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Hydrogen Sulphide

Toxicological Overview

Key Points

Kinetics and metabolism

- hydrogen sulphide is a gas that is rapidly absorbed by the lungs into the bloodstream
- it is widely distributed throughout the body
- metabolism of hydrogen sulphide occurs by oxidation, methylation or reaction with metalloproteins; the principal product is sulphate
- hydrogen sulphide is excreted rapidly from the body in the form of sulphate in urine

Health effects of acute exposure

- the major route of exposure is by inhalation
- acute inhalation exposure to high concentrations may result in collapse, respiratory paralysis, cyanosis, convulsions, coma, cardiac arrhythmias and death within minutes
- exposure to low concentrations may irritate the eyes and respiratory tract, resulting in sore throat, cough and dyspnoea
- following acute ocular exposure to high concentrations, irritation, with keratoconjunctivitis, punctate corneal erosion, blepharospasm, lacrimation and photophobia may occur

Health effects of chronic exposure

- limited data suggest that effects from repeated exposure are similar to those for acute exposure, with respiratory, neurological and ocular effects at high concentrations
- There are limited data available on the reproductive and developmental effects of hydrogen sulphide

PHE publications gateway number: 2014790

Published: November 2016

Summary of Health Effects

Hydrogen sulphide is a gas and, therefore, inhalation is the most relevant route of exposure to humans.

Acute inhalation exposure to low concentrations of hydrogen sulphide will irritate the eyes and respiratory tract, resulting in sore throat, cough and dyspnoea. Acute exposure to high concentrations of hydrogen sulphide results in collapse (“knockdown”), respiratory paralysis, cyanosis, convulsions, coma, cardiac arrhythmias and death within minutes. Other health effects have been reported, the most sensitive being on the respiratory, neurological and ocular systems.

Data on chronic exposure to hydrogen sulphide in humans are largely from “polluted communities” and from occupational exposure. The reported features include respiratory, ocular and neurologic effects. There is some limited evidence to suggest an association with spontaneous abortions, but the effects seen were often not significant and confounded by exposure to other chemicals, therefore no conclusions can be drawn.

Studies in experimental animals exposed to high concentrations of hydrogen sulphide via inhalation have resulted in respiratory and cardiovascular effects. The most sensitive target organ in animals following acute inhalation exposure is the respiratory tract. Following chronic exposure to hydrogen sulphide, histopathological changes to the nasal epithelium are seen in rodents.

There are inadequate data on the carcinogenicity of hydrogen sulphide in humans or experimental animals. Hydrogen sulphide is not listed as a carcinogen by the International Agency for Research on Cancer (IARC).

Kinetics and Metabolism

Hydrogen sulphide is produced endogenously in humans from the metabolism of sulphydryl containing amino acids, e.g. cysteine, by bacterium in the intestinal tract and mouth [1]. It can compose up to 10% of intestinal gasses [2]. It is also produced enzymatically in the brain and smooth muscle [1]. At normal levels in the human body hydrogen sulphide acts as a “gasotransmitter”; it has been shown to be involved in the regulation of a number of physiological functions including vasodilation and vasorelaxation, and neuromodulation [2].

Exogenous hydrogen sulphide is absorbed rapidly through the respiratory tract, into the bloodstream and is subsequently distributed throughout the body (partially dissociated as HS-) [1-3]. It is distributed to the brain, liver, kidney, pancreas and small intestine; the brainstem has the greatest net uptake following exposure [3]. Hydrogen sulphide is rapidly metabolised and excreted, therefore storage in the body is limited [2].

Metabolism of hydrogen sulphide occurs via three pathways: oxidation, methylation and reaction with metalloproteins or disulphide-containing proteins. The major detoxification pathway for hydrogen sulphide in humans is via oxidation in the liver to form thiosulphate, which is further metabolised to sulphate [1].

Hydrogen sulphide is rapidly eliminated from the body in the form of sulphate (free sulphate or thiosulphate) in urine[2]. It may also be excreted unchanged in exhaled air and, in faeces and flatus [1].

Mechanism

Hydrogen sulphides mechanism of action is thought to be the direct inhibition of cellular enzymes, such as cytochrome *c* oxidase, which is involved in cellular oxidative processes and energy production. Such enzyme inhibition leads to disruption of the electron transport chain and impairs oxidative metabolism, leading to anaerobic metabolism, decreased ATP production and generation of lactic acid [1, 2]. The nervous and cardiac tissues are most sensitive to the disruption of oxidative metabolism [2].

Sources and Route of Human Exposure

Hydrogen sulphide is produced from both natural and anthropogenic processes, the former accounting for 90% of total emissions. It is a component of the natural sulphur cycle; bacteria, fungi and actinomycetes release hydrogen sulphide during the decomposition of sulphur containing proteins. Raised levels have been observed in areas with active biological decomposition, such as in pig barns and some coastal areas [2]. Other natural sources include sulphur springs and lakes, and geothermally active areas including volcanoes [4].

In industry, hydrogen sulphide is manufactured by one of two routes; recovery from gas mixtures or by chemical reaction [2]. It is also produced as a by-product in a number of industries including the production of coke from sulphur-containing coal, the refining of some crude oils and the production of wood pulp [5]. Hydrogen sulphide is used in adsorbents, metal surface treatment products, laboratory chemicals, semiconductors and as an intermediate in the production of other chemicals. It is also used to manufacture food products, rubber products, fabricated metal products and electrical equipment [6].

As hydrogen sulphide is a gas at atmospheric pressure, it is most likely to partition to the air following environmental release [2].. In the atmosphere hydrogen sulphide may be degraded though oxidation by oxygen and ozone, or it may undergo photochemical reaction with hydroxyl radicals. The lifetime of hydrogen sulphide in air has been estimated to range from 1 day in the summer to 42 days during the winter months [2].

Hydrogen sulphide is readily soluble in water and has been shown to sorb to some soils. Biodegradation of hydrogen sulphide occurs in soil and water; it may be oxidised to form elemental sulphur. The half-life of hydrogen sulphide in these environments has been estimated to be between one to several hours [2].

Hydrogen sulphide is ubiquitous in the atmosphere and as such, inhalation is likely to be the main route of exposure for the general public (besides endogenous production). Populations living close to natural or anthropogenic sources of emission (such as those described above) may be exposed to higher levels [2]. There are limited up to date data on the levels of hydrogen sulphide in air.

The World Health Organization (WHO) has not set a health-based guideline value for hydrogen sulphide in drinking water. The taste and odour (i.e. “rotten eggs”) of hydrogen sulphide in drinking water is thought to be easily detectable by most people; therefore consumption of amounts sufficient to cause harm is not thought to be a likely occurrence [4].

Higher levels of exposure may also occur in occupations where it is produced, used or generated such as petroleum refineries and offshore oil facilities [2]. Workplace exposure limits (WELs) are enforced to protect workers from the harmful effects of hydrogen sulphide; in the UK the long-term WEL is 7 mg/m^3 (5 ppm) and the short-term WEL is 14 mg/m^3 (10 ppm) [7].

Health Effects of Acute/Single Exposure

Human data

Inhalation

The respiratory tract and the nervous system are the main targets for the acute toxicity of hydrogen sulphide.

Exposure to low concentrations of hydrogen sulphide will irritate the eyes and respiratory tract, resulting in sore throat, cough and dyspnoea [2, 5]. Reliable data report irritant effects from hydrogen sulphide exposure above 28 mg/m^3 (20 ppm); however effects cannot be ruled out at lower exposure levels [3]. Prolonged exposure may also cause rhinitis, pharyngitis and bronchitis [5].

A range of neurological effects have been observed following exposure to hydrogen sulphide, these include nausea, headache, delirium, dizziness, drowsiness, disturbed equilibrium and reaction time, vertigo, effects on vision and verbal recall, poor memory, insomnia, neurobehavioral changes, olfactory paralysis, loss of consciousness and tremors [1, 2, 5].

A number of other systemic effects may follow inhalation of hydrogen sulphide, including vomiting, diarrhoea, muscular weakness, tachycardia and hypotension.

Exposure to high concentrations of hydrogen sulphide can cause collapse, respiratory paralysis, cyanosis, convulsions, coma, cardiac arrhythmias and death within minutes. Respiratory failure or arrest appeared to be the cause of death in a number of cases following a large single exposure [1, 2]. Exposure to concentrations of about 700 mg/m^3 (500 ppm) hydrogen sulphide and above may be fatal; 1112 mg/m^3 (800 ppm) is regarded as the lethal concentration for 50% of an exposed human population for an exposure period of 5 minutes (LC_{50}) [8].

The odour threshold for hydrogen sulphide is approximately 0.011 mg/m^3 (0.008 ppm), however at concentrations greater than 140 mg/m^3 (100 ppm) olfactory paralysis can occur. The loss of odour perception makes hydrogen sulphide especially dangerous [1].

A number of case reports describe individuals abruptly collapsing and becoming unconscious following only a few breaths of hydrogen sulphide, an effect described as “knockdown”. In some cases individuals appear to make a rapid and complete recovery where exposure is promptly terminated [2, 9].

In a human volunteer study, no adverse cardiovascular effects were seen in healthy individuals exposed to 7 or 14 mg/m^3 (5 and 10 ppm) hydrogen sulphide during 30 minutes of submaximal exercise, nor were any changes seen in pulmonary function tests in a separate study when healthy volunteers were exposed to 14 mg/m^3 (10 ppm) for 15 minutes. However, asthmatics were potentially more sensitive, with 2 out of 10 showing evidence of bronchoconstriction and 3 complaining of headache after exposure to 2.8 mg/m^3 (2 ppm)

hydrogen sulphide [1]. A rise in blood lactate has been observed in volunteers exposed to 7 mg/m^3 (5 ppm) hydrogen sulphide for over 16 minutes and in a separate study at 14 mg/m^3 (10 ppm, duration not specified) [3].

Dermal/ocular exposure

Acute exposure of six men to an estimated concentration of 11-22 mg/m^3 (8-16 ppm) hydrogen sulphide resulted in facial peeling in one of the men [2].

Hydrogen sulphide gas is irritating to the eye. Keratoconjunctivitis, punctate corneal erosion, blepharospasm, lacrimation, and photophobia has been observed in individuals exposed briefly to high concentrations (concentration not specified) [1, 2]. A study on workers exposed to hydrogen sulphide at concentrations of 15-29 mg/m^3 (11-21 ppm) for 6-7 hours reported eye irritation while another reported severe damage to eye tissues following exposure to concentrations of >70 mg/m^3 (50 ppm) for 1 hour or more [1].

Hydrogen sulphide gas stored under pressure as a compressed liquid expands rapidly on liberation, resulting in vaporisation and a large endothermic reaction. The result may be evaporative freezing of any tissue in contact with the liquid.

Delayed effects following acute exposure

Following exposure to hydrogen sulphide, a range of delayed neurological sequelae have been observed; some features have taken months to years to resolve while others have been permanent. A number of persistent features include psychomotor slowing, effects on balance and reaction time, extrapyramidal signs, ataxia, psychosis and deficits in learning and executive functioning (including concentration and attention span) [2, 5].

Following acute exposure, respiratory symptoms typically subside within a matter of weeks; although symptoms have persisted for months in some cases [2].

Animal and in-vitro data

Inhalation

Observations in experimental animals exposed to acute high levels of hydrogen sulphide are similar to those seen in humans. A range of lethal concentrations for hydrogen sulphide has been reported in the literature, varying with species, strain and study [1, 2].

Damage (necrosis and cell exfoliation) of the nasal epithelium in rats was observed following exposures to 400 ppm (560 mg/m^3) for 4 hours or 200 ppm (280 mg/m^3) for 3 hours [2].

Mild perivascular oedema was observed in rats exposed to 116 mg/m^3 hydrogen sulphide, whereas pulmonary oedema was evident at higher concentrations, as well as effects on the bronchiolar epithelium and alveoli and a decrease in the number of viable pulmonary alveolar macrophage cells. Pulmonary oedema, increasing in severity with dose was observed in rats following exposure to over 105 mg/m^3 (75 ppm) hydrogen sulphide for 1 to 4 hours [2].

Decreased heart rate and slight pulmonary congestion were reported in male Wistar rats exposed to 0 or 105 mg/m^3 (75 ppm) hydrogen sulphide for 1 hour. Wistar rats (sex not specified) exposed to 140-279 mg/m^3 (100-200 ppm) for 1 hour showed increased heart and respiratory rates, as well as changes in a number of histological and biochemical parameters in the respiratory tissues and fluids [1, 2].

Neurological effects are seen in rats exposed to hydrogen sulphide, with severity of features increasing with dose; observed effects include lethargy, fatigue, dizziness, neurochemical changes, neurological function, neuropathy, changes in absolute brain weight and unconsciousness. Rabbits and rats (sex and strain not specified) exposed to 100 mg/m^3 (72 ppm) hydrogen sulphide for 1.5 hours or 1115 mg/m^3 (800 ppm) for 20 minutes were found to lose consciousness [2].

Dermal/ocular exposure

F344 rats (sex not specified) were exposed to 0, 279 or 558 mg/m^3 (0, 200 and 400 ppm) hydrogen sulphide for 4 hours. Epiphora (watery eyes) was observed in rats exposed to the highest concentration [2].

Health Effects of Chronic/Repeated Exposure

Human data

Inhalation

Studies measuring changes in atmospheric levels of hydrogen sulphide, those studying "polluted communities" and occupational exposure have shown associations between increased levels of hydrogen sulphide in air and respiratory symptoms (including nasal irritation, cough, shortness of breath, worsening of asthma and changes in lung function); however interpretation of these studies is complicated by numerous confounders [2].

Studies of workers chronically exposed to hydrogen sulphide report increased eye complaints, fatigue, poor memory, dizziness and irritability; however it is not clear if these symptoms are the result of chronic exposure or recurring acute exposures [1]. Other, subclinical neurological effects have been observed in patients chronically exposed to hydrogen sulphide; these include effects on balance, reaction time, verbal recall and memory [2].

Studies of communities exposed to higher levels of hydrogen sulphide (e.g. populations located near certain industrial sites) have reported increased incidences of fatigue, irritability, headaches, poor memory, stress and nausea; however such studies have a number of limitations including limited monitoring data, exposure to other chemicals and limited control for confounders [2].

Genotoxicity

No data could be located regarding genotoxicity in humans following chronic exposure to hydrogen sulphide.

Carcinogenicity

There are limited data available to assess the carcinogenicity of hydrogen sulphide. No increase in cancer incidence was reported in a residential cohort study of individuals living downwind of a natural gas refinery [2].

Reproductive and developmental toxicity

There are limited data available on the reproductive and developmental effects of hydrogen sulphide.

Two studies (detailed below) suggest a link between chronic occupational exposure and an increased risk of spontaneous abortions [10].

A Finish retrospective registry-based study examined birth outcomes for women employed in different industries. A non-statistically significant ($p<0.10$) increase in the rate of spontaneous abortions was shown for women who were employed to work with rayon textile or paper products and amongst those whose husbands were in similar occupations; against

the general finish population. The study also considered environmental exposure by residential area. Women living in areas with mean annual hydrogen sulphide concentrations exceeding 4 µg/m^3 (0.03 ppm) were found to have a non-statistically significant rise in the incidence of spontaneous abortions compared those women living in areas with mean annual concentrations below 4 µg/m^3 [2].

In another study, a statistically significant increase in the risk of spontaneous abortion was found amongst female employees exposed to petrochemicals and specifically hydrogen sulphide (levels not given), compared to unexposed women. As with the previous study, there were a number of confounders that were not accounted for, including information on length of exposure and additional workplace exposure to other chemicals [10].

Animal and in-vitro data

Inhalation

There are numerous studies documenting the effects of hydrogen sulphide on the respiratory and neurological systems of experimental animals following repeat or chronic low level exposure. The most sensitive tissue in rodents appears to be the nasal epithelium. Loss of olfactory neurones and basal cell hyperplasia were observed in rats following exposure to 42 mg/m^3 (30 ppm) and higher for 6 hours a day, 7 days a week for 10 weeks; at higher doses the severity of the basal cell hyperplasia decreased with increasing dose of hydrogen sulphide. Damage to the nasal epithelium was observed in rats following exposure to 112 mg/m^3 (80 ppm) for 3 hours a day, for 5 days [2].

A 5% decrease in absolute brain weight was observed in rats exposed to 112 mg/m^3 (80 ppm) but not 42 mg/m^3 (30 ppm) hydrogen sulphide for 6 hours a day 5 days a week for 13 weeks; although no changes in histopathological or neurological function were observed, a result mirrored in studies on other rat strains and mice [2].

One 90 day repeat dose toxicity study in rats and mice was conducted to modern protocol, conforming to Good Laboratory Practice principle. Male and female F344 rats, Sprague-Dawley rats or B6C3F1 mice were exposed via inhalation to hydrogen sulphide at time-weighted average concentrations of 0, 14, 42 or 112 mg/m^3 (0, 10, 30 and 80 ppm) for 6 hours/day, 5 days/week for 90 days. No treatment-related changes in histopathological or haematological parameters were observed nor were any changes in renal function. A significant decrease in body weight was evident in the Sprague-Dawley rats and B6C3F1 mice exposed to the highest concentration of hydrogen sulphide whereas no changes were noted in F344 rats. Absolute brain weights were decreased in male Sprague-Dawley rats exposed to the highest concentration of hydrogen sulphide, but there was no change to neurological function or neuropathology. Similarly, neurological function and neuropathology was not altered in F344 rats or B6C3F1 mice. The only effect observed at autopsy in the mice was minimal to mild irritation of the nasal mucosa at the highest dose. No pathological effects were seen at any exposure level in the rat [2].

Male Sprague-Dawley rats exposed to 0 or 70 mg/m^3 (0 and 50 ppm) did not exhibit any neurotoxic effects [2].

Guinea pigs (strain and sex not specified) were exposed daily to 0 or 28 mg/m^3 hydrogen sulphide (0 and 20 ppm) for 1 hour/day for 11 days. Fatigue, somnolence and dizziness were reported, with decreased cerebral hemisphere and brain stem total lipids and phospholipids at autopsy [2].

Ingestion

There were limited data available on the ingestion of hydrogen sulphide in animals.

Pigs (strain and sex not specified) were fed hydrogen sulphide at a dose of 0 or 6.7 mg/kg bw/day for 105 days. Body weight gain was decreased in treated animals compared to controls [2].

Adult pigs (strain and sex not specified) were fed hydrogen sulphide at a dose of 15 mg/kg bw/day for a few days. Diarrhoeic digestive disorder was observed. In a repeat study using younger pigs that weighed less, no diarrhoeic disorder was noted [2].

Ocular/dermal

Eye irritation was observed in guinea pigs exposed 1 hour a day for 20 days to 28 mg/m^3 (20 ppm) hydrogen sulphide [2].

Genotoxicity

Hydrogen sulphide gas was not mutagenic in the Ames test employing Salmonella typhimurium strains TA97, TA98 or TA100, with or without a metabolic activation systems [1, 2].

Carcinogenicity

No data could be located regarding the carcinogenicity of hydrogen sulphide in experimental animals.

Reproductive and developmental toxicity

Female Sprague-Dawley rats were exposed to hydrogen sulphide concentrations of 0, 14, 42 or 112 mg/m^3 (0, 10, 30 and 80 ppm) for 6 hours/day, 7 days/week for 2 weeks prior to, and during the 2 week mating period, and on gestational days 0-19. The male animals were exposed to similar levels for 70 days up to and including the mating period. No significant changes in gestation length, fertility, number of females with live pups, litter size or number of implants per female were observed. Furthermore, sperm count and morphology were not altered in the exposed males during this study. No significant alterations in the incidence of structural anomalies were found in the offspring. Continued exposure of offspring on postnatal days 5-18 did not show any developmental delays, performance on developmental neurobehavioral tests or brain histopathology [2].

Sprague-Dawley rat dams were exposed to hydrogen sulphide concentrations of 0, 28, 70 or 110 mg/m^3 (0, 20, 50 and 75 ppm) for 7 hours a day from gestation day 1 through to postnatal day 21. A significant decrease in time for pinna detachment and hair growth was

reported in the offspring, but no other changes in developmental landmarks including incisor eruption, eyelid opening and surface righting, were noted [1, 2].

Pregnant Sprague-Dawley rats were exposed to 0, 140 or 210 mg/m^3 hydrogen sulphide (0, 100 and 150 ppm) on gestation days 6-20. No external fetal abnormalities were noted, but a significant decrease in fetal body weight (4% over controls) was observed at the highest concentration [1, 2].

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This document from the PHE Centre for Radiation, Chemical and Environmental Hazards reflects understanding and evaluation of the current scientific evidence as presented and referenced here.

First published: December 2016

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