Hydrogen sulphide

Health-based recommended occupational exposure limit in the Netherlands

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

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Mijnheer de staatssecretaris,

Graag bied ik u hierbij het advies aan over de beroepsmatige blootstelling aan zwavelwaterstof. Het maakt deel uit van een uitgebreide reeks, waarin gezondheidskundige advieswaarden worden afgeleid voor concentraties van stoffen op de werkplek. Dit advies over zwavelwaterstof is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de minister van Volksgezondheid, Welzijn en Sport, de minister van Sociale Zaken en Werkgelegenheid en de staatssecretaris van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

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Health-based recommended occupational exposure limit in the Netherlands

Dutch Expert Committee on Occupational Standards
a committee of the Health Council of the Netherlands
In cooperation with the Nordic Expert Group for
Criteria Documentation of Health Risks from Chemicals

to:

the Minister and State Secretary of Social Affairs and Employment

No. 2006/07OSH, The Hague, July 13, 2006

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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Samenvatting

Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in lucht waaraan mensen beroepsmatig blootgesteld kunnen worden. Deze aanbevelingen vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden, aangeduid als maximaal aanvaarde concentraties (MAC-waarden).

Het voorliggende rapport is samengesteld in samenwerking met de Nordic Expert Group for criteria Documentation of Health Risks from Chemicals (NEG). In 2001 werd al gezamenlijk gepubliceerd over de gevolgen van beroepsmatige blootstelling aan zwavelwaterstof voor de gezondheid. Dat rapport verscheen in Zweden in 2001 (Arbete och Hälsa 2001:14). Het is nu in zijn geheel opgenomen in deel 2 van het huidige document. Deel 1 geeft een overzicht van de kennis over de meest relevante gevolgen van blootstelling aan zwavelwaterstof en bevat een gezondheidskundige evaluatie van deze stof. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór augustus 2004 zijn verschenen.

Fysische en chemische eigenschappen

Zwavelwaterstof is een kleurloos gas met een sterke geur van ‘rotte eieren’ (geurdrempel is 0.18 mg/m^3). Het smeltpunt bedraagt -85.5°C en het kookpunt -60.7°C. De oplosbaarheid in water en ether is respectievelijk 0.4 en 2.1% (w/w). Zwavelwaterstof heeft een relatieve dichtheid van 1.19 en een dampspanning van 2026 kPa. De verbinding is brandbaar en explosief in de lucht.

Grote hoeveelheden zwavelwaterstof worden gebruikt bij de productie van zwaar water. Zwavelwaterstof wordt daarnaast gevormd bij processen waarbij zwavel of zwavelverbindingen worden gebruikt in combinatie met organische oplosmiddelen en hoge temperaturen. Dit gebeurt bijvoorbeeld in de petrochemische industrie, in cokesovens, in de viscoserayonindustrie en in looierijen.

Methoden voor monitoring

De belangrijkste meetmethode maakt gebruik van filters die geïmpregneerd zijn met zilvernitraat. Het ontstane zilversulfide, opgelost in een cyanide oplossing, kan worden geanalyseerd met een polarografische methode (detectie limit is 0.6 mg/m^3). H_2S kan ook worden geanalyseerd met behulp van een gaschromatograaf met een vlam ionisatie detector (GC-FID)* of een vlam fotometrische detector (GC-FPD)**.

Huidige grenswaarden

De huidige MAC-waarde (maximaal aanvaarde concentratie) (8 uur tgg) in Nederland is 10 ppm (14 mg/m^3). Ook in Denemarken, Finland, Duitsland, IJsland, Noorwegen en de USA (ACGIH***) is een grenswaarde van 10 ppm (14 mg/m^3) van kracht. In Finland is daarnaast ook een 15 minuten grenswaarde van 21 mg/m^3 aangeraden. Het Verenigd Koninkrijk heeft een grenswaarde (gerekend over 8 uur) van 5 ppm (7 mg/m^3) afgeleid en hanteert een STEL**** van 10 ppm (14 mg/m^3).

*	Gas chromatografie (GC) met een vlamionisatie dectector (FID)
**	Gas chromatografie (GC) met een fotometrische dectector (FID)
***	American conference of governmental Industrial Hygienists (ACGIH)
****	Short term exposure Limit (STEL)

Een plafondwaarde (ceiling) van 15 ppm (21 mg/m^3) is geldig in IJsland en Zweden. In de VS, wordt door NIOSH* een plafondwaarde van 10 ppm (14 mg/m^3) geadviseerd, en door OSHA** een van 20 ppm (28 mg/m^3), met een 10 minuten grenswaarde van 50 ppm (70 mg/m^3).

Kinetiek

De opname van H_2S geschiedt voornamelijk via inademing. Na blootstelling, worden in ratten en muizen oplopende sulfide concentraties gemeten in de longen, de nieren, het luchtweg epitheel en in de hersenen. H_2S wordt gemetaboliseerd tot (thio)sulfaat en uitgescheiden via urine.

Effecten

Bij mensen

Blootstelling aan H_2S-gas lijkt bij mensen irritatie van de ogen te veroorzaken. In de viscoserayonindustrie worden effecten op de ogen al waargenomen bij concentraties lager dan 28 mg/m^3 (20 ppm). Er is dan echter gelijktijdige blootstelling met CS_2.

De belangrijkste effecten die worden gerapporteerd na korte blootstelling aan H_2S bij mensen zijn longfunctieschade en neurologische (gedrag)veranderingen. De gegevens zijn echter beperkt. Acute effecten na hoge blootstelling zijn longoedeem (vanaf 700 mg/m^3) en “flauwvallen”. In mensen met astma zijn geen aanwijzingen gevonden voor significante effecten op de luchtwegen na blootstelling aan 2.8 mg/m^3 (2 ppm) H_2S gedurende 30 minuten. Gezonde proefpersonen vertoonden na blootstelling aan 14 mg/m^3 (10 ppm) H_2S gedurende 15 minuten geen significante veranderingen in de longfunctie. Deze proefpersonen waren echter alleen via de mond blootgesteld aan H_2S.

Over de effecten van langdurige blootstelling is gerapporteerd in een onderzoek bij medewerkers van een pulpfabriek. Daar werd een verhoogde kans op sterfte als gevolg van hart en vaat ziekten waargenomen na gecombineerde blootstelling aan H_2S en organische zwavelverbindingen. Blootstellingsmetingen zijn echter niet verricht. Ook wordt een verminderd reukvermogen gerapporteerd na langdurige blootstelling

* National Institute for Occupational Safety and Health
** Occupational Safety and Health Administration

Bij proefdieren

Blootstelling aan 140-420 mg/m^3 (100-300 ppm) H_2S gedurende enige uren leidt bij proefdieren tot oogirritatie en irritatie van de slijmvliezen, keel en neusholte. De inhalatoire concentatie waarbij 50% van de blootgestelde ratten sterft is 617-691 mg/m^3 (~500 ppm). Daarbij worden cytotoxiciteit in de longen en longoedeem geconstateerd. Verder blijken na kortdurende blootstelling aan hoge concentraties de neurotransmitterconcentraties in delen van de hersenstam verhoogd.

In knaagdieren die zijn blootgesteld aan 25-100 ppm H_2S (35-140 mg/m^3), is de cerebrale cytochroom oxidase activiteit verlaagd. De L-glutamaat niveaus in de hippocampus zijn verhoogd. Daarnaast zijn veranderingen in EEG, beschadigingen aan het slijmvlies en hartritmestoornissen waargenomen. Studies met ratten laten gedragseffecten zien na blootstelling aan 112 mg/m^3 en hoger.

Effecten op de neusslijmvliezen worden zichtbaar in ratten na blootstelling aan 30 ppm H_2S (42 mg/m^3) per dag (70-90 dagen). Daarnaast zijn effecten waargenomen op het bronchiale epitheel (hypertrofie en hyperplasie) van ratten na blootstelling gedurende 90 dagen. De NOAEL bedroeg 14 mg/m^3 (10 ppm).

Genotoxische effecten zijn niet gemeld in de literatuur. Andere effecten na langdurige blootstelling zijn niet onderzocht. Daarnaast worden geen effecten op de reproductie gemeld in ratten na blootstelling aan H_2S (14, 42 and 112 mg/m^3). In dezelfde studie is ook geen verandering geconstateerd in de groei, de ontwikkeling en het gedrag van pups.

Evaluatie en advies

De gegevens over de gevolgen van acute blootstelling aan H_2S voor mensen zijn beperkt. Er zijn enkele individuele gevallen beschreven waarin acute hoge blootstelling (aan concentraties hoger dan 1400 mg/m^3) leidde tot haperen van de ademhaling. Er zijn geen aanwijzingen dat in mensen met astma blootstelling aan 2.8 mg/m^3 H_2S (2 ppm) gedurende 30 minuten kan resulteren in significante effecten op de ademhaling. Inhalatoire blootstelling gedurende 15 minuten (aan 14 mg/m^3, 10 ppm) via alleen de mond, veroorzaakte bij gezonde vrijwilligers geen veranderingen in de longfunctie.

Uit dierexperimenteel onderzoek blijkt dat kortdurende blootstelling aan H_2S in proefdieren de cytochroom oxidase activiteit in de longen remt, en lokale irritatie van de ogen en keel veroorzaakt.

De commissie is van mening dat de gegevens over de effecten na kortdurende blootstelling geen aanleiding zijn voor het vaststellen van een gezondheidskundige advieswaarde voor blootstelling gedurende 15 minuten (STEL).

De gegevens over de gevolgen van langdurige blootstelling van mensen aan H_2S zijn schaars. Langdurige blootstelling aan 1-5.6 mg/m^3 H_2S bleek oogirritatie bij medewerkers in de viscoserayonindustrie te veroorzaken. Er wordt echter gesuggereerd dat deze effecten het gevolg zijn van een gecombineerde blootstelling van H_2S en CS_2. Er zijn geen gegevens over de gevolgen van blootstelling aan alleen H_2S bij concentraties lager dan 28 mg/m^3.

In ratten veroorzaakt blootstelling gedurende 10 weken (6 uur per dag, 7 dagen per week) aan H_2S weefselschade in de neus (neuronen verlies en basale cel hyperplasie) en schade aan het bronchiale epitheel. De NOAEL is 14 mg/m^3. De commissie beschouwt dit als het kritische effect voor blootstelling aan H_2S.

Bij het vaststellen van de gezondheidskundige advieswaarde houdt de commissie rekening met verschillende onzekerheden. Omdat er sprake is van een lokaal effect, meent de commissie dat het niet nodig is te compenseren voor de verschillen tussen proefdier en mens (zogenaamde interspecies variatie). Om te compenseren voor (1) de verschillen in blootstellingduur (van subchronisch in het dierexperiment naar chronische beroepsmatige blootstelling) en (2) de beperkte gegevens over de pathologie, stelt de commissie een factor 2 voor. Tot slot hanteert de commissie een onzekerheidsfactor van 3, om te compenseren voor de interindividuele verschillen.

Uitgaande van een NOAEL van 14 mg/m^3, en gebruikmakend van een onzekerheidsfactor van 6, beveelt de commissie een gezondheidskundige advieswaarde aan voor H_2S van 2.3 mg/m^3 gedurende 8 uur (~1.6 ppm), om op die manier de lange termijn effecten van blootstelling aan zwavelwaterstof op de werkplek te voorkomen.

Gezondheidskundige advieswaarde

De commissie beveelt een gezondheidskundige advieswaarde voor beroepsmatige blootstelling voor H_2S aan van 2.3 mg/m^3 (~1.6 ppm), gemiddeld over een acht urige werkdag (tgg 8 uur).

Summary

Scope

At request of the Minister of Social Affairs and Employment, The Health Council of the Netherlands sets health-based recommended occupational exposure limits (HBR-OEL) for toxic substances in the workplace air. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). It constitutes the first step in a three step procedure which leads to legally binding occupational exposure limits.

The present report on hydrogen sulphide was prepared in cooperation with the Nordic Expert Group (NEG). The joint report on the consequences of occupational exposure to hydrogen sulphide, published in Sweden in 2001 (Arbete och Hälsa 2001:14), is included in part two of this document. Part 1 mainly consists of a summary of the most important health effects and a health hazard assessment by DECOS.

The committee's conclusions are based on scientific publications obtained from data retrieval systems from prior to August 2004.

Physical and chemical properties

H_2S is a colourless gas (CAS number 7783-06-4) with a strong odour of "rotten eggs" (odour threshold 0.13 ppm, 0.18 mg/m^3). Its melting point is –85.5°C and the boiling point is –60.7°C. Solubility in water and ether is 0.4 and 2.1% (w/w),

respectively. Hydrogen sulphide has a relative density of 1.19 and a vapour pressure of 2026 kPa. The substance is flammable and explosive in air and may even be ignited by static discharge.

Large quantities of H_2S are used in the production of deuterated water. Hydrogen sulphide is formed in manufactoring processes whenever elemental sulphur or sulphur compounds are present with organic compounds at high temperatures. Examples of industries where H_2S can be generated include petrochemical plants, coke oven plants, viscose rayon industries and tanneries.

Monitoring

The main sampling method is sampling on filters impregnated with silver nitrate. The resulting silver sulphide is dissolved in alkaline cyanide solution and analyzed for sulphide by differential pulse polarography (detection limit is 0.6 mg/m^3). H_2S can also be analysed by gaschromatography (with flame ionization detection or a flame photometric detection) on the spot or after collection in plastic laminate bags. Several other reading methods are available.

Current limit values

In the Netherlands, the present MAC-value (maximal allowed concentration) is 10 ppm (14 mg/m^3). In Denmark, Finland, Germany, Iceland, Norway, the USA (ACGIH*) 10 ppm (14 mg/m^3) is recommended as occupational exposure limit. In Finland in addition a 15 minutes value of 21 mg/m^3 is available. The United Kingdom derived and OEL (twa 8 hours) of 5 ppm (7 mg/m^3) and a STEL ** (15 minutes) of 10 ppm (14 mg/m^3). Ceiling values of 15 ppm (21 mg/m^3) are found in Iceland and Sweden. In the USA a ceiling value of 10 ppm (14 mg/m^3, NIOSH***), 20 ppm (28 mg/m^3, OSHA****) and a 10 minutes peak value of 50 ppm (70 mg/m^3, OSHA) are recommended.

*	American Conference of Governmental Industrial Hygienists (ACGIH)
**	Short Term Exposure Limit (STEL)
***	National Institute for Occupational Safety and Health
****	Occupational Safety and Health Administration (OSHA)

Kinetics

Uptake of H_2S is mainly via the inhalatory route. After exposure of mice and rats increased sulphide concentrations were shown in the lungs, liver, kidney, olfactory epithelium and the brain. H_2S is mainly metabolised mainly by the liver to (thio)sulphate and excreted via urine. Due to rapid metabolism there is no bioaccumulation of sulphide.

Effects

Human data

H_2S is a gas which seems to cause irritation of the eyes. In viscose rayon workers effects on eyes were observed at levels lower than 20 ppm (28 mg/m^3), however, in these industries simultaneous exposure to CS_2 was measured as well.

Short term occupational exposure might lead to lung function impairment and neurobehavioral changes. Data are, however, limited. Acute effects after exposure to high concentrations include pulmonary oedema (at ca. 700 mg/m^3 and above) and "knock down". In asthmatics, no significant effects on the airway resistance were found after exposure to 2.8 mg/m^3 (2 ppm) H_2S for 30 minutes. Exposure to 14 mg/m^3 (10 ppm) H_2S for 15 minutes caused no significant changes in pulmonary function in human volunteers. However, they were only exposed through the mouth.

In pulp-mill workers, an excess mortality from cardiovascular disease (and coronary heart disease) has been observed after exposure to H_2S and organic sulphur compounds, however exposure measurements were not performed. Other effects reported after prolonged exposure include olfactory fatigue (>100 ppm or 140 mg/m^3).

Animal studies

In laboratory animals, exposure to 140-420 mg/m^3 H_2S (100-300 ppm for a few hours) leads to irritation of the eyes and the mucous membranes of throat and nasal cavity. The LC50 (ie. concentration at which 50% of the animals died) in rats after inhalation exposure (for four hours) was 617-691 mg/m^3 (~500 ppm). Effects seen after short exposure to high concentrations were cytotoxic lesions in the lungs and pulmonary oedema. Neurotransmitter levels in the respiratory centers in the brainstem were increased as well.

Rodents exposed to H_2S at 25-100 ppm (35-140 mg/m^3) showed inhibition of cerebral cytochrome oxidase activity, increased L-glutamate levels in the hippocampus and EEG changes, lesions of the olfactory mucosa, various cardiac arrhythmias and an increased number of reticulocytes. Additional studies in rats on behavioural effects (motor activity, learning) showed an increased latency time in the (re)acquisition of performance in mazes at concentrations of 175 mg/m^3 and above and decreased motoractivity at 112 mg/m^3 and above.

Effects on the olfactory mucosa became apparent in rats sub-chronically (70-90 days) exposed to 30 ppm H_2S (42 mg/m^3). The effects reported included olfactory neuronal loss, basal cell hyperplasia of the mucosal lining. In addition, bronchial epithelial hypertrophy and hyperplasia was observed after exposure to H_2S for 90 days. The NOAEL was 14 mg/m^3.

No genotoxic effects were reported. Toxicity due to long-term exposure was not investigated.

No effects on reproduction and development were reported in rats exposed to H_2S (14, 42 and 112 mg/m^3) during mating, gestation and lactation. In the same study no effects on growth, development and behaviour of the pups were found. No gross or microscopic abnormalities were observed in the central nervous system of the offspring.

Hazard Assessment and recommended occupational exposure limit.

There is limited information concerning the effects of H_2S after acute exposure. Only a few cases have been described in which acute exposure (to concentrations exceeding 1400 mg/m^3) caused a cessation of respiration. In asthmatics, exposure to 2.8 mg/m^3 H_2S for 30 minutes did not result in statistically significant respiratory effects. Mouth only exposure for 15 minutes (to 14 mg/m^3) did not cause significant changes in pulmonary functions.

Acute or short-term exposure to H_2S, resulted in experimental animals to inhibition of cytochrome oxidase in the lung cells, and local irritation of eyes and throat.

The committee is of the opinion that the data concerning acute of short term exposure show that a short term exposure limit is not indicated.

There is limited human information concerning the health effects after prolonged exposure to H_2S as well. Exposure to 1-5.6 mg/m^3 H_2S caused eye irritation in viscose rayon workers. However, eye irritation in these industries might be a result of combined exposure with CS_2. There are no data concerning the effects of H_2S alone below levels of 28 mg/m^3.

In rats, exposure to H_2S causes nasal lesions (olfactory neuron loss and basal cell hyperplasia) and bronchial epithelial hyperthophy and hyperplasia after exposure to H_2S for 70-90 days (6 hours/day, 7 days/week). The NOAEL (no observed adverse effect level) for these effects is 14 mg/m^3. The committee is of the opinion that these are the critical effect. For the establishment of the health based occupational exposure limit (HBROEL) to committee takes several aspect into account. As default, the committee usually compensates for differences between rats and man. However, as the critical effect is local, the committee did not find such factor necessary. For the differences in exposure pattern (sub-chronic in the experimental setting versus the chronic occupational exposure) and the limited data concerning the pathology, the committee uses a factor 2. Finally, to compensate for interindividual differences the committee uses a factor 3 as well.

Considering all these aspects, starting from a NOAEL of 14 mg/m^3 and using an extrapolation factor of 6 the committee recommends an HBROEL twa 8 hours for H_2S of 2.3 mg/m^3 (~1.6 ppm).

Health based recommended occupational exposure limit

DECOS recommends an HBROEL twa 8 hours for H_2S of 2.3 mg/m^3 (~1.6 ppm).

Hoofdstuk 1

Scope

1.1 Background

In the Netherlands occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by The Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, at the request of the Minister of Social Affairs and Employment (Annex A). The purpose of the committee's evaluation is to set a health-based recommended occupational exposure limit for the concentration of the substance in air, provided the database allows the derivation of such value.

In the next phase of the three-step procedure the Social and Economic Council advises the Minister on the feasibility of using the health based value as a regulatory Occupational Exposure Limit (OEL) or recommends a different OEL. In the final step of the procedure the Minister of Social Affairs and Employment sets the official Occupational Exposure Limit.

1.2 Committee and method of work

This document contains the assessment of the health hazard of hydrogen sulphide (H_2S) and is a co-production of the DECOS and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). It is a result

of an agreement between both groups to prepare jointly scientific criteria documents, which can be used by the national regulatory authorities in the Netherlands and the Nordic countries for establishing exposure limits. The members of the DECOS and NEG are listed in annex B.

The joint draft document on the harmful effects of hydrogen sulphide has been prepared by Dr K Svendsen at the University Hospital of Trondheim, Norway. In addition, the draft was reviewed first by the NEG and subsequently by DECOS. The final document was published by the Swedish National Institute of Occupational Health (Arbete och Hälsa 2001:14) and is included in part two of this report.

Part one contains a brief summary of the relevant effects from the final document in part two, supplemented with additional published data. DECOS used the data from both parts in assessing a health based recommended occupational exposure limit for tin and inorganic tin compounds. The first draft of part one was prepared by WMLG Gubbels-van Hal, from NOTOX BV, 's-Hertogenbosch, by contract with the Dutch Health Council.

In 2005, the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

Starting point in searching literature on health effects of exposure to hydrogen sulphide was the report of the NEG on hydrogen sulphide (see Part 2 of this report). Unless otherwise indicated, data were retrieved from this document. In addition, literature was retrieved from the on-line data bases Medline and Toxline starting from 2001. The final search has been carried out in August 2004. Studies published between 2004 and 2006 were no reason for the committee to adjust her recommendations and were therefore not included in this report. The searches were performed using CAS 7783-06-04 and hydrogen sulph(f)ide as search profile.

In the sections below the first part is a short summary of the findings from the report of the NEG on hydrogen sulphide*, while any additional information retrieved from the literature search is included in the second part under additional information.

* References from Arbete och Hälsa 2001:14 are refered to as 'NEGxx'

Hoofdstuk 2

Kinetics

2.1 Toxicokinetics

Summary of the data in Arbete och Halsa 2001:14

Hydrogen sulphide is primarily absorbed via the respiratory tract. It enters the circulation and partly dissociates to HS^-. It is distributed to the brain, liver, kidney, pancreas and small intestine. The net uptake of sulphide is the greatest in the brainstem. The primary metabolic fate of hydrogen sulphide is oxidation to (conjugated) sulphate and excretion via urine. Thiosulfate is therefore used as an indicator of H_2S exposure. Methylation is another detoxification pathway.

Additional information

Male CD rats (6/treatment) exposed to 0, 10, 30, 80, 200 and 400 ppm H_2S (0, 14, 42, 112, 280 and 560 mg/m^3) for 3 hours. At the end of exposure, sulphide concentration in the lungs showed a dose dependent increase (significant at 80 ppm and above). In the liver significantly increased concentrations of sulphide were found at 200 and 400 ppm. In addition, lung sulphide and sulphite, sulphate and thiosulphate concentrations were measured in 6 rats/timepoint at 0, 1.5, 3, 3.25, 3.5, 4, 5 and 7 hours after the start of a 3-hour exposure to 400 ppm (560 mg/m^3). Lung sulphide concentrations rose during the exposure period and decreased to about pre-exposure levels 15 minutes after cessation of exposure.

Sulphite, sulphate and thiosulphate concentrations showed a peak 15 minutes after the end of the exposure period and decreased to normal values within minutes thereafter.[6]

In a second experiment, male CD rats (6 per treatment group) were exposed to 0, 30, 80, 200 and 400 ppm H_2S once for 3 hours (0, 42, 112, 280 and 560 mg/m^3). At the end of exposure, sulphide concentration was measured in the hind brain and respiratory and olfactory epithelium of the nose. Sulphide concentration was increased significantly compared to control values only in the olfactory epithelium after exposure to 400 ppm[6].

The metabolism of H_2S is either via (1) oxidation (in the mitochondria) or (2) methylation (in cytosol) or (3) scavenging by methaemoglobin or glutathione.[24]

Incubation of mucosa from the caecum, right colon, mid-colon, ileum and stomach as well as liver, muscle, erythrocytes and plasma derived from Sprague-Dawley rats with radio-labelled $H_2{}^{35}S$ confirmed that the main detoxification pathway of H_2S is oxidation to thiosulphate. Caecal and proximal colonic mucosa metabolised H_2S to thiosulphate (and sulphate) about 10 times more rapidly than the upper part of the gastro intestinal tract mucosa and 5 times more rapid than liver tissue.[9]

2.2 Mechanism of toxicity

Summary of the data in Arbete och Halsa 2001:14

Toxicity of H_2S is most likely related to inhibition of metal-containing enzymes. Important target enzymes are cytochrome oxidase, the final enzyme of the mitochondrial respiratory chain, and carbonic anhydrase. By this mechanism H_2S affects cellular energy production and respiration. Most susceptible tissues are mucous membranes and tissues with a high oxygen demand, like nervous and cardiac tissues. In addition, sulphide also seems to act on the respiratory drive through other mechanisms. Among these are inhibition of monoamine oxidase, suppression of synaptic activity, a direct action on respiratory centres in the brain and stimulation of the glutamate receptors in the brain.

Additional information

H_2S inhibits mitochondrial electron transport by selective reaction with cytochrome aa3. Target sites are eyes, lungs, olfactory parts, nervous system, heart blood, brain, gastro intestinal-system and liver.[8]

In a review article, three possible mechanisms for brain neurotoxicity of H_2S were discussed: (1) H_2S affects the neuronal membrane depolarisation, (2) causes changes in neurotransmitter levels and (2) shows effects on (respiratory)

enzymes. The authors concluded that the primary cellular targets of H_2S are the respiratory enzymes. The precise mechanism and site of action in the brain have yet to be resolved.[21]

Endogenous H_2S can be produced by mammalian cells from cysteine (mainly in brain and vascular tissues).[13] The production is either enzyme catalysed (cystathionine β-synthase (CbS) and cystathionine γ-lyase (CSE)) or non-enzymatic (reduction of elementary sulphur).[5,13,24] Normal, physiological concentrations of H_2S are known to facilitate long-term potentiation in the rat hippocampus. Higher concentrations lead to increased excitability.[5]

H_2S has a relaxing effect in vascular smooth muscle preparations from Wistar rats.[5,13] This effect is mediated via K_{ATP}-channels.[24] An *in vivo* experiment in rats (n=3/ treatment, strain not indicated) receiving an *intravenous* bolus injection of 2.8 and 14 μmol/kg bw showed a reduction of arterial blood pressure. Heart rate was not altered. Blockage of K_{ATP}-channels by glibenclamide, antagonised the effect on blood pressure.[26] *In vitro* rat aortic tissues were relaxed in a similar manner.

Chronic exposure of neonatal rats increased brain serotonin and norepinephrine levels in cerebellum and frontal cortex.[24]

Hoofdstuk 3

Effects

3.1 Observations in humans

3.1.1 Irritation and sensitisation

Summary of the data in Arbete och Halsa 2001:14

In viscose rayon workers, eye irritation ('spinners eye') has been reported to occur after 6-7 hours of exposure to 10 ppm (14 mg/m^3) H_2S (Nesswetha 1969).[NEG57*] Prolonged exposure led to irritation and keratoconjuncvitis in workers in 'sour gas' plants (ACGIH 1991, Beauchamp 1984, Deng 1992, Reiffenstein 1992).[NEG1, NEG5, NEG16, NEG68] In another study concerning workers in the rayon viscose industry, increased prevalence of eye irritation was seen after prolonged exposure to 0.7-4 ppm (1-5 mg/m^3) (Vanhoorne 1995).[NEG86] However, all these H_2S-exposed workers were co-exposed to CS_2 (concentration at least 26 mg/m^3) and a combined effect cannot be excluded[**]. Irritant effects of H_2S as a single agent at exposure levels below 20 ppm (28 mg/m^3) are not well documented.

Olfactory fatigue is reported at high concentrations of H_2S (>140 mg/m^3) and/or after prolonged exposure (Glass 1990, Reiffenstein 1992).[NEG18, NEG68] One person has been described who lost his smell for 3 years after exposure to a high (not specified) concentration of H_2S (Tvedt 1991).[NEG85]

* For references 'NEGxx' see Arbete och Hälsa 2001:14, chapter 18 References.

** CS_2 causes adverse effects in the eye (retinal microaneurysms and haemorrhages) in US-workers exposed to 3-48 mg/m^3 CS_2. In Chinese workers no such effects were observed. In addition, Japanese workers exposed to CS_2 (60-95 mg/m^3) showed an increased incidence of retinopathy, but these effects were not observed in Finnish workers exposed to CS_2 under similar occupational conditions.[1]

No information on skin irritation and sensitisation is available.

An overview of the dose-effect relationship of hydrogen sulphide after short term exposure can be found in table 1.

Table 1 Dose-effect relationships in man after short term exposure.

Effect level mg/m^3 (ppm)	NOEL mg/m^3 (ppm)	Effects	Reference
0.028 (0.02)		Minimum perception threshold	Beliles 1993[NEG7]
0.07 – 7.3 (0.05-5.2)		Changes in haem synthesis in pulp production workers	Tenhunen 1983[NEG82]
0.18 (0.13)		Generally accepted smell threshold	Deng 1992[NEG16]
2.8 (2)		Non significant effects in asthmatic subjects (exposure for 30 min)	Jäppinen 1990[NEG36]
4.2-7 (3-5)		Offensive smell	Beliles 1993[NEG7]
7 (5)	2.8 (2)	Increased muscle lactate levels during exercise (exposure > 16 min) and increased oxygen uptake	Bhambhani 1991[NEG12]
14 (10)		Exposure for 15 minutes did not alter the pulmonary function significantly.	Bhambhani 1996[NEG9]
14 (10)		Reduced oxygen uptake during exercise (exposure two times 30 minutes)	Bhambhani 1997[NEG8]
> 140 (>100)		No smell due to olfactory fatigue	Glass 1990, OSHA 2000[NEG18, NEG63]
700-1400 (500-1000)		Stimulation of carotid bodies	ACGIH 1991[NEG1]
1400-2800 (1000-2000)		Paralysis of respiratory center and cessation of breathing	ACGIH 1991[NEG1]

Additional information

Luck et al reported six cases who were exposed briefly to H_2S in the sausage manufacturing industry. Occular examination showed blepharospasm, photophobia and lacrimation, and superficial punctuate cornela erosions.[16]

3.1.2 Toxicity due to acute and short-term exposure

Summary of the data in Arbete och Halsa 2001:14

In humans the targets of acute toxicity of hydrogen sulphide are the nervous system (knock-down) and the lung (ACGIH 1991, Beauchamp 1984, Arnold 1985, Guidotti 1996, Hessel 1997, Mehlman 1994).[NEG1, NEG5, NEG3, NEG23, NEG28, NEG54] (Temporary) unconsciousness and (severe) effects on the respiratory system (with or without neurological changes) are the main symptoms. Pulmonary oedema is also relatively often seen in patients after H_2S exposure (Schneider 1998, Tvedt 1991, Vuorela 1987, Wasch 1989).[NEG76, NEG85, NEG88, NEG92] At low exposure concentrations the characteris-

tic odour of "rotten eggs" can be an early warning for exposure (odeur threshold 0.13 ppm, 0.18 mg/m^3) (Belilies 1993, Deng 1992).[NEG7, NEG16] At concentrations above 100 ppm (140 mg/m^3) humans are not able to smell H_2S most probably to olfactory fatigue (Glass 1990, Reiffenstein 1992).[NEG18, NEG68] Several case reports are available that describe persistent neurological and neuropsychological abnormalities following acute hydrogen sulphide exposure (exposure levels not known) (Wasch 1989, Callender 1993, Snyder 1995, Schneider 1998, Kilburn 1993, Vuorela 1987, Tvedt 1991).[NEG92, NEG14, NEG79, NEG76, NEG42, NEG88, NEG85] However, complete recovery of victims of H_2S poisoning is also possible (Deng 1992, Glass 1990, Guidotti 1994).[NEG16, NEG18, NEG22]

Short-term exposure of humans (workers, duration not reported) led to lung function impairment (Richardson 1995)[NEG69] and changes in neurobehavioral functions at unknown exposure levels (De Fruyt 1998, Hessel 1997).[NEG15, NEG28] At 1.4-16 mg/m^3 (exposure during 30 minutes), no significant changes in respiratory function and bronchial responsiveness were found in healthy paper mill workers (pre-exposed daily to 14 mg/m^3 H_2S). However, asthmatic subjects showed a (not significant) increased airway resistance after exposure at 2.8 mg/m^3 for 30 minutes (Jäppinen 1990).[NEG36]

16 Healthy male volunteers were randomly exposed to 0, 0.5, 2.0, 5.0 ppm (> 16 min) on four separate occasions. Exposure to 5 ppm during exercise resulted in increased blood lactate concentrations and oxygen uptake (Bhambhani 1991).[NEG12] Exposure to 10 ppm (14 mg/m^3) for 15 minutes during submaximal exercise revealed no significant changes in routine pulmonary function parameters (Bhambhani et al, 1996)[NEG9] and exposure for 30 minutes (10 ppm) reduced the maximal aerobic power (VO_2, oxygen uptake) (Bhambhani et al, 1997).[NEG8] Other studies concerning volunteers showed no significant cardiovascular or metabolic responses after exposure to 5 ppm H_2S. However, a major limitation of these studies was that the volunteers inhaled the gas through the mouth from a bag (mouth only exposure). Therefore, the possible effects on eyes found in other studies, could not be detected.

Additional information

Four workers were accidentally exposed to hydrogen sulphide at a construction site of a gas refinery. None lost consciousness but all experienced a variety of irritating local effects, ie lacrimation, eye irritation, nausea, vomiting, headache, sore throat and skin irritation.[10] The concentration of H_2S was estimated to be 243 ppm (340 mg/m^3). In addition, the late effects of the exposure were studied. Several neuropsychiatric clinical sequelae were reported.[10]

Two workers were exposed to hydrogen sulphide from a leaking valve. Both lost consciousness, were cyanotic and had generalised seizure activity. In both cases X-rays showed bilateral infiltrates in the lungs indicative of pulmonary oedema. An ECG showed sinus tachycardia. Both patients showed symptoms of keratoconjunctivitis (inflammation of both cornea and conjunctiva). Based on the

symptoms observed exposure concentration was estimated to be 500-1000 ppm (700-1400 mg/m^3).[23]

A 55 year-old male Caucasian was found dead after he had accidentally been exposed to hydrogen sulphide. Autopsy revealed pulmonary oedema and passive congestion of lungs, spleen, kidneys and adrenal glands. H_2S in blood was determined to be 1.68 μg/mL, which is similar to the values found in other cases of H_2S poisoning (0.8-5.0 μg/mL).[4]

Four workers were accidentally exposed to ca. 1400 ppm H_2S (~1960 mg/m^3, measured value). All lost consciousness. Two died very soon after exposure. One worker died after 22 days and the other survived.[11]

A man and a woman were exposed in their basement to initial concentrations of 500-700 ppm H_2S (calculated from 130 ppm (180 mg/m^3, the concentration measured in the basement one hour after exposure)). They were hospitalised with signs of pulmonary oedema.[19]

3.1.3 Effects of repeated and long-term exposure

Summary of the data in Arbete och Halsa 2001:14

Epidemiological studies of workers who have been exposed to H_2S are difficult to interpret because of the combined exposure to other toxic agents. After prolonged exposure, eye-irritation, hazy sight and photophobia (at concentrations from 1-5 mg/m^3) (Vanhoorne 1995, Masure 1950),[NEG86, NEG53] lung function impairment (no concentrations indicated) (Richardson 1995, Melbostad 1994),[NEG69, NEG55] effects on enzyme levels in reticulocytes and erythrocyte protoporphyrin concentration (at concentrations between 0.07 and 7.2 mg/m^3 as 8-hour TWA) (Tenhunen 1983)[NEG82] were found. These effects were seen in single studies and were confirmed in other studies as the main effects related to H_2S exposure. Furthermore, an excess mortality from cardiovascular disease and coronary heart disease was reported (Jäppinen 1990b)[NEG35] in a Finnish sulphate mill (no exposure data available). Exposure measurements (of H_2S and other organic sulphur compounds) in the sulphate mill were performed 20-40 years later (Kangas et al 1984)[NEG37], and the level of H_2S was between 0-28 mg/m^3.

There are no studies on the carcinogenic effect of H_2S alone. Concerning combined exposure in pulp and paper as well as in viscose rayon manufacture, there is no support for a carcinogenic effect of H_2S (IARC 1987, MacMahon 1988, Swaen 1994, Peplonska 1996, Zambon 1994).[NEG31, NEG52, NEG80, NEG65, NEG95]

In a retrospective epidemiological study in 106 non-smoking pregnant women working in a Chinese petrochemical company an increased risk of spontaneous abortion was found (Odds Ratio 2.5, (95% 1.7-3.7) for exposure to unknown level of H_2S). Corrections were included for exposure to benzene, gasoline, MN and NH_3. In addition the influence of age, educational level, shift work, noise

level, hours with standing and kneeling, hours at work, passive smoking and diet was included in the evaluation (Xu 1998).[NEG94] Other reports on the fertility and developmental effects are difficult to interpret, because of the co-exposure to CS_2, a known tetatogen (Reiffenstein, 1992).[NEG68]

An overview of the dose-effect relationship of hydrogensulphide after prolonged exposure can be found in table 2.

Table 2 Dose-effect relationships in man after prolonged exposure.

Effect level mg/m^3 (ppm)	NOEL mg/m^3 (ppm)	Effects	Reference
1-8.9 (0.7-6.4)		Increased prevalence of eye irritation symptoms in viscose rayon workers (co-exposure) to CS_2 (4-112 mg/m^3)	Vanhoorne 1995[NEG86]
28 (20)		Effects on the cornea and conjunctiva	Masure 1950[NEG53]
>70 (>50)		Effects on the epithelia of the conjunctiva and the cornea of the eye	Ammann 1986[NEG2]
350-740 (250-600)		Pulmonary oedema after prolonged exposure	ACGIH 1991[NEG1]

Additional information

Forty-seven workers (45 males and 2 females) of an aircraft factory were exposed to H_2S (duration and concentration not indicated). No controls were included. Bias due to smoking was excluded only partially as smokers, non-smokers and previous smokers were included in the study design. However, these subgroups were not evaluated separately. Lung function tests were performed according to standardised methods and lung volumes and gas transfer were measured. Mean Residual Volume (MRV) was reduced in 23% of the male subjects.* This isolated reduction of MRV (without any changes in other lung parameters) may be an indicator of respiratory disease. It was concluded by the author that the effect might be related to H_2S exposure[3].

In 1998, a school in Pennsylvania was monitored for exposure to H_2S (due to nearby mush-room composting operations) and H_2S related complaints. Air was monitored and students with health complaints visiting the school nurse had to complete a questionnaire on specific symptoms and their general medical condition. An unexposed school was used as control. In the exposed school, 24 hour indoor and outdoor concentrations of H_2S remained below 24-hour air quality standards (i.e. 5 ppb, 0.007 mg/m^3) except for 3 days in autumn. Both in spring

* Any physiological index of pulmonary function falling outside 1.65 standard deviations of the predicted value was considered abnormal.

and autumn 1-hour air quality standards were above 100 ppb (0.14 mg/m^3) during 7 and 9 days respectively. For the control school all measured values were below air quality standards. No consistent relationship between exposure and reported symptoms could be established. It was concluded by the author that low exposure to H_2S did not impose a significant health risk.[15]

A multi-symptom health survey with multiple descriptive variables was performed by trained interviewers to compare self-reported symptoms in two communities exposed to low levels of H_2S (mean annual level 7-27 ppb (0.01-0.038 mg/m^3), 24-hour level up to 150-300 ppb (0.21-0.42 mg/m^3), 8 hour up to 335-503 ppb (0.47-0.70 mg/m^3) with self-reported symptoms in unexposed communities. In the exposed communities, the number of African Americans was much higher than in the control communities and the number of 60+ people was lower. Another reason for bias according to the committee may be over-reporting in the exposed communities and recall bias. In one of the exposed communities concurrent exposure to other chemicals may have occurred. Smokers were discarded from the evaluation of respiratory complaints. People (n=223) of the two exposed communities reacted similar to the questions about the major categories. The symptoms with the highest Odds-Ratio (OR) were CNS effects (fatigue, restlessness, depression, memory loss, imbalance, sleeping difficulties, anxiety, numbness, lethargy, headaches, dizziness, tremors and changes in senses; OR 12.7, 95% confidence interval 7.59-22.09), respiratory effects (coughing up blood, wheezing, shortness of breath, persistent cough, bronchitis, pneumonia and lung disease; OR 11.92, 95% confidence interval 6.03-25.72) and blood-related effects (clotting disorders, bruises, abnormal blood count, spleen problems and anaemia; OR 8.07, 95% confidence interval 3.65-21.18). The author concluded that within its limitations this study provides indications for adverse health effects due to long-term, chronic exposure to H_2S [14]. The committee, however, noted that from the data available it cannot be established whether the effects found were due to continuous low exposure values or related to high peak exposures that occurred during the study period. In addition, the committee is of the opinion that the exposure assessment was weak, the self reported symptoms may be susceptible to response enhancement bias and recall bias.

A population of residents living near a landfill on Staten Island (New York), who had been diagnosed with asthma, was investigated to determine the effects of emissions of H_2S on respiratory function. The investigations were performed via completion of a daily diary on symptoms (e.g. wheeze), peak flow, odours in their residential area, activity and medication use. The outcome was linked to air monitoring values of H_2S, particulate matter and ozone performed in the vicinity

of the residential area. Mean measured H_2S values (15 minutes maximum) were ca. 6.6 ppb (0.009 mg/m^3, range <2 ppb to 33 ppb). No relationship between measured H_2S and respiratory morbidity was established.[25]

3.2 Animal experiments

3.2.1 Irritation and sensitisation

Summary of the data in Arbete och Halsa 2001:14

Hydrogen sulphide leads to irritation of the eyes in laboratory animals (few hours exposure to 100-300 ppm, 139-417 mg/m^3). Moreover, effects on the mucous membranes of the throat and nasal cavity are reported in laboratory animals (IPCS 1981, Lopez 1988).[NEG32, NEG50]

No information on skin irritation and sensitisation is available.

Additional information

No new data were found.

3.2.2 Toxicity due to single exposure

Summary of the data in Arbete och Halsa 2001:14

Inhalation exposure of rats during 4 hours to hydrogen sulphide gave a LC50 of 444-501 ppm (622-701 mg/m^3). Acute effects included oedema in the lungs (Prior 1988).[NEG67] Sublethal concentrations produced cytotoxic lesions in the lungs with depression of the activity of cytochrome oxidase (Warenycia 1989).[NEG91] Amino acid neurotransmitter levels in the respiratory centers in the brainstem were increased (Kombian 1988).[NEG46]

An overview of the studies available can be found in table 3.

Additional information

No new data were found.

3.2.3 *Toxicity due to short-term exposure*

Summary of the data in Arbete och Halsa 2001:14

In several studies, rodents were exposed to H_2S at 25-100 ppm (35-140 mg/m^3). The observed effects include inhibition of cerebral cytochrome oxidase activity (Savolainen 1980,1982), increased L-glutamate levels in the hippocampus and concomitant changes in the EEG (Nicholson 1998, Skrajny 1992)[NEG58, NEG77], various cardiac arrhythmias (Kosmider 1967)[NEG47] and effects on blood parameters (increased number of reticulocytes) (Savolainen 1982).[NEG74]

Brenneman et al (2000)[NEG13] exposed rats to H_2S 6 hours/day, 5 days/week for 10 weeks. Dose related lesions of the olfactory mucosa were found after exposure to 30 and 80 ppm. No effects were observed after exposure to 10 ppm H_2S.

Exposure of rabbits for 6 days (10 hours/day) to H_2S alone (50-100 mg/m^3) did not produce corneal lesions (Masure 1950).[NEG53]

An overview of the studies available can be found in table 3.

Additional information

Male fischer rats were exposed to 0, 1, 10, 100 ppm H_2S (0, 1.4, 14, 140 mg/m^3) for 8 hours/day, 5 days/week for 5 weeks. Exposure to 1 ppm did not cause any biochemical changes in de lung, brain or liver mitochondria (cytochrome oxidase) and in erythrocytes (superoxide dismutase and glutathione dismutase). Rats exposed to 10 and 100 ppm showed significantly lower activity of cytochrome oxidase in de lung mitochondria than the control animals.[12] The toxicological relevance of this biochemical finding is unclear. Male CD rats were exposed (whole body) to concentrations of 0, 10, 30 and 80 ppm H_2S ((0, 14, 42 and 112 mg/m^3, 3 hours/day, 5 consecutive days). Animals were evaluated daily immediately after exposure for fixed interval (FI) operant behaviour (5-7 rats/treatment), Morris water maze (10 rats/treatment) and spontaneous motor activity (6 rats/treatment). No significant treatment effects on learning and memory in the water maze or on overall motor activity were found. Performance in the FI-schedule applied was stable during the whole treatment period and the week thereafter.[22]

In a second experiment male CD rats were exposed (nose only) to concentrations of 0, 30, 80, 200 and 400 ppm ((0, 42, 112, 280 and 560 mg/m^3, 3 hours/day, 5 consecutive days). Neurotoxicity was evaluated daily immediately after exposure by examining behaviour in a Morris water maze (5-7 rats/treatment). After the fifth day of exposure, spontaneous motoractivity was measured

in 10 rats/treatment (as number of photobeam breaks). In addition, striatal, hippocampal and hindbrain catecholamines (eg dopamine) were measured with reverse phase HPLC with electrochemical detection. One animal exposed to 400 ppm died (cause of death not indicated). Animals exposed to 400 ppm showed a significantly increased latency time both in the acquisition phase (day 1-4) and on day 5. Motoractivity was significantly less at 80, 200 and 400 ppm compared to values found in controls. No effects on brain catecholamine levels were reported at any test concentration.[22]

The effect of repeated exposure to H_2S (whole body exposure to 175 mg/m^3) on neurobehavioral function in adult male SD rats was measured using a 16-arm radial arm maze (RAM). In the first experiment, 10 rats/treatment were exposed for 5 consecutive weeks (5 days/week, 4 hours/day). Effects on memory were assessed by daily testing the retention of a previous learned complex RAM-task. Animals were trained for 4 months and the experiment began 8 days after completion of the training. No effect compared to controls on maze performance became apparent.[20]

In the second test 12 animals/treatment were exposed during acquisition of a novel RAM task (total experiment 11 weeks, 4-5 days/week, 4 hours/day). Animals, matched for activity level between treatment and control group, were trained to find reinforcers (fruit loops cereal) in 10 of 16 maze arms. Both control and treated animals showed improvement of their performance during the trial. The total number of correct arm entrances was significantly lower in treated animals, indicating less efficiency in completing the trial. The number of entrance errors was significantly increased compared to controls during week (3 and) 4. H_2S is concluded to have an effect on the rate of performance, not on acquisition.

In the third experiment, the 8 best performing animals of the control and treatment group of experiment 2 were retested during 20 training sessions over a four week period (5 daily trainings/week). The maze used was the same as used in the previous experiment, but the reinforcements were placed in the six formally empty arms of the maze. A significant increase of the overall number of entries (correct and not correct) was reported for the animals that were treated with H_2S. This is reflected in a significant increase of working memory errors during the trials on day 11-20. Overall maze performance was not affected.[20] No overt signs of eye irritation, respiratory distress, behavioural dysfunction or impaired consciousness were observed during any of the experiments.

The authors concluded that repeated exposure to 125 ppm H_2S has no influence on the retention of a previously learned task, but induces slight but signifi-

cant impairment of re-acquisition of a reversed contingency RAM task. The effects persist well beyond the period of exposure.[20]

Male rats (CD) were exposed to target concentrations of 0, 30, 80, 200 or 400 ppm H_2S ((0, 42, 112, 280 and 560 mg/m^3, 3 hours/day) for 1 or 5 consecutive days.[2] After the exposure period, rats were sacrificed and six sections of the nose of 5 rats/concentration/endpoint were examined histopathologically. In addition, 5 rats per concentration per endpoint were necropsied and examined 2 and 6 weeks after the 5 day-exposure period. The olfactory mucosa of the nose of 3 rats/concentration/time was examined by transmission electron microscopy. Nose sections of control rats were immunostained with monoclonal antibodies against cytochrome oxidase.

After a single exposure, bilaterally symmetrically mucosal necrosis in the olfactory epithelium lining the dorsal medial meatus was found in one rat at 80 ppm, in 3 rats at 200 ppm and in 4 rats at 400 ppm[2]. Regenerating respiratory epithelium was found in 1 rat at 80 ppm and all rats at 200 and 400 ppm. Electron microscopy revealed severe swelling of the mitochondria in both sustentacular cells and olfactory neurons. In the sustentacular cells endoplasmatic reticulum was extensively swollen. Dendrites and olfactory vesicles of the olfactory neurons were swollen with reduced numbers of cilia compared to controls.

Repeated exposure resulted in 100% incidence of olfactory lesions (located at the dorsal meatus and the ethmoid recess) at 80 ppm and above.[2] No lesions of the respiratory epithelium were observed. After 2 weeks the olfactory epithelium was partly regenerated and after 6 weeks complete recovery was observed. In the olfactory epithelium of control only a limited number of cells responded to cytochrome oxidase immunostaining. According to the author a low level of cytochrome oxidase may explain the lack of reserve against cytochrome oxidase toxicity due to H_2S in the olfactory epithelium in contrast to the respiratory epithelium.[2]

Adult male CD rats were exposed to H_2S at 0, 10, 30 and 80 ppm ((0, 14, 42 and 112 mg/m^3, 6 hours/day) for 70 consecutive days. After the last exposure, animals were sacrificed and noses were dissected. Four transverse sections were examined histopathologically. Bilaterally, symmetrical olfactory neuronal loss and basal cell hyperplasia were observed in the mucosa lining the dorsal medial meatus, the nasal septum, dorsal wall of the nasal cavity and margins of the ethmoturbinates. These findings increased with concentration (50% effect at 30 ppm and 70% effect at 80 ppm). No effects were found after exposure to 10 ppm.

Comparison with modeled H_2S fluxes showed a correlation between flux and lesion incidence[18].

Male CD rats (6/treatment) were exposed once to 0, 10, 30, 80, 200 and 400 ppm H_2S ((0, 14, 42, 112, 280 and 560 mg/m^3) for 3 hours. At the end of exposure, cytochrome oxidase activity in the lung showed a dose-related decrease (significant at 30 ppm and above). In the liver, cytochrome oxidase activity was increased significantly in all dose groups without a relationship with dose.[6]

Male CD rats (6/treatment) were exposed to 0, 30, 80, 200 and 400 ppm H_2S for 3 hours during 1 day or 5 consecutive days. At the end of exposure, cytochrome oxidase activity was measured in the hindbrain and respiratory and olfactory epithelium of the nose. Cytochrome oxidase activity was decreased significantly at all tested concentrations in both respiratory and olfactory epithelium after a single exposure and in the olfactory epithelium after 5 exposure days (no concentration-related effects).[6]

In male CD rats used in a reproduction and developmental study (70 days exposure to 0, 10, 30, and 80 ppm H_2S ((0, 14, 42 and 112 mg/m^3) during 6 hours/day) cytochrome oxidase activity was significantly decreased in lungs of animals treated at 80 ppm, but not at the lower concentrations tested[6]. Reducton of cytochrome oxidase activity is a very sensitive biomarker for H_2S exposure. An effect is seen in the lung and nose after exposure to 30 ppm.

In 2004, Dorman et al.[7] described the results of a re-assessment of the nasal and lung histologic specimens obtained from a subchronic CIIT inhalation study.[17] Rats (Fischer-344 and Sprague Dawley) and mice ($B_6C_3F_1$) were exposed to 0, 10, 30 or 80 ppm H_2S (whole body) for 6 hours/day, for at least 90 days. Exposure to 80 ppm was associated with reduced feed consumption during the first exposure week (rats) or throughout the 90 day exposure (mice). Rats (male Fischer and female Sprague Dawley) and female $B_6C_3F_1$ mice exposed to 80 ppm had depressed terminal body weights when compared to controls. Inhalatory exposure did not result in toxicological relevant alterations in hematological indices, serum chemistries or gross pathology. Histological evaluation of the nose showed an exposure related increased incidence of olfactory neuronal loss after exposure to 30 or 80 ppm (except for male Sprague Dawley rats which showed effect after exposure to 80 ppm). In addition, rhinitis was observed in all mice exposed to 80 ppm. Finally, exposure to 30 ppm H_2S and higher was associated with bronchiolar epithelial hyperthropy and hyperplasia in male and female Sprague Dawley rats. Comparable effects were observed in male Fischer-344 rats exposed to 80 ppm.

Table 3 Dose-effect and dose-response data for animals exposed (single and short-term) to H_2S.

Effect level mg/m^3 (ppm)	NOEL mg/m^3 ppm)	Duration of exposure	Effects	Reference
1.4 (1)		8 h/day, 5 weeks	Some rats with hyperreactive response in the airways	Reiffenstein 1992[NEG68]
35 (25)		Repeated, 3 h/day	Cumulative change in hippocampal type 1 EEG activity in rat	Skrajny 1992[NEG77]
42 and 112 (30 and 80)	14 (10)	6 h/day, 7 days/ week 10 weeks	Dose related olfactory neuron loss and basal cell hyperplasia in rats	Brenneman 2000[NEG13]
$\geq$ 70 ($\geq$50)	14 (10)	4 h	Inhibition of cytochrome oxidase in rat lung cells	Khan 1990[NEG40]
100 (72)		1.5 h/day several days	Various cardiac arhythmias including ventricular extrasystoles in rabbits and guinea pigs	Kosmider 1967[NEG47]
140 (100)		2 h, 4-day intervals, 4 times	Increasing inhibition of cerebral cytochrome oxidase activity and decreased protein synthesis in mouse brain	Savolainen 1980,1982[NEG74, NEG75]
140 (100)		3 h/day, 5 days	Increased level of L-glutamate in hippocampus of rats	Nicholson 1998[NEG58]
280 (200)		4 h	Detectable histologic lesions in nasal epithelium of rats	Lopez 1988[NEG50]
280 (200)		4 h	Increase protein and lactate dehydrogenase in lavage fluids from rat lung	Green 1991[NEG19]
280-560 (200-400)	70 (50)	4 h	Particle-induced oxygen consumption reduced in pulmonary alveolar macrophages from rats	Khan 1991[NEG41]
420 (300)		4 h	Marked abnormality in surfactant activity in lavage fluids from rat lungs	Green 1991[NEG19]
459 (335)		6 h	LC_{50} and pulmonary oedema in rats	Prior 1988[NEG67]
560 (400)		4 h	Transient increase in protein concentration and activity of lactate dehydrogenase in nasal lavage fluids or rats	Lopez 1987[NEG49]
615 (439)		4 h	Transient necrosis and exfoliation of nasal respiratory and olfactory mucosal cells in rat. Reversible pulmonary oedema	Lopez 1988[NEG48]
622 (444)		4 h	LC_{50} for rats	Tansy 1981[NEG81]
701 (501)		4 h	LC_{50} and pulmonary oedema in rats	Prior 1988[NEG67]
> 700 (>500)		4 h	Lethal for rats	Khan 1990[NEG40]
822 (587)		2 h	LC_{50} and pulmonary oedema in rats	Prior 1988[NEG67]
2317 (1655)		5 min	Pulmonary oedema and death in rats	Lopez 1989[NEG51]

3.2.4 *Toxicity due to long-term exposure and carcinogenicity*

Summary of the data in Arbete och Halsa 2001:14

No data were available concerning the carcinogenic effects of H_2S.

Additional information

No new data were found.

3.2.5 *Genotoxicity*

Summary of the data in Arbete och Halsa 2001:14

No genotoxic effects were demonstrated at non-cytotoxic concentrations (Beauchamp 1984, Reiffenstein 1992).[NEG5, NEG68]

Additional information

No new data were found.

3.2.6 *Reproduction toxicity*

Summary of the data in Arbete och Halsa 2001:14

Effects of H_2S on amino acid neurotransmitter levels in the developing rat brain (cerebellum) were reported at 20 and 75 ppm (28 and 102 mg/m^3). Affected were the levels of aspartate, glutamate and GABA (gamma aminobutyric acid) (at 75 ppm), and serotonin and noradrenaline (at 20 ppm) (Hannah 1989).[NEG25] Neuropathological alterations of the purkinje cells in rat offspring were found at 20 ppm (28 mg/m^3) (Skrajny 1992).[NEG77]

Dorman et al (2000)[NEG17] examined wether perinatal exposure to H_2S had an adverse effect on pregnancy outcome, offspring prenatal ad postnatal development or offspring behaviour. Male and female Sprague Dawley rats (12/sex/concentration) were exposed to H_2S (0, 10, 30, 80 ppm), 6 h/day, 7 days/week. The exposure of the female rats started two weeks prior to breeding and the females were additionally exposed during the 2-week mating period, and then from gestation day 0 to 19. Exposure of the dams and their pups resumed from postnatal day 5 and 18. Adult males were exposed 70 consecutive days starting two weeks before mating. The test protocol was, to the extent possible,

similar to the OECD screening test for reproductive and developmental toxicity (OECD guideline 421).

A statistically significant decrease in feed consumption was observed in F_0 male rats from the 80 ppm exposure group during the first week of exposure. There were no effects on the reproductive performance (number of females with live pups, litter size, average length of gestation, and the average number of implants per pregnant female). Exposure to H_2S did not affect pup growth, development, performance of any of the behavioral tests.

Studies are summarised in table 4.

Table 4 Summary of dose-effect data of hydrogen sulphide from reproductive and developmental studies in rats.

Exposure mg/m^3(ppm)	Duration of exposure	Effects	Reference
28 (20)	7 h/day during pregnancy until 21 days postnatal	Severe alternations in the architecture and growth characteristics of the purkinje cell dendritic fields of the rat offspring	Hannah 1991[NEG26]
28 and 98 (20 and 70)	7h/day during pregnancy until 21 days postnatal	Altered levels of serotonin (5-HT) and norepinephrine in the developing rat cerebellum and frontal cortex	Skrajny, 1992[NEG77]
105 (75)	7h/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.	Hannah, 1989[NEG25]
112 (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	Dorman 2000[NEG17]

Additional information

No new data were found.

3.2.7 *Conclusion*

DECOS concludes from the studies of Dorman (2004)[7], Brenneman (2000)[NEG13] and Moulin (2002)[18] that 10 ppm (14 mg/m^3) can be considered a NOAEL for effects on the nasal mucosa. No effects on reproduction and development were apparent.

Hoofdstuk **4**

Existing Guidelines, standards and evaluations

4.1 Working populations

Table 5 Occupational standards in various Countries (adapted from Arbete och Hälsa) and updated

Country	mg/m^3	Ppm	Comments	Year
Denmark	15	10		2000
Finland	14	10		1998
	21	15	15 min	1998
Germany	14	10		2000
Iceland	14	10		1999
	20	15	Ceiling value	
Netherlands	15	10		2001
Norway	15	10	Ceiling value	2000
Sweden	14	10		2000
	20	15	Ceiling value	2000
United Kingdom	7	5	8 hours	2002
	15	10	15 minutes	
USA (ACGIH)	15	10		2001
	1.4	1	8 hours	2004 (Draft proposal)
	7.0	5	15 min	2000
NIOSH	15	10	ceiling value	2000
OSHA		20	ceiling value	2000
		50	10 min max peak	

Hoofdstuk **5**

Hazard Assessment

There is limited information on the acute effects of exposure to hydrogen sulphide in man. Only a few cases have been described in which (single) exposure to high concentrations (1400 mg/m^3 and higher) causes breathing stops (ACGIH, 1991).[NEG1]

Based on the outcome of a number of new case reports unpredictable high peak exposures to H_2S (> 500 ppm, 700 mg/m^3), however, remain the greatest hazard associated with H_2S.[4,11,19,23] One study has been described in which asthmatics, exposed to 2.8 mg/m^3 (2 ppm) for 30 minutes, showed no statistically significant respiratory effects (Jäppinen et al, 1990).[NEG36] Studies with healthy volunteers, exposed to 14 mg/m^3 (10 ppm) H_2S for 15 minutes, showed no significant changes in routine pulmonary functions variables (Bhambhani et al, 1996).[NEG9] Exposure of volunteers to 7 mg/m^3 (> 16 min) increased the blood lactate levels during exercise (Bhambhani et al 1991)[NEG12] and exposure to 14 mg/m^3 (2 times 30 minutes) increased the oxygen uptake during exercise (Bhambhani et al, 1997).[NEG8] However, the relevance of these latter studies of Bhambhani et al [NEG8] for the occupational setting is limited as the subjects were only inhalatory exposed through the mouth.

Acute or short term exposure to H_2S in experimental animals resulted in inhibition of cytochrome oxidase in rats lung cells (4 hours exposure, NOAEL is 15 mg/m^3) (Khan et al, 1990)[NEG40], local irritation of eyes and throat (IPCS 1981; Lopez,1988)[NEG32, NEG50], and at higher concentrations (466 mg/m^3) death and

pulmonary oedema after several hours of exposure (Tansy, 1981; Prior, 1988, Khan, 1990).[NEG81, NEG67, NEG40]

The committee is of the opinion that the data concerning acute of short term exposure show that a short term exposure limit is not indicated.

There is limited information concerning the health effects after prolonged exposure to H_2S in humans. In general, the exposure assessments are either lacking or weak in the human studies. Eye irritation has been reported after exposure to 1-5.6 mg/m^3 (0.7-4 ppm) H_2S in viscose rayon workers (Vanhoorne et al, 1995).[NEG86] However, eye irritation at this exposure levels seemed to result from combined exposure, in particular with CS_2 (at least 26 mg/m^3) and a NOAEL could not be determined. There are no data concerning the effects of H_2S alone at exposure levels below 28 mg/m^3 (20 ppm). At exposure levels above 28 mg/m^3 (20 ppm) ocular effects became more serious (Masure 1950, Ammann 1986).[NEG53, NEG2] Regarding the irritation, the committee concluded that the results from epidemiological studies are difficult to interpret as exposure to H_2S is often accompanied by exposure to other toxic agents (CS_2 or acids). These agents might reduce the corneal threshold for irritation. Finally, one epidemiological study found effects on reproduction (increased spontaneous abortion) in women exposed to petrochemicals, including H_2S. However, these (limited) data are difficult to interpret due to the simultaneous exposure to CS_2, a known teratogen.

In rats, subchronic exposure to H_2S causes nasal lesions (olfactory neuron loss and basal cell hyperplasia) and bronchial epithelial hypertrophy and hyperplasia (Brenneman 2000, Moulin 2002, Dorman 2004).[NEG13, 7,18] The NOAEL for this effect was 14 mg/m^3.

No data are available concerning the carcinogenic effects of H_2S.

No effects on reproduction and development were reported in rats exposed to H_2S (14, 42 and 112 mg/m^3) during mating, gestation and lactation (Dorman et al, 2000).[NEG17] In the same study no effects on growth, development and behavior of the pups were found. No gross or microscopic abnormalities were observed in the central nervous system of the offspring. In the studies from Hannah et al (1989 and 1991)[NEG25, NEG26] and Skrajny et al (1992)[NEG77], slight neurological effects on offspring were found at levels of 20 ppm (7 h/day during pregnancy until 21 days postnatal) and higher.

DECOS is of the opinion that the nasal lesions found in rats after exposure to H_2S are the critical effect. In deriving a health based recommended occupational exposure limit (HBROEL), the committee takes the NOAEL of 14 mg/m^3

(10 ppm) found in the studies of Dorman (2004)[7], Brenneman (2000)[NEG13] and Moulin (2002)[18] as a starting point. For the establishment of the HBROEL, several aspects have to considered. On the one hand, the committee finds an extrapolation factor to compensate for the differences between rats and humans unnecessary, as the critical effects found are local (non systemic) effects and rats are predominantly nose breathers which might lead to higher local (nasal) concentrations. On the other hand, the committee considers it necessary to compensate for differences in exposure pattern in the experimental setting (subchronic) and occupational setting (chronic) and for the limited dataset concerning the pathological effects. For these aspects together, the committee proposes a factor of 2, Moreover, differences among people should be taken into account. Therefore, the committee uses a factor of 3 to compensate for the inter-individual differences.

Considering all these aspects, starting from a NOAEL of 14 mg/m^3 and using an extrapolation factor of 6, the committee recommends an HBROEL twa 8 hours for H_2S of 2.3 mg/m^3 (~1.6 ppm).

5.1 Groups at extra risk

Asthmatic persons could be susceptible at levels as low as 2 ppm (2.8 mg/m^3) (Jappinen, 1990).[NEG36]

Results from a epidemiological study suggests that pregnant women might have an increased risk of spontaneous abortion (Xu, 1998).[NEG94]

5.2 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards (DECOS) recommends a health based occupational exposure limit for H_2S of 2.3 mg/m^3 (1.6 ppm) as an eight hours TWA.

5.3 Recommendations for research

The committee recommends more research on the neurological effects after long-term exposure.

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Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The committee

- GJ Mulder, *chairman*
  emeritus professor of toxicology, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- LJNGM Bloemen
  epidemiologist; Exponent Inc., Terneuzen
- PJ Boogaard
  toxicologist; SHELL International BV, The Hague
- PJ Borm
  toxicologist; Centre of Expertise in Life Sciences, Hogeschool Zuyd, Heerlen
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  professor of risk assessment in occupational epidemiology; IRAS, University of Utrecht, Utrecht
- TM Pal
  occupational physician; Dutch Centre for Occupational Diseases, Amsterdam
- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.
- H Roelfzema, *advisor*
  ministery of Health, Welfare and Sport, The Hague

- T Smid
  occupational hygienist/epidemiologist; KLM Health Safety & Environment, Schiphol; and, professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Dow Chemical Company, the Netherlands
- RA Woutersen
  toxicologic pathologist; TNO Quality of Life, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex C

Comments on the public review draft

A draft of the present report was released 2005 for public review. The following organisations and persons have commented on the draft document:

- H Fergusson, Health and Safety Executive (HSE), United Kingdom
- R Zumwalde, National Institute for Occupational Safety and Health (NIOSH), USA
- Urbanus, Concawe, Brussels
- A Aalto, Ministry of Social Affairs and Health, Finland
- E González-Hernández, Ministerio de Trabajo y Asuntos Sociales, Spain

Arbete och Hälsa: Hydrogen sulphide

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards

2001:14

Kristin Svendsen

NR 2001:14

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards

127. Hydrogen sulphide

Kristin Svendsen

Nordic Council of Ministers

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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.

We acknowledge the Nordic Council for its financial support of this project.

G.J. Mulder
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

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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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