from 0 to 20 ppm (0-28 mg/m^3) hydrogen sulphide were measured in a hygiene survey in kraft and sulphite mills (37). The greatest emissions were detected at chip chutes and evaporation vacuum pumps.

The level of hydrogen sulphide varied between <0.07 and 53 mg/m^3 (<0.05-38 ppm) under normal operating conditions in 18 Finnish municipal wastewater treatment plants (38). The highest concentration was found at the sludge presses. The pumping stations had sulphide gas levels varying from 0.07 to 0.5 mg/m^3 (0.05-0.36 ppm). In all these measurements area and process measure-

ments samples were collected in plastic bags and analysed by gas chromatography.

In 24 personal measurements in municipal sewage plants in Norway, the time weighted average (TWA) level over 8 hours never exceeded 1 ppm (1.4 mg/m^3) (55). However, exposure peaks of 3, 12 and 45 ppm (4, 17, and 63 mg/m^3) were recorded in 3 measurements.

Exposure levels (personal measurements) of hydrogen sulphide from 0.2 to 8.9 mg/m^3 (0.14-6.4 ppm) were reported in an epidemiological study of eye irritation in viscose rayon workers (86).

In spite of the low levels of hydrogen sulphide reported from normal process conditions, high concentrations may be reached in certain situations. A level of 14 000 ppm (19 500 mg/m^3) H_2S was recorded in connection with an accident where an offshore oil well tester was wearing an H_2S sensor (42).

Several cases of "knockdowns" or deaths from H_2S exposure in farming, wastewater treatment and oil industry demonstrate that the concentration could be unpredictably high (21, 22, 28, 79).

In regard to environmental exposure, concentrations of hydrogen sulphide in urban areas are generally below 0.0015 mg/m^3 (0.001 ppm), but may occasionally be as high as 0.05 mg/m^3 (0.04 ppm) (32).

6. Measurements and analysis of workplace exposure

Sampling methods for hydrogen sulphide includes sampling on filters impregnated with silver nitrate (62). The resulting silver sulphide is dissolved in an alkaline cyanide solution and analysed for sulphide by differential pulse polarography using a dropping mercury electrode. The qualitative detection limit is 0.4 ppm (0.6 mg/m^3) in a 2-liter air sample.

Hydrogen sulphide has also been analysed by gas chromatography on the spot or after collection in plastic laminate bags (37, 38).

In addition, there is a wide range of direct reading instruments available. These instruments have different operating principles upon which the measurements are based (93). Most frequently used are electrochemical sensors. Several direct reading colorimetric detector tubes are available for both short-term and long-term measurements.

Previously, hydrogen sulphide was collected in a midget impinger containing an alkaline suspension of cadmium hydroxide. The sulphide was precipitated as cadmium sulphide and subsequently analysed by the methylene blue colorimetric procedure (62). Another method is to collect hydrogen sulphide on coconut shell charcoal with a Zefluor PTFE prefilter (60). This method has however been withdrawn because the charcoal sampling tubes have a high sulphate/H_2S background.

7. Toxicokinetics

7.1 Uptake

The knowledge of the toxicokinetics of hydrogen sulphide is limited and has only been obtained from animal studies. The primary route of absorption is the respiratory tract. Absorption through skin appears to be minimal (5, 16). In one study, however, the exposure of large areas of the skin to pure hydrogen sulphide gas was lethal in guinea pigs after 45 minutes of exposure (89).

7.2 Distribution

Hydrogen sulphide enters the circulation after inhalation, and partly dissociates into HS^- while some remains as free H_2S in blood. Results from animal inhalation studies indicate that H_2S is distributed to the brain, liver, kidneys, pancreas, and small intestine (16, 87). In most disposition studies, H_2S has been administered either parenterally or orally as H_2S solutions or as various sulphide salts. When administered to animals, both sodium sulphide and sodium hydrosulphide generate, as expected, H_2S *in vivo* (5, 90). Both sodium sulphide and sodium hydrosulphide have been widely used in H_2S toxicity studies.

Studies on naturally occurring sulphide of various rat brain regions (brainstem, cerebellum, hippocampus, striatum and cortex) showed that the endogenous sulphide level is significantly lower in the brainstem than in the other brain regions. However, when sulphide was administered, the net uptake of sulphide was greatest in the brainstem (90).

7.3 Biotransformation

The metabolism of H_2S can be divided into three distinct pathways: oxidation to sulphate, methylation, and reaction with metallo- or disulphide-containing proteins (5). While the first two metabolic pathways can be regarded as detoxification routes, the reaction of H_2S with essential proteins is largely responsible for the toxic action of hydrogen sulphide.

Oxidation yielding sulphates is the primary detoxification pathway of H_2S in the body (2). Methylation of H_2S results in methanethiol and dimethyl sulphide. The importance of this route for detoxification of exogenously administered H_2S has not yet been investigated thoroughly (5).

7.4 Excretion

Absorbed sulphide is primarily oxidised to free sulphate or conjugated sulphate, which can be directly excreted in the urine (16). Measurable amounts of thiosulphate have been found in the urine of men after exposure to an 8-hour TWA of <10 ppm (14 mg/m^3) (39).

The excretion of H_2S by the lungs in animals was minimal after parenteral administration of H_2S (16, 74).

8. Methods of biological monitoring

Analysis of blood sulphide is a way of verifying hydrogen sulphide poisoning. However, to achieve reliable results in blood sulphide analysis, the sample has to be taken no later than two hours after an accidental exposure situation and has to be analysed without delay (34).

The only practical test for biological monitoring in workers with hydrogen sulphide exposure is to measure urinary thiosulphate (56). The bromobimane complex of urinary thiosulphate can be analysed by liquid chromatography. This method has revealed a preceding hydrogen sulphide exposure (39). The highest thiosulphate concentration was detected 15 hours after exposure.

9. Mechanism of toxicity

Hydrogen sulphide reacts with many enzymes, which contain metal ions, and these reactions result in enzyme inhibition. The interaction of hydrogen sulphide with vital metalloenzymes such as cytochrome oxidase is the well-known toxic mechanism of H_2S (2, 5, 16).

Cytochrome oxidase is the final enzyme of the mitochondrial respiratory chain, where it transfers electrons and hydrogen ions to oxygen to form water. If the enzymes in the respiratory chain are inhibited, or oxygen is lacking as the final electron acceptor, the electron transport down the chain is stopped. In that case, oxidative metabolism, which is the primary energy source for mammalian cells, ceases (2). The inhibition of the oxidative metabolism may lead to membrane leakage, oedema, the release of cellular enzymes, and disturbances in ionic gradients (58). Most organ systems are susceptible to these cellular effects and H_2S is therefore regarded as a broad-spectrum toxicant (68). The tissues most susceptible to H_2S toxicity are the exposed mucous membranes and those with high oxygen demands, such as nervous and cardiac tissues (2).

Inhibition of cytochrome oxidase has been demonstrated *in vitro* (58, 72), and *in vivo* in mouse brain (75) and in lung tissue of rats (40). In addition, sulphide inhibits carbonic anhydrase (78). The inhibition of carbonic anhydrase in brain tissue may impair the acid:base regulation, transport of carbon dioxide from tissues during cellular respiration, neuronal lipid biosynthesis, and/or reorganisation of myelin membranes (58, 72).

The inhibition of cytochrome oxidase has, however, been regarded as being too slow to account for the rapid lethality of an acute sulphide exposure, in which death occurs within three minutes (45, 46). The major cause of death is thus thought to be due to the inhibition of central respiratory mechanisms (4), in particular as a result of the loss of the central respiratory drive from brainstem

neurones (90). However, the mechanisms of sulphide influence on the respiratory drive is not completely understood (20, 45, 58, 72).

High doses of NaHS have also been demonstrated to inhibit monoamine oxidase *in vitro*. The IC_{50}, the concentration at which 50% inhibition occurs, was 39.1 μM (91). This inhibition is supposed to lead to the elevated level of brain amino acid neurotransmitters found after sulphide administration (91). It is also demonstrated that sulphide immediately, but reversibly, inhibits synaptic transmission in area CA1 of the rat hippocampus and also reversibly activates K+ conductance in the hippocampal CA1 cells and serotonergic dorsal raphe neurons in the brainstem (68). Thus, the acute apnoea induced by sulphide may be due to a reversible suppression of synaptic activity and hyperpolarisation in brainstem respiratory networks, leading to cessation of autonomous breathing (4). It has also been proposed that sulphide depresses breathing by changes in neuronal excitability within respiratory rhythm-generating centres (20).

In addition to these mechanisms, it has been suggested that the increased stimulation of glutamate receptors may contribute to the neurotoxic mechanism of hydrogen sulphide in the mammalian brain (58). Another proposed effect is that sulphide at millimolar concentrations can directly inhibit muscle contraction by a yet unknown mechanism (33).

In summary, it seems to be well documented that sulphide inhibits important enzymes in the regulation of cellular energy production and respiration, cytochrome oxidase and carbonic anhydrase. In addition, sulphide also seems to act on the respiratory drive through other mechanisms. These mechanisms are not fully understood, but it has been shown that sulphide inhibits monoamine oxidase, suppresses synaptic activity, has a direct action on respiratory rhythm generating centres, and increases the stimulation of glutamate receptors in the brain.

10. Effects in animals and *in vitro* studies

10.1 Irritation and sensitisation

Studies on several animal species show that exposure to hydrogen sulphide at a concentration of 100-150 ppm (139-209 mg/m^3) for several hours results in local irritation of the eyes and the throat. Ocular and mucous membrane irritation appeared after 1 hour at 200-300 ppm (278-417 mg/m^3) H_2S (32). Another study of local effects in rats showed that a 4-hour exposure at >280 mg/m^3 (>200 ppm) induced detectable histologic lesions in the nasal cavity (50).

Subchronic studies in rats described in a previous review showed that exposure at 1, 10 and 100 ppm (1.4, 14 and 140 mg/m^3) H_2S for 8 hours per day for 5 weeks had no effects on baseline measurements of airway resistance, dynamic lung compliance, tidal volume, minute volume or heart rate. It was also found that maximal changes in airway resistance and dynamic lung compliance with a methacholine challenge were comparable in all exposed groups. However,

individual animals in all groups showed a significant increase in their bronchial responsiveness as a result of the exposure (68).

10.2 Effects of single exposure

10.2.1 Nervous system

Numerous reports and reviews describe nervous system effects resulting from single exposures to hydrogen sulphide (5 16, 54, 68, 74).

In two rat studies the concentration of H_2S which led to the death of 50% of the animals (LC_{50}) was 444 ppm (617 mg/m^3) (81) and 501 ppm (696 mg/m^3) (67), respectively, after exposure for 4 hours. The LC_{50} decreases with the exposure duration from 587 ppm (816 mg/m^3) at 2 hours to 501 (696 mg/m^3) and 335 ppm (466 mg/m^3) at 4 and 6 hours, respectively. All rats that died had pulmonary oedema (67).

The lethal dose for 50% of the exposed animals (LD_{50}) of NaHS in rats was 15 mg/kg when injected intraperitoneally (90). Earlier studies have reported the LD_{50} of sodium sulphide given intraperitoneally to CD-1 female mice to be between 40 and 50 mg/kg (5). More recently, the LD_{50} for Na_2S given intraperitoneally was reported to be 94 mg/kg for rats (4).

The effects of sodium sulphide have been tested on two enzyme systems. Sulphide inhibited whole brain cytochrome c oxidase in a concentration-dependent manner. The IC_{50} was calculated to be 0.13 μM (58, 72). The IC_{50} for bovine erythrocyte carbonic anhydrase was 2.17 μM (72).

The acute effects of hydrogen sulphide on brain amino acid neurotransmitter levels have been examined in five different regions of the rat brain after intraperitoneal administration of 10 mg/kg and 30 mg/kg ($0.66 \cdot LD_{50}$ and $2 \cdot LD_{50}$) NaHS. The region showing the greatest change in neurotransmitter levels was the brainstem where the respiratory centres are found. Aspartate, glutamate, glutamine, gamma aminobutyric acid (GABA), glycine, taurine, and alanine all increased at both doses in the brainstem (46) whereas no significant changes were found in the cerebral cortex, striatum or hippocampus. The selective uptake of sulphide by the brainstem has earlier been demonstrated by the measurement of brain sulphide levels (90). Catecholamine levels increased in some parts of the rat brain after intraperitoneal administration of 30 mg/kg NaHS. The hippocampus, striatum and brainstem all showed increases in noradrenaline and adrenaline. Brainstem dopamine and 5-hydroxytryptamine levels increased as well. This rapid increase in catecholamine levels has been suggested to be due to the inhibition of the degradative enzymes of monoamine metabolism (monoamine oxidase) (91).

A study that investigated whether sulphide was capable of producing neural cell necrosis in the brain by a direct histotoxic effect could not find evidence for such a mechanism. One group of rats in the experiments was mechanically ventilated, and another group of rats was unventilated. Sodium sulphide was administered intraperitoneally in doses up to 200 mg/kg and the LD_{50} for Na_2S was found to be 94 mg/kg in unventilated rats and 190 mg/kg in ventilated rats. Doses of 150 and

200 mg/kg sulphide led to precipitous hypotension in the rats. The electroencephalographic (EEG) activity ceased gradually during exposure as the animals fainted, and recovered when the animals regained consciousness (4). Based on these results, the authors suggested that profound hypotension, which in turn induces cerebral ischemia, may explain the brain damage caused by hydrogen sulphide.

The absorption of hydrogen sulphide gas by sciatic nerve bundles from frogs (*Rana pipiens)* produced an anaesthetic effect of short duration. Subsequent compound action potential levels were higher than before exposure (6). A direct action of HS^- on spontaneous muscle contraction has also been suggested (33).

10.2.2 Respiratory tract

Inhalation exposure to H_2S appears to have a very steep dose-effect curve. Inhalation of 200 ppm (278 mg/m^3) for 4 hours produced no adverse clinical signs or visible gross changes in the lungs of rats, but there was a statistically significant increase in protein and lactate dehydrogenase levels in the lavages from these rats. A marked abnormality in surfactant activity was also found in the lavages at 300 ppm (417 mg/m^3). At approximately 500 ppm (695 mg/m^3) lesions of the cells in the respiratory tract appeared rapidly and in a dramatic fashion (19).

It has been shown that the irritant effects of H_2S are caused by cytotoxic lesions in various regions of the respiratory tract (48, 49). Exposure to 400 ppm (556 mg/m^3) of H_2S resulted in a significant and transient increase in the protein content, and increased activity of lactate dehydrogenase of nasal and bronchoalveolar lavage fluids (49). In another study, inhalation of 439 ppm (610 mg/m^3) H_2S for 4 hours induced necrosis and exfoliation of nasal respiratory and olfactory mucosal cells in rats. It was also observed that injured respiratory mucosa regenerated rapidly, whereas olfactory mucosa continued to exfoliate at 44 hours after exposure (50). In addition, 4 hours inhalation of 439 ppm (610 mg/m^3) H_2S produced a reversible pulmonary oedema. Ciliated bronchiolar cells were the main target cells for acute H_2S toxicity in the lung. However, necrotic cells were rapidly replaced by mitosis (48).

No mortality was observed in rats exposed to 10-400 ppm (14-556 mg/m^3) H_2S for 4 hours, whereas exposure to concentrations >500 ppm (>695 mg/m^3) was lethal. A concentration of 10 ppm (14 mg/m^3) caused no significant changes in the activity of lung mitochondrial enzymes. However, the sublethal concentrations (50-400 ppm) (70-556 mg/m^3) produced depressions in the activities of the enzyme cytochrome c oxidase and succinate oxidase complexes in the respiratory chain in pulmonary tissue. A marked recovery in cytochrome c oxidase activity of pulmonary cells was observed in these rats at 24 and 48 hours postexposure. The inhibition of cytochrome c oxidase activity in lungs was most severe in rats that died from acute exposure to >500 ppm (695 mg/m^3) H_2S (40).

In contrast to findings with sublethal concentrations, peracute exposure (5 minutes) to 1655 ppm (2300 mg/m^3) H_2S resulted in the rapid and massive accumulation of fluids in the lungs of rats, resulting in massive alveolar flooding and death (51). The injection of 30 mg/kg NaHS ($2 \cdot LD_{50}$) intraperitoneally did

not, however, induce any sign of pulmonary oedema, although all animals died within 3 minutes. In the same study, rats were exposed to 1660 ppm H_2S for 5 minutes, and all animals died from pulmonary oedema, within 3 minutes (51).

Particle-induced oxygen consumption was markedly reduced in pulmonary alveolar macrophages (PAM) from rats exposed to 200 and 400 ppm (278 and 556 mg/m^3) H_2S (41). Results from earlier *in vitro* studies have shown that PAM lose their phagocytic ability after exposure to H_2S (70). The incomplete inactivation of *Staphylococcus epidermidis* in rat lung pre-exposed to 45 ppm (63 mg/m^3) H_2S for 4 and 6 hours was also suggested to be due to the impairment in PAM ability to inactivate the bacteria (41, 71).

10.3 Effects of short term exposure

10.3.1 Nervous system

Repeated exposure (4 times) to 100 ppm (140 mg/m^3) H_2S for 2 hours at 4-day intervals resulted in a gradually increasing inhibition of the cerebral cytochrome oxidase activity and decreased protein synthesis in mouse brain as compared to a control group (74, 75).

Another study showed that rats exposed to 100 ppm (140 mg/m^3) for 3 hours/day for 5 days had increased levels of L-glutamate in the hippocampus (58).

Repeated exposure to concentrations of 25, 50, 75 or 100 ppm (35, 70, 104 or 140 mg/m^3) H_2S (3 hours/day for 5 consecutive days) produced a cumulative change in the total hippocampal type 1 theta activity recorded by EEG in the rats. Repeated exposures for 5 consecutive days resulted in a cumulative effect that required 2 weeks for complete recovery (78). It was concluded that repeated exposure to low levels of hydrogen sulphide could produce cumulative changes in the hippocampal function.

10.3.2 Cardiovascular system

Electrocardiograms from rabbits exposed to 72 ppm (100 mg/m^3) of H_2S for 1.5 hour demonstrated disorders in repolarisation, as indicated by flattened and inverted T-waves. Exposure to 72 ppm H_2S for 0.5 hour/day for 5 days produced various arrhythmias including ventricular extrasystoles (47). It has also been observed that the administration of NaHS caused arrhythmias and a progressive increase in tension in isolated rat atria (68).

10.3.3 Blood

exposed to H_2S (68, 82). Rats exposed to 30 ppm (42 mg/m^3) H_2S for 90 days had an increased number of reticulocytes and an increased mean blood cell volume. Rabbits exposed to 107 ppm (150 mg/m^3) 0.5 hour/day for 4 months showed a decreased number of leukocytes and an increased number of lymphocytes (74).

10.3.4 Eyes

Experimental exposure to mixtures of H_2S (50-100 mg/m^3) (36-72 ppm) and CS_2 (40-50 mg/m^3) caused corneal injury in albino rabbits. When the concentration of

H_2S in this experiment was lowered to 40-50 mg/m^3 (29-36 ppm), it was not possible to reproduce the corneal lesions. Exposure to H_2S alone at 50-100 mg/m^3 (36-70 ppm) did not produce any signs of corneal lesions. The duration of exposure was 10 hours/day for 6 days (53).

10.3.5 Respiratory tract

Another olfactory study, where rats were exposed to 0, 10, 30, and 80 ppm (0, 14, 42 and 111 mg/m^3) H_2S for 10 weeks (6 hours/day, 5 days/week) showed lesions in the olfactory mucosa at 30 and 80 ppm (42 and 111 mg/m^3) (13). The no observed effect level (NOEL) was reported to be 10 ppm (14 mg/m^3). The lesions consisted of multifocal, bilaterally symmetrical olfactory neuron loss and basal cell hyperplasia of the olfactory region of the nasal cavity of the rats. The changes affected approximately 50% of the olfactory mucosa at 30 ppm (42 mg/m^3) and 70% at 80 ppm (111 mg/m^3).

10.4 Effects of long term exposure and carcinogenicity

No data are available.

10.5 Mutagenicity and genotoxicity

To elucidate a possible mutagenic or genotoxic effect of H_2S, a limited number of studies have been conducted using sodium sulphide, which yields hydrolysis products equivalent to aqueous H_2S. Two such studies have failed to demonstrate genotoxic effects, but it has been stated that both studies also suffered from technical deficiencies, which may limit their value (5). Reported genotoxic effects may be limited to cytotoxicity (5, 68). A third study has found Na_2S to be a weak mutagen in the Ames´ test and in *Drosophila melanogaster* (5).

10.6 Reproductive and developmental studies

Putative amino acid neurotransmitter levels in the rat brain were determined in order to evaluate the effects of exposure to hydrogen sulphide during perinatal development. Pregnant rats were exposed to 75 ppm (102 mg/m^3) H_2S for 7 hours per day from day 5 postcoital until day 21 postnatal. The offspring were euthanised on day 21 postnatal. Aspartate, glutamate and GABA in the cerebrum and aspartate and GABA in the cerebellum were significantly depressed (25). The same study showed that the exposure produced a significant increase in the level of taurine in the developing rat central nervous system. The level of taurine returned to normal approximately at the same time as the blood-brain barrier to taurine was established. This increased level of taurine in the central nervous system of the offspring was therefore supposed to be maternal in origin, transferred from the mothers to the young both transplacentally and via the milk, and not endogenously produced (24). However, it was suggested that the abnormally high taurine level in the brains of the offspring occurred at a time of maximum

susceptibility to disturbances of neuronal growth, and thus would have the potential of producing neuronal abnormalities.

In addition, when pregnant rats were exposed to 20 or 50 ppm (28 or 70 mg/m^3) H_2S for 7 hours per day from day 5 postcoitus until day 21 postnatal, severe alterations were found in the architecture and growth characteristics of the purkinje cell dendritic fields of the offspring (26). Later it has been observed that levels of serotonin(5-HT) and norepinephrine in the developing rat cerebellum and in the frontal cortex were altered following exposure to 20 and 75 ppm (28 and 102 mg/m^3) H_2S (77).

Another study, designed to determine the effects of perinatal exposure to low levels (20 and 75 ppm) (28 and 102 mg/m^3) of H_2S on the levels of monoamines in specific regions of the rat brain during the development period from day 21 postnatal, showed that the monoamine levels approached normal values from day 21 to day 60 postnatal (73).

It has also been observed in one study that low levels (<75 ppm) (<102 mg/m^3) of H_2S during gestation and neonatal development to day 21 post partum altered observed ear detachment and hair development in the young rats. In the same study some dams exhibited a dose-dependent increase in delivery time which could have resulted in the loss of foetuses owing to asphyxiation (27).

Another study has examined whether perinatal exposure by inhalation to H_2S had an adverse impact on pregnancy outcomes, offspring prenatal and postnatal development, or offspring behaviour (17) The rats were exposed to 0, 10, 30 or 80 ppm (0, 14, 42 or 111 mg/m^3) H_2S, 6 hours/day, 7 days/week for 2 weeks prior to breeding, during the mating period and through the whole pregnancy. The exposure to H_2S did not affect pup growth, development or performance in any of the behavioural tests.

11. Observations in man

11.1 Effects by contact and systemic distribution

Hydrogen sulphide is known by its characteristic odour of "rotten eggs". The perception threshold of this odour varies individually but 0.13 ppm (0.18 mg/m^3) has generally been established as a threshold (16). The odour of the gas is reported to be detectable in concentrations as low as 0.02 ppm (0.03 mg/m^3), distinct at 0.3 ppm (0.4 mg/m^3) and offensive at 3-5 ppm (4-7 mg/m^3) (7). Humans are usually not able to smell H_2S above 100 ppm (140 mg/m^3) probably owing to olfactory fatigue. The same olfactory fatigue also seems to occur after prolonged exposure to lower concentrations (18, 68). Such acute effects on the olfactory system have generally been described as transient (29). A chronic effect of hydrogen sulphide on the olfactory system has been described only in one person who lost his sense of smell for 3 years after a short but high exposure (85). In another study, 6 out of 8 subjects, who had continuing problems with smell and taste after an accidental exposure to H_2S, had olfactory deficits of various degrees

2-3 years after the accident. However, the authors concluded that the deficits might have been associated with confounding factors because concomitant toxic exposures and head traumas also had occurred (29).

"Gas eye", a keratoconjunctivitis, is a superficial inflammation of the cornea and conjunctiva which have been described in workers in "sour gas" plants who are exposed for prolonged periods to relatively low concentrations of H_2S (1, 5, 16, 68). The symptoms are blepharospasm, tearing and photophobia (23). This inflammatory reaction can be accompanied by reversible chromatic distortion and visual disturbances. Eye irritation has been reported to occur at concentrations of hydrogen sulphide varying from 5 to 30 ppm (7-42 mg/m^3) (1) and 5 to 100 ppm (7-140 mg/m^3) (2, 5). However, the reported irritant effects of H_2S as a single agent at exposure levels below 20 ppm (28 mg/m^3) is not well documented (1). Based on experiences from a heavy-water plant it was concluded that irritation of the eyes does not occur at concentrations of H_2S beneath 10 ppm (14 mg/m^3). No further details were given (66). A summary of observations among workers with "spinners eye" (eye irritation in viscose rayon workers) reports that eye irritation occurs after 6-7 hours of exposure to 10 ppm (14 mg/m^3) H_2S or after 4-5 hours of 13 ppm (18 mg/m^3) H_2S (57). Eye irritation has, however, been reported in viscose rayon workers exposed to 1-8.9 mg/m^3 of H_2S (0.7-6.4 ppm) with concomitant exposure to CS_2 (4-112 mg/m^3) (86).

The acute toxicity of hydrogen sulphide on the nervous system and the lung has been extensively documented (1, 3, 5, 54). H_2S induces acute central toxicity leading to reversible unconsciousness. Given sufficient exposure, this effect is so fast that it is called a "knockdown" (23, 28). Lethal hydrogen sulphide intoxication following inhalation of 1000-2000 ppm (1390-2780 mg/m^3) leads to the paralysis of the respiratory centre and the cessation of autonomous breathing. Stimulation of the carotid bodies has been observed at concentrations between 500 and 1000 ppm (695-1390 mg/m^3). This leads to hyperpnea, followed by apnoea. Pulmonary oedema is a rather common effect following "prolonged" (a more precise time estimate is not given) exposure at concentrations of the order of 250-600 ppm (375-834 mg/m^3) (1, 7). Pulmonary oedema is also relatively often seen in patients surviving loss of consciousness due to H_2S poisoning (76, 85, 88, 92).

Postmortem examinations in seven victims of H_2S intoxication have revealed that the central nervous system and the respiratory system are usually involved, and that hepatic congestion or cardiac petechiae may also be present (3). In 5 out of 8 sewer workers who died from H_2S intoxication postmortem findings included pulmonary oedema, myocarditis, hemorrhagic gastric mucosa, and a greenish colour of the brain and the upper region of the intestine (21). The cause of death in 1 of the 5 sewer workers was cardiac arrest 36 hours after the accident. Of the 3 survivors, one survived a cardiac arrest 6 hours after the exposure while another died 2 months later from acute myocardial infarction (21).

Workers in the oil and gas industry in Alberta, Canada, who had reported at least one episode of a "knockdown", later showed a significant excess of symptoms in the respiratory system consistent with airway dysfunction. The symptoms were shortness of breath while hurrying on the level or walking up a slight hill,

wheezing with chest tightness, and attacks of wheeze. Exposures "severe enough to cause central nervous symptoms" but without loss of consciousness were not associated with any excess respiratory symptoms (28).

When 26 male pulp mill workers with previous exposure to H_2S daily below 10 ppm (14 mg/m^3) were exposed to 1-11 ppm (1.4-16 mg/m^3) hydrogen sulphide, no significant changes in respiratory function or bronchial responsiveness were found. Testing were performed before and 30 minutes after workplace exposure to H_2S. However, some effects were found in a group of asthmatic subjects (3 men and 7 women) exposed to 2 ppm (3 mg/m^3) hydrogen sulphide in an exposure chamber. In this group, 8 of 10 had increased airway resistance (Raw) and 6 of 10 had decreased airway conductance (Sgaw) after exposure to 2 ppm for 30 minutes. The average increase in Raw was 26.3% and in Sgaw 8.4%. However, neither change was significant. In two subjects changes were over 30% in both Raw and Sgaw indicating bronchial obstruction (36).

There is one case report of delayed lung injury after exposure to hydrogen sulphide. A person who was exposed to hydrogen sulphide without fainting (he had however noticed eye, nose and throat irritation) developed dyspnea, chest tightness, and haemoptysis 3 weeks after the exposure, and was given the diagnosis pneumonitis. After 5 months he still had dyspnea on exertion and a decreased lung volume and CO diffusion capacity, D_LCO (64).

There are several case-reports that describe persistent neurological and neuro-psychological abnormalities following acute hydrogen sulphide poisoning. Three patients exposed under different circumstances had persistent neurological symptoms, neuropsychological deficits, and alterations in EEG response after auditory stimuli (prolonged P-300 event-related potential latencies) for as long as 6 months and up to 3 years post-exposure. One of these cases had a history of acute H_2S exposure without loss of consciousness. This patient improved with normalisation of the P-300 latency over a 2-year period (92). Other case studies have described toxic encephalopathy as a sequela following H_2S-exposure without loss of consciousness. Reported long-term symptoms after such exposure include reduced concentration and memory, headache and hypersensibility for the smell of air pollution (83). In a study, which included 5 subjects with the diagnosis toxic encephalopathy after reported H_2S exposure, none of the subjects had reported loss of consciousness in connection with the exposure (14).

Another case study has described persistent neurological sequelae in a person who had lost consciousness due to H_2S exposure. Symptoms and findings up to 18 months after the accident included "slow speech, flat affect, moderately impaired attention span, easy distractibility, isolated retrograde amnesia with confabulation, reduced ability to communicate, and markedly impaired visual memory with poor acquisition, retention, and recall of new information" (79). When followed up for 4 more years, the patient still had persistent cognitive and motor deficits (76).

Other case studies of patients surviving accidental H_2S exposure have described the development of profound neurobehavioral deficits (42, 88). One of these cases was reported to be partially conscious during and after the exposure and was therefore released from hospital after 30 minutes. The next day he was readmitted

with nausea, vomiting, diarrhoea, and other signs that lead to a diagnosis of transient toxic encephalopathy. Recall and cognitive abilities, and psychomotor speeds had improved while reaction time, sway speed and colour vision had not improved 49 months post-exposure (42).

A delayed neuropsychiatric sequela has been described in a person after exposure to a concentration of hydrogen sulphide below 1000 ppm (1390 mg/m^3) for 15-20 minutes. After having been deeply comatose for 2 days, he sat up and seemed to recover. The next evening he appeared psychotic with a generalised dysrhythmia in his EEG. During the following weeks he was unconscious with periods of motor excitements before he gradually recovered after 4 weeks. At a re-examination 6 years after the accident, he still had difficulties walking up and down stairs, a reduced understanding of speech and a migrainous headache (84).

In a Norwegian survey, 5 patients who had been unconscious in H_2S atmospheres for 5 to 20 min showed persisting impairment at neurological and neuropsychological examinations 5 years or longer after the poisoning. Memory and motor function were most severely affected (85).

Despite these case reports, there are also numerous clinical observations showing that victims of massive hydrogen sulphide poisoning recover completely, even from an unresponsive status (16, 18, 22).

There is a limited amount of research that has aimed at examining the effects of low exposure levels of hydrogen sulphide in humans. In healthy volunteers, exposure to 10 ppm (14 mg/m^3) for 15 minutes during submaximal exercise revealed no significant changes in routine pulmonary function variables (9). Other studies that have examined the acute effects of 5 ppm (7 mg/m^3) H_2S exposure on physiological responses during exercise have not observed any significant cardiovascular or metabolic responses (10, 11, 12). The only effect observed was a tendency for muscle lactate to increase and citrate synthase activity to decrease. This effect was not seen at 2 ppm (3 mg/m^3) (12). It was also observed that 10 ppm (14 mg/m^3) hydrogen sulphide inhalation reduced oxygen uptake in the blood (VO_2) during exercise, most likely by inhibiting the aerobic capacity of the exercising muscle (8).

11.2 Effects of repeated exposure on organ systems

Epidemiological studies of workers who have been repeatedly exposed to H_2S are difficult to interpret because of the different degree of combined exposure with other irritants or toxic agents.

11.2.1 Eyes

In an epidemiological study of viscose rayon workers, 123 males exposed to H_2S (≤8.9 mg/m^3, ≤6.4 ppm) and CS_2 and 67 referents not exposed to either substance answered a questionnaire on eye complaints. Pain, tension, burning, hazy sight, photophobia, and irritation at work were significantly more common in the 34 workers exposed to >5 mg/m^3 (>4 ppm) H_2S and the 38 workers exposed to >90 mg/m^3 CS_2 (all $p<0.01$). The prevalences of these symptoms were at least

doubled compared to the unexposed referents. In the 49 workers exposed to 1-5 mg/m^3 (0.7-4 ppm) H_2S, the symptom prevalences were also increased, but significantly so only for one of them (”eye tension”, 40.8% versus 21.5% in the referents, $p<0.05$). Multiple logistic regression revealed strong dependencies for the eye symptoms on exposure to H_2S and CS_2 and weak and generally non-significant dependencies on age and smoking. Due to the nature of the exposure (all H_2S-exposed workers were also exposed to CS_2) the authors were unable to conclude which agent was responsible for the eye effects. Based on this and previous studies, however, they considered H_2S as the prime irritant, with CS_2 as an enhancer (86).

Both the cornea and conjunctiva have been shown to be affected when air concentrations of H_2S exceed 30 mg/m^3 (21.5 ppm) in the viscose rayon factory. At the same time the concentrations of CS_2 and H_2SO_4 were 100 mg/m^3 and 40 mg/m^3, respectively. Forty percent of the affected workers had no symptoms for the first 3 days of continuous exposure. Short term workers were more often affected. The symptoms resolved within 2 days in 84% of the workers. No long-term effects were observed in this study from the early 1950s in Belgium (53).

11.2.2 Respiratory system

The results of a study of sewage workers have indicated that workers exposed to H_2S experienced a lung function impairment compared to water treatment workers (69).

Another investigation, which aimed to study a possible relationship between exposure to bacteria-containing aerosols, endotoxins and hydrogen sulphide, and different kind of work-related symptoms among sewage workers, did not find any relationship between symptoms and exposure to hydrogen sulphide (55).

11.2.3 Hematopoietic system

When analysing enzyme activities in reticulocytes from 17 workers in pulp production with low-level H_2S and methyl mercaptan exposure, 8 had a decreased (below the control range) δ-aminolaevulinic acid synthase activity, while 6 had a decreased activity in hem synthase. The erythrocyte protoporphyrin concentration was below the control range in 7 cases. The workers had held the same job for 10-40 years and had been exposed to 0.05-5.2 ppm (0.07-7.2 mg/m^3) H_2S calculated as a TWA over 8 hours (82).

11.2.4 Cardiovascular system

An excess mortality from cardiovascular disease (standard mortality ratio=150, 95% confidence interval 105-206) and coronary heart disease (standard mortality ratio=150, 95% confidence interval 97-222) has been observed in Finnish sulphate mill workers exposed to hydrogen sulphide and organic sulphur compounds (35). The workers (only men, 4179 person years) included in the study had been employed for at least one year between 1945 and 1961. The excess of coronary deaths increased with longer follow up periods. Measurements in sulphate mills were performed in the early 1980s and the level of H_2S was then between 0 and

20 ppm (0-28 mg/m^3). Concentrations of methyl mercaptan varied from 0 to 15 ppm. The highest levels of dimethyl sulphide and dimethyl disulphide were 12 and 1.5 ppm, respectively (37). The processes had been the same throughout the years of the study.

11.2.5 Central nervous system

When looking at possible cognitive dysfunctions, the viscose rayon workers in Belgium with exposure to low levels of H_2S (0.14-6.4 ppm) (0.19-8.9 mg/m^3) did not show any significant impairment of memory or attention (15).

Thirteen former workers and 22 neighbours living downwind from a processing plant for "sour" crude oil in Canada complained of different symptoms such as headache, nausea, vomiting, depression, personality changes, nose bleeds, and breathing difficulties. Their neurobehavioral functions and a profile of mood states were studied and compared to 32 matched controls. The mean values for the exposed subjects were statistically significantly different from the controls for two-choice reaction time, balance, colour discrimination, digit symbol, trail making A and B, and the immediate recall of a story (43).

11.3 Genotoxic effects in humans

No data are available.

11.4 Carcinogenic effects in humans

There are no studies on the possible carcinogenic effect of H_2S alone. Concerning combined exposure pulp and paper as well as viscose rayon manufacture is associated with exposure to H_2S. In 1987, IARC concluded that the evidence for carcinogenicity to humans was inadequate for pulp and paper manufacturing (31). With respect to rayon manufacture, epidemiological cancer studies are largely negative (52, 80). One study reports an excess mortality from colon cancer (9 observed, 3.9 expected, standard mortality ratio 233, 95% confidence interval 107-442), but no excess mortality from all cancers (65). Another study reports a tendency of excess mortality from lung cancer (not significant at the 0.05 level) (95). In all, these data do not support a carcinogenic effect of H_2S.

11.5 Reproductive and developmental effect

In a retrospective epidemiological study in a large petrochemical complex in Beijing, China, an increased risk of spontaneous abortion among women was found to be associated with the exposure to petrochemicals, including hydrogen sulphide (94). In this study both exposure and outcome were measured by interview. In the analyses for exposure to specific chemicals, an increased risk was found for exposure to hydrogen sulphide with an odds ratio of 2.5 (95% confidence interval 1.7-3.7). There were 106 never smoking women with self-reported exposure to H_2S and with at least one pregnancy in this study. The

abortion rate was calculated from the outcome of the women's first pregnancy. Odds ratios were calculated with multiple logistic regression. The logistic model also included exposure to benzene, gasoline, Mn, and NH_3 in addition to age, educational level, shift work, noise level, hours with standing and kneeling, hours at work, passive smoking and diet. The level of exposure to H_2S was not reported.

Other reports on reproductive outcome or teratogenicity of H_2S are difficult to interpret because of simultaneous exposure to CS_2, which is a known teratogen (68).

12. Dose-effect and dose-response relationships

Most information on dose-effect and dose-response relationships for H_2S has been derived from animal studies in various experimental settings and different routes of administration. Studies in humans have been conducted at exposure levels where mild irritative effects have been expected. There is surprisingly little information on exposure levels in the literature reporting on cases of intoxication. The dose-effect and dose-response relationships are given in tables 1 to 4.

At 30 ppm (42 mg/m^3) nasal lesions have been observed in rats. The NOEL for this effect has been reported to be 10 ppm (14 mg/m^3). At doses from 25 ppm (38 mg/m^3) systemic effects in animals have been reported. The systemic effect at 25 ppm is a change in EEG activity. From exposure levels of 50 ppm (70 mg/m^3) effects of cytochrome oxidase inhibition have been observed in rat lung cells. An inhibition of cerebral cytochrome oxidase has been observed at exposure levels of 100 ppm (140 mg/m^3). The lowest exposure level that has been reported to result in death and pulmonary oedema following several hours of exposure is 335 ppm (466 mg/m^3).

Eye irritation has been reported to occur from exposure levels of 0.7-4 ppm (1-5 mg/m^3) H_2S in humans. However, eye irritation at this exposure level of H_2S seems to result from combined exposures, in particular with CS_2. There is one report of respiratory effects in asthmatic persons exposed to 2 ppm H_2S (3 mg/m^3).

12.1 Single / short term exposures to hydrogen sulphide gas in animals

Table 1. Some dose-effect and dose-response data for animals exposed to hydrogen sulphide. (See chapter 10.1-10.3.)

Effect level (ppm)	NOEL (ppm)	Duration of exposure	Effects	Ref.
1		8 h/day, 5 weeks	Some rats with hyperreactive response in the airways.	(68)
25		Repeated, 3 h/day	Cumulative change in hippocampal type 1 EEG activity in rat	(78)
30 and 80	10	6 h/day, 7 days/week 10 weeks	Dose related olfactory neuron loss and basal cell hyperplasia in rats	(13)
≥50	10	4 h	Inhibition of cytochrome oxidase in rat lung cells	(40)
72		1.5 h/day several days	Various cardiac arrhythmias including ventricular extrasystoles in rabbits and guinea pigs	(47)
100		2 h, 4-day intervals, 4 times	Increasing inhibition of cerebral cytochrome oxidase activity and decreased protein synthesis in mouse brain	(74, 75)
100		3 h/day, 5 days	Increased level of L-glutamate in hippocampus of rats	(58)
200		4 h	Detectable histologic lesions in nasal epithelium of rats	(50)
200		4 h	Increase in protein and lactate dehydrogenase in lavage fluids from rat lung	(19)
200-400	50	4 h	Particle-induced oxygen consumption reduced in pulmonary alveolar macrophages from rats	(41)
300		4 h	Marked abnormality in surfactant activity in lavage fluids from rat lungs	(19)
335		6 h	LC_{50} and pulmonary oedema in rats	(67)
400		4 h	Transient increase in protein concentration and activity of lactate dehydrogenase in nasal lavage fluids of rats	(49)
439		4 h	Transient necrosis and exfoliation of nasal respiratory and olfactory mucosal cells in rat. Reversible pulmonary oedema	(48)
444		4 h	LC_{50} for rats	(81)
501		4 h	LC_{50} and pulmonary oedema in rats	(67)
>500		4 h	Lethal for rats	(40)
587		2 h	LC_{50} and pulmonary oedema in rats	(67)
1655		5 min	Pulmonary oedema and death in rats	(51)

Table 2. Summary of dose-effect data from reproductive and developmental studies of hydrogen sulphide. (See chapter 10.6.)

Exposure level (ppm)	Duration of exposure	Effects	Ref.
20	7 h/day during pregnancy until 21 days postnatal	Severe alterations in the architecture and growth characteristics of the purkinje cell dendritic fields of the rat offspring	(26)
20 and 75	7 h/day during pregnancy until 21 days postnatal	Altered levels of serotonin(5-HT) and norepinephrine in the developing rat cerebellum and frontal cortex	(77)
75	7 h/day during pregnancy until 21 days postnatal	Decreased level of aspartate, glutamate and GABA in the cerebrum and aspartate and GABA in cerebellum of the rat offspring	(25)
80	6 h/day, 7 days/week for 2 weeks prior to breeding and through the whole pregnancy	No effect on pup growth, development or performance on any of the behavioural tests on the offspring	(17)

Table 3. Dose-effect and dose-response data from animal studies using a single intraperitoneal administration of NaHS or Na_2S. (See chapter 10.2.)

Dose (mg/kg)	Species	Effects	Ref.
10 (NaHS)	Rat	Increased levels of aspartate, glutamate, glutamine, GABA, glycine, taurine, and alanine in brainstem of rats	(46)
15 (NaHS)	Rat	LD_{50}	(90)
30 (NaHS)	Rat	Increased level of catecholamines in hippocampus, striatum and brainstem of rats	(91)
40-50 (Na_2S)	Mouse	LD_{50}	(5)
94 (Na_2S)	Rat	LD_{50}	(4)

Table 4. Dose-effect relationships in man. (See chapter 11.)

Effect level (ppm)	NOEL (ppm)	Effects	Ref
0.02		Minimum perception threshold	(7)
0.05-5.2		Changes in haem synthesis in pulp production workers	(82)
0.13		Generally accepted smell threshold	(16)
0.7-4		Increased prevalence of eye irritation symptoms in viscose rayon workers (co-exposure to CS_2)	(86)
2		Effects in asthmatic subjects	(36)
3-5		Offensive smell	(7)
>4		Markedly increased prevalence of eye irritation symptoms in viscose rayon workers (co-exposure to CS_2)	(86)
5	2	Increased muscle lactate levels during exercise	(12)
10		Reduced oxygen uptake during exercise	(8)
0-20		Excess mortality from cardiovascular disease in pulp mill workers exposed also to organic sulphur compounds	(35, 37)
20		Effects on the cornea and conjunctiva	(53)
>50		Effects on the epithelia of the conjunctiva and the cornea of the eye	(2)
>100		No smell due to olfactory fatigue	(18, 63)
250-600		Pulmonary oedema after prolonged exposure	(1)
500-1000		Stimulation of carotid bodies	(1)
1000-2000		Paralysis of respiratory centre and breathing stops	(1)

13 Previous evaluations by (inter)national bodies

The Nordic Expert Group for Documentation of Occupational Exposure Limits concluded in 1982 that irritation, with a threshold of 10 ppm (14 mg/m^3) for eye irritation should be taken into consideration in the establishment of the standard for an occupational limit (74).

In the documentation for the threshold limit values of hydrogen sulphide, ACGIH recommends a TWA occupational exposure limit of 10 ppm (14 mg/m^3) and a STEL (short term exposure limit for max 15 minutes) of 15 ppm (21 mg/m^3). It is considered that these limits should provide sufficient protection against the

risks of sudden death, neurasthenic symptoms, permanent central nervous system effects, and eye irritation, which may result from acute, subchronic, or chronic exposure to hydrogen sulphide (1).

OSHA´s proposed rule for this substance is 10 ppm (14 mg/m^3) as an 8-hour TWA and 15 ppm (21 mg/m^3) as a STEL (63). These limits are based on the avoidance of ocular effects, and are consistent with those of the ACGIH.

NIOSH has a REL (recommended exposure limit) for hydrogen sulphide of 10 ppm as a 10 minute ceiling value (59), and an IDLH (immediately dangerous to life or health) concentration of 100 ppm (61).

14. Evaluation of human health risk

14.1 Groups at extra risk

One study indicates that asthmatic persons could be susceptible to low levels of hydrogen sulphide. Asthmatic attacks were provoked at levels as low as 2 ppm (3 mg/m^3) in some persons (36).

Results from one epidemiological study and animal studies suggest that pregnant women might have an increased risk of spontaneous abortion after exposure to H_2S (94).

14.2 Assessment of health risks

Hydrogen sulphide is a gas that can be generated in nature whenever organic material containing sulphur is present, and oxygen is depleted. In addition it can be generated in several industrial settings. It is difficult to predict the rate of gas emission from biological processes, but evidently hydrogen sulphide, when generated, can rapidly reach lethal levels. There is an additional problem (or risk) that the unpleasant smell of the gas disappears before the concentration of the gas becomes harmful. Hydrogen sulphide, whenever it may occur, must therefore be regarded as a dangerous gas with a potential to entail a significant risk of health injury in various occupational settings.

An important effect of hydrogen sulphide is on the nervous system. When the gas is absorbed into cells, it inhibits enzymes of the respiratory chain in the cells. Furthermore, the direct local action on mucous membranes results in irritation and inflammation of the eyes and respiratory tract. This can result in pulmonary oedema at sublethal exposure. Acute exposure at nonfatal levels can also result in long-lasting or permanent cognitive injuries and other injuries to the nervous system, and in permanent lung damage. In this context, toxic encephalopathy has also been described in persons accidentally exposed to H_2S but who did not lose consciousness.

There is limited information on actual exposure levels in reports of the health effects of H_2S in humans. Moreover, results from epidemiological studies are difficult to interpret as exposure to hydrogen sulphide is often accompanied by

exposure to other harmful agents. Changes in haem synthesis and increased mortality from coronary heart diseases have been found among workers in the Finnish pulp industry with exposure levels of hydrogen sulphide in the range 0-20 ppm, but with concomitant exposure to organic sulphur compounds. In addition, an exposure level of 2 ppm H_2S has been reported in one study to provoke attacks in asthmatic subjects. Increased prevalences of eye irritation symptoms were seen in viscose rayon workers exposed to 0.7-4 ppm (1-5 mg/m^3), and markedly increased prevalences were seen at levels above 4 ppm. Since viscose workers are also exposed to CS_2, eye irritation may be a result of combined exposure to the two agents.

14.3 Scientific basis for an occupational exposure limit

Based on an epidemiological study on viscose rayon workers, the critical effect of H_2S is eye irritation. Increased prevalences of various eye irritation symptoms were seen at 0.7-4 ppm (1-5 mg/m^3). However, since all H_2S-exposed workers were also exposed to CS_2, a combined effect of the two agents cannot be excluded.

An olfactory study, where rats were exposed to H_2S for 10 weeks (6 hours/day, 7 days/week) showed lesions in the olfactory mucosa at 30 and 80 ppm (42 and 111 mg/m^3). The NOEL was reported to be 10 ppm (14 mg/m^3).

The greatest hazard associated with H_2S exposure is, however, the unpredictable exposure peaks that may occur whenever H_2S is generated. The margin between no observed effects and life-threatening effects is very small. This has to be taken into consideration in the risk assessment and management of H_2S. The implementation of written and enforced procedures to ensure safe entry into areas that may contain H_2S is therefore essential.

15. Research needs

There is a lack of information on health effects and exposure levels from low level exposure situations where H_2S is the principal agent. In addition more studies on health effects should be performed among humans who have been repeatedly exposed to high levels of sulphide, with or without loss of consciousness. More efforts have to be made in new investigations on exposure characterisation, and on how to practice exposure control. Further studies on the effect of H_2S on reproduction are also recommended.

16. Summary

Svendsen K. *Hydrogen sulphide.* Arbete och Hälsa 2001;14:1-31.

Hydrogen sulphide (H_2S) is a gas that can be generated in nature whenever organic material containing sulphur is present and oxygen is depleted. In addition it can be generated in several industrial settings. It is difficult to predict the rate of gas emission from biological processes, but evidently H_2S, when generated, may rapidly reach lethal levels. There is an additional risk in that the unpleasant smell of the gas disappears before harmful levels are reached. H_2S must therefore be regarded as a dangerous gas whenever it may occur, with a potential to entail a significant risk of health injury or death in various occupational settings.

The main and most quoted effect of H_2S is on the nervous system, as the gas, when absorbed into cells, inhibits enzymes of the respiratory chain. The acute toxicity of H_2S on the nervous system has been extensively documented. Furthermore, the direct local action on mucous membranes results in irritation and inflammation of the eyes and respiratory tract. Eye irritation is reported at exposure levels of 0.7-4 ppm (1-5 mg/m^3) of H_2S with concomitant exposure to CS_2. Acute exposure at nonfatal levels can result in long-lasting or permanent injury of the nervous system, and in pulmonary oedema. In this context, toxic encephalopathy has also been described in persons accidentally exposed to H_2S without losing their consciousness. Exposure levels as low as 2 ppm (3 mg/m^3) has caused respiratory effects in asthmatic persons, and an increased mortality of coronary heart diseases has been demonstrated in workers exposed to H_2S levels below 20 ppm (28 mg/m^3). Results from animal studies and an epidemiological study have given reason to take precautions against any exposure of pregnant women.

Keywords: hydrogen sulfide, hydrogen sulphide, irritation, neurotoxicity, occupational exposure limits, toxicity

17. Summary in Norwegian

Svendsen K. *Hydrogen sulphide.* Arbete och Hälsa 2001;14:1-31.

Hydrogensulfid (H_2S) er en gass som kan produseres i naturen når organisk materiale som inneholder svovelforbindelser nedbrytes uten tilførsel av oksygen. I tillegg utvikles gassen i forskjellige industrielle prosesser. Hvilke konsentrasjonsnivåer som kan oppstå fra biologiske prosesser er vanskelig å forutsi, men det er vist ved flere tilfeller at konsentrasjonen av gass hurtig kan bli meget høy. Hydrogensulfid har en kraftig og ubehagelig lukt, men ved høye konsentrasjoner vil luktecellene lammes. Man kan derfor ikke stole på lukt som advarsel for høye konsentrasjonsnivåer. Som følge av dette må H_2S alltid betraktes som en gass med høyt risikopotensiale.

Den toksiske effekten som er viktigst og mest kjent er effektene på nervesystemet. Når gassen opptas i cellene hindrer den enzymene i cellens respirasjonskjede. Akutteffekten av H_2S på nervesystemet er godt dokumentert. I tillegg til denne effekten vil gassen ved direkte kontakt med øyne og slimhinner forårsake irritasjon og inflammasjon. Øyeirritasjon er rapportert fra eksponeringsnivåer på 0.7-4 ppm (1-5 mg/m^3) av H_2S og samtidig eksponering for CS_2. Når høy akutt eksponering ikke forårsaker øyeblikkelig død kan slik eksponering føre til langvarig eller permanent skade på nervesystemet eller skade på lungene i form av lungeødem. Langvarig eller permanent skade på nervesystemet er også rapportert etter forgiftning uten bevissthetstap. Eksponeringsnivåer ned til 2 ppm (3 mg/m^3) har forårsaket luftveissymptomer i astmatikere. Det er vist en økt dødelighet av hjerte-karsykdommer blant arbeidstakere som har vært eksponert for H_2S-nivåer under 20 ppm (28 mg/m^3). Dyreforsøk med gravide rotter og en epidemiologisk studie av graviditetsutfall og selvrapportert hydrogensulfid eksponering har gitt grunn til å advare mot at gravide eksponeres for hydrogensulfid.

Nøkkelord: hydrogensulfid, neurotoksisitet, irritasjonseffekter, administrative normer, toksisitet

18. References

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19. Data bases used in the for search for literature

In the search for literature the following data bases were used:

-Chemical Abstract
-HSDB
-Medline
-NIOSHTIC
-Toxline

Last search was performed 2000-08-22.

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Appendix 1

Occupational exposure limits for hydrogen sulphide in air.

Country	ppm	mg/m^3	Comments	Year	Ref
Denmark	10	15		2000	1
Finland	10	14		1998	2
	15	21	15 min	1998	2
Germany	10	14		2000	3
Iceland	10	14		1999	4
	15	20	Ceiling value		
Netherlands	10	15		2001	5
Norway	10	15	Ceiling value	2000	7
Sweden	10	14		2000	7
	15	20	Ceiling value	2000	7
USA (ACGIH)	10	15		2001	8
	5[1]				
(NIOSH)	10	15	Ceiling value	2000	9
(OSHA)	20		Ceiling value	2000	9
	50		10 min max peak	2000	9

[1] Proposed value

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