Hydrogen Sulfide

99

Aaron Skolnik and C. William Heise

Contents

Biochemistry and Clinical Pharmacology 1964

Pathophysiology of Toxic Effects 1965

Clinical Presentation and Life-Threatening Complications 1965
Ocular Effects 1966
Knockdown Effects 1966
Pulmonary Effects 1966
Cardiovascular Effects 1966
Neurologic Effects 1966
Metabolic Acidosis 1967
Death 1967

Diagnosis 1967

Treatment 1967
Methemoglobin Induction 1968
Hydroxocobalamin and Cobinamide 1968
Hyperbaric Oxygen 1968
Prehospital Treatment 1969
Prevention 1969

References 1970

Hydrogen sulfide (H_2S), cyanide, azide, and carbon monoxide are collectively referred to as *cellular asphyxiants* or *chemical asphyxiants* because of their ability to disrupt aerobic cellular respiration. Exposure to H_2S is associated with a "knockdown" effect and may be rapidly fatal. The American Association of Poison Control Centers reported 766 H_2S exposures in 2013, with 327 treated in a healthcare facility and 10 deaths [1]. Hydrogen sulfide is the second most common cause of fatal gas inhalation in the workplace [2]. Olfactory fatigue to the smell of H_2S occurs quickly and has led to fatal poisoning of rescuers on multiple occasions [3, 4].

Hydrogen sulfide is known as "sewer gas" and is naturally produced by the putrefaction of organic substances such as sewage, manure, offal, and fish in ships' holding tanks. Decomposition of sulfur-containing proteins by bacteria produces H_2S. Hydrogen sulfide gas can therefore be anticipated whenever organic material containing sulfur is in an anaerobic environment.

Major industrial uses for H_2S include production of elemental sulfur, inorganic sulfides, and sulfuric acid. Hydrogen sulfide is also found as an additive in high-pressure lubricants and cutting oils. Hydrogen sulfide is a commonly encountered toxin in several industries including paper making, leather tanning, and most notably, oil and natural gas production. "Sour gas" refers specifically to natural gas that contains significant quantities of hydrogen sulfide; H_2S must be removed from the gas prior to its use as fuel [5].

A. Skolnik (✉)
Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA
e-mail: skolnikab@upmc.edu

C.W. Heise (✉)
Center for Toxicology and Pharmacology Education and Research, University of Arizona College of Medicine Phoenix, Phoenix, AZ, USA

Department of Medical Toxicology, Banner – UMCP, Phoenix, AZ, USA
e-mail: Craig.Heise@bannerhealth.com

J. Brent et al. (eds.), *Critical Care Toxicology*,
DOI 10.1007/978-3-319-17900-1_143

Table 1 Selected natural and industrial sources of hydrogen sulfide

Natural gas wells	Sewers/waste water treatment
Oil wells	Manure pits
Sulfuric acid production	Fish in ship holds
Coke ovens	Undersea vents
Tanneries	Volcanos
Iron smelting	Tar and Asphalt manufacturing
Rayon production	Food processing plants
Kraft paper mills	Chemical refineries

Hydrogen sulfide is also naturally produced and liberated from volcanos and undersea vents. One example occurs in the Puna District on the island of Hawaii, where an active volcano emits H_2S, typically in concentrations of less than 20 parts per billion (ppb) [6]. A similar volcanic off-gassing site exists in the City of Rotorua on the north island of New Zealand [7] (Table 1).

In 2007, the first case of "detergent suicide" was reported in Japan. This method of suicide involves mixing a commercially available, sulfur-containing product with an acidic toilet bowl cleaner to produce hydrogen sulfide gas. Instructions and ingredient lists were published and rapidly popularized through internet message boards. By 2008, an epidemic of detergent suicides was underway in Japan, with nationwide deaths due to hydrogen sulfide poisoning increasing from 27 in 2007 to 1,027 in 2008 [8]. In the United States, hydrogen sulfide suicides increased from 2 in 2008, to 10 in 2009, and 18 in 2010 [9]. Detergent suicides have caused evacuation of commercial and residential buildings; fatalities among family members with secondary exposure have also been reported [8, 10].

Biochemistry and Clinical Pharmacology

Hydrogen sulfide is normally present in small amounts in the human body. As a component of intestinal gas, H_2S has been found in concentrations of 1–4 ppm with some high levels of 18 ppm [11]. Hydrogen sulfide is synthesized in small amounts in neuronal cells and within the cardiovascular system, in addition to being released from intracellular sulfur stores. Recent studies demonstrate many physiological effects of endogenous H_2S, and it has been proposed as the third gasotransmitter, a family of small molecules that participate in cell signaling via diffusion across cell membranes [12].

Hydrogen sulfide appears to be an important vasoactive agent similar to nitric oxide. It has been reported to have an inotropic effect and alter the growth of vascular endothelial cells [13]. There is also a link between H_2S and insulin release [14]. In the CNS, there appear to be physiological roles in GABA and NMDA transmission [15]. Hydrogen sulfide can reduce reactive oxygen species both directly and via increasing glutathione production, protecting neuronal cells from death [16]. Hydrogen sulfide is currently being investigated for neuroprotective, cardioprotective, antioxidant, and anti-inflammatory effects, with several experimental H_2S-donating drugs under study [12]. At higher doses, however, predictable toxic effects of H_2S occur that are discussed in detail below.

Hydrogen sulfide is a colorless gas, slightly heavier than air, with a relative vapor density of 1.19, and is slightly less volatile than water at room temperature. It has a molecular weight of 34.08 g/mol. Hydrogen sulfide has a water solubility (3.2 g/L at 30 °C) between ammonia, which is highly soluble, and chlorine, which has low solubility. Its metabolism is rapid; no bioaccumulation occurs [11]. H_2S smells like rotten eggs. However, olfactory fatigue and the loss of the ability to smell H_2S can occur in seconds. The odor threshold is reported in the range of 1–130 ppb, with olfactory fatigue occurring around 100 ppm [17].

The principle pathway of exposure is via inhalation. It has minimal absorption through the gastrointestinal tract and intact skin. Hydrogen sulfide is highly lipid soluble and rapidly diffuses across cellular membranes. Following human exposure, distribution to tissues is rapid [18].

Hydrogen sulfide is metabolized by three major pathways. The primary metabolic

elimination pathway is via oxidation of sulfide to thiosulfate, which is converted into sulfate, ultimately being excreted in the urine [19]. Hydrogen sulfide is also metabolized by methylation and reactions with metalloproteins or disulfide-containing proteins. Though in vitro studies demonstrated H_2S-induced sulfhemoglobinemia, recent evidence suggests that clinically significant sulfhemoglobinemia does not occur in acute hydrogen sulfide poisoning [20].

Pathophysiology of Toxic Effects

Hydrogen sulfide causes cellular anoxia by the inhibition of mitochondrial cytochrome *c* oxidase. This inhibition results in disruption of the electron transport chain, impairing oxidative metabolism and the resultant production of ATP. Tissues with high metabolic demands (e.g., brain and heart) are therefore especially susceptible [11].

Hydrogen sulfide also may reduce disulfide bridges in proteins, which is thought to be the mechanism of its inhibition of succinate dehydrogenase. Because of its water solubility, H_2S has irritant effects on moist mucous membranes but also may result in distal airway injury if a high respiratory rate is maintained while exposed. Minimal H_2S is excreted via the lungs.

Hydrogen sulfide directly stimulates carotid arterial chemoreceptors, causing an increased respiratory rate. Noncardiogenic pulmonary edema may develop prior to respiratory arrest. Terminal respiratory depression likely results from H_2S being selectively taken up by respiratory center of the brainstem with an end point similar to anoxia. The underlying mechanism is thought to be inhibition of monoamine oxidase [21, 22].

Clinical Presentation and Life-Threatening Complications

Two common adverse effects occur after H_2S poisoning: mucous membrane irritation and systemic toxicity. These occur in a dose–response fashion (Table 2). Hydrogen sulfide reacts with water to form irritating acid sulfides. Mucous membranes are especially susceptible to the effects of H_2S because of their moisture and anatomic proximity to the environment. The irritant effects of H_2S to the face are sensed by the trigeminal nerve and the olfactory nerve detects its odor, although there may be significant overlap between these two domains.

Table 2 Range of toxicity of hydrogen sulfide (Adapted from references [11, 23, 24])

Clinical effect	Concentration (ppm)
Eye irritation	20–100
Olfactory fatigue	100
Respiratory irritation, possible pulmonary edema	50–500
Symptomatic	50 for 0.5 h
Severely toxic	200 for 1 min
Bronchitis, noncardiogenic pulmonary edema	250 for 24–72 h
Coma and death	500–1,000
Fatal	800 – immediate; 600 – 30 min
Immediate collapse	700–1,000

Membrane irritation begins to occur with H_2S exposures in the range of 2–5 ppm. Mild nausea, vomiting, and lacrimation tend to occur in the range of 80–100 ppm. Higher concentrations, in the range of 500 ppm, typically are required to cause immediate respiratory symptoms. Obvious signs of systemic toxicity tend not to occur until H_2S concentrations of approximately 250 ppm have been attained. Findings at these concentrations may include cough, tachypnea, chest pain, headache, dizziness, lethargy, and confusion. At still higher concentrations, seizures and coma occur. Concentrations of 1,000 to 3,000 ppm were fatal to dogs; death occurred within 15–20 min at 1,000 ppm. At the higher concentration, respiration ceased after a few breaths [21]. The most common clinical findings after H_2S exposures are headache, nausea, vomiting, dyspnea, disequilibrium, conjunctivitis, sore throat, and unconsciousness [25]. A toxidrome for hydrogen sulfide poisoning has been proposed by Guidotti, consisting of any one or combination of the following effects:

- Odor perception (followed by olfactory paralysis)
- Conjunctivitis
- Pulmonary edema
- Acute central neurotoxicity ("knockdown") [2].

Ocular Effects

The eyes react first to the irritant effects of H_2S. As levels increase, the conjunctivae may become inflamed and swollen. After major exposures, the cornea may develop erosions and ulcerations. Associated signs and symptoms include photophobia, lacrimation, and pain. Because both the cornea and the conjunctivae are affected, the term *keratoconjunctivitis* is used to describe the eye effects. This is known in industry as "gas eye." Visual impairment lasting for days has been reported. The possibility of permanent blindness after hydrogen sulfide exposure remains controversial [26].

Knockdown Effects

Hydrogen sulfide is known for its rapid "knockdown" capability. At ambient concentrations of 700–1,000 ppm H_2S, exposed persons may suddenly collapse. If the exposure is terminated promptly, this situation may result in no residual effects [27]. Frequently, workers in the oil fields report this effect; after recovering, they resume their work [5]. If exposure is not terminated, respiratory arrest may occur rapidly.

Pulmonary Effects

Inhaled irritants tend to increase the respiratory rate and decrease the minute volume. Hydrogen sulfide directly produces an increase in ventilation mediated by carotid arterial chemoreceptors at doses below those sufficient to cause central apnea [28]. Significant H_2S exposure may result in redness, inflammation, sloughing, or exfoliation of the airways as H_2S reacts with the moisture of the mucosal surfaces. Hemorrhagic bronchitis has been reported and may require ventilatory support [29].

Due to the moderate water solubility of H_2S, the gas can penetrate the deep airways of the lung and injure alveoli, causing pulmonary edema. The prevalence of pulmonary edema in H_2S-poisoned patients reaching the emergency department has been reported from 4% to 20% [2, 27]. Pulmonary edema appears to make a small contribution to mortality in H_2S poisoning, presumably because respiratory arrest occurs so rapidly in those severely poisoned. Cases of interstitial pulmonary fibrosis following hydrogen sulfide poisoning have also been reported, but appear to be exceptionally rare [30].

Cardiovascular Effects

Typical and atypical chest pain, dysrhythmias, and acute myocardial infarction with heart failure are reported after H_2S exposure [31]. Cardiovascular effects are most likely due to cellular anoxia, rather than direct toxic effects of H_2S on cardiac myocytes. In fact, recent literature describes *protective* effects of low levels of H_2S against myocardial ischemia/reperfusion injury, infarction, and cardiac dysrhythmias in animal and in vitro models [32, 33].

Neurologic Effects

Early-onset neurologic symptoms (dizziness, ataxia, headache, "knockdown") are believed to be due to direct toxic effects of hydrogen sulfide. Coma, seizures, or signs of increased intracranial pressure from edema may occur in the setting of cerebral anoxia. Those who survive acute exposures to high levels of H_2S frequently make a complete neurologic recovery. However, some H_2S poisonings with loss of consciousness have been associated with long-term neurological dysfunction, including headaches, memory problems, motor dysfunction, and neuropsychiatric effects [24]. These are proposed to result from secondary anoxic brain injury caused by respiratory arrest, seizures, or other hypoxia resulting from H_2S

poisoning (i.e., pulmonary edema) [2]. Trauma may also accompany acute H_2S exposures due to knockdown effects, confounding the causality assessment of neurological sequelae [34, 35]. Although acute high-level exposures may result in altered neurological function, quality evidence that chronic low-level exposures cause long-term harm is lacking.

Metabolic Acidosis

Metabolic acidosis, with elevated lactate concentration, may occur in individuals with serious H_2S poisoning due to impairment of oxidative phosphorylation, ATP consumption exceeding production, and the resulting shift to anaerobic metabolism.

Death

Twenty-nine deaths from 5,563 H_2S exposures in the United States were reported to the American Association of Poison Control Centers over a 9-year period [23]. Most fatal cases involved exposures occurring in confined spaces, such as sewers, animal-handling and processing plants, waste dumps, sludge plants, tanks and cesspools, pulp mills, and other confined environments. In case reports of deaths occurring after acute H_2S exposure, individuals lost consciousness after only one or two breaths; this is known as the "slaughterhouse sledgehammer" effect [23, 36–39]. In these fatal cases, patients seemed to succumb from respiratory failure, acute pulmonary edema, or coma. Patients exposed to only H_2S gas do not have a substantial risk of secondary contamination to personnel outside the so-called hot zone. Rescuers should be trained and attired properly with positive-pressure, self-contained breathing apparatus before entering the hot zone.

Diagnosis

The exposure history and clinical presentation are the keys to making the diagnosis of acute hydrogen sulfide poisoning. A rotten egg odor on a patient or their belongings is suggestive of H_2S, though other agents have a similar smell, including sulfur compounds such as mercaptans, carbon disulfide, and trimethylamine. Historically, dark discoloration of a patient's coins and jewelry has been suggested as a clue to H_2S poisoning.

Important toxicologic differential diagnoses with presentation similar to H_2S poisoning include other cellular asphyxiants, such as carbon monoxide, cyanide, azide, and cyanide-related substances.

The presence of metabolic acidosis can be further evaluated by assessment of arterial blood gases with co-oximetry, electrolytes, and lactate concentrations. If the diagnosis of H_2S poisoning is not immediately obvious, cyanide, toxic alcohols (ethylene glycol, methanol), salicylate, and carboxyhemoglobin concentrations should be obtained, if indicated by the clinical history.

Sulfide ion levels can be measured on whole blood. However, lack of specificity, difficulty in performing the test accurately, and limited availability make sulfide levels useless in initial diagnosis [18]. One case series found urine thiosulfate concentrations elevated in nonfatal H_2S poisoning, despite undetectable blood sulfide levels. Urine thiosulfate may therefore be a useful means of confirming H_2S poisoning in patients who survive exposure [40]. Industrial hygienists, hazardous materials responders, and firefighters can measure H_2S concentrations in the ambient atmosphere around the site of an incident. In the case of an identified H_2S release or exposure, it is critical that H_2S concentrations are directly communicated with the individuals on site, so that appropriate precautions can be taken and secondary casualties prevented.

Treatment

Supportive care is the mainstay of therapy for exposures to H_2S. This includes removal from exposure, administration of supplemental oxygen, and decontamination of the eyes and skin. Decontamination can be accomplished by copiously irrigating exposed skin and eyes with normal saline or water. Ventilatory support, administration of

anticonvulsants if there is seizure activity, intravenous fluids, and vasopressors may be necessary. Cycloplegics and antibiotics may be needed for eye injuries. Systemic antibiotics may be indicated if there is evidence of superinfected aspirated pulmonary secretions.

Indications for ICU Admission in Hydrogen Sulfide Poisoning

Respiratory distress, respiratory failure, or signs of airway injury
Unconsciousness
Seizures or persistent neurological impairment
Electrocardiogram changes

Methemoglobin Induction

One possible antidotal therapy is induction of methemoglobinemia. Hydrogen sulfide poisoning causes lactic acidosis by the inhibition of cytochrome *c* oxidase and depletion of ATP. The formation of methemoglobinemia by nitrites creates a large pool of ferric iron, which has a greater affinity than cytochrome *c* oxidase for H_2S. Methemoglobin may therefore serve as a sink, allowing cytochrome *c* to be reactivated and reestablishing aerobic metabolism [41–43]. However, the period during which H_2S is available in blood after removal from exposure is short-lived. One animal model found no benefit to infusion of a methemoglobin solution 90 s after termination of a toxic H_2S exposure [44]. Future research is needed to determine if antidotes that propose to work by binding diffusible H_2S, including methemoglobin induction, are truly effective.

One method of inducing methemoglobinemia is by use of sodium nitrite, which may be found as a component of a cyanide antidote kit. The use of nitrites in H_2S poisoning is supported by animal studies and human case reports (Grade III evidence) [45, 46]. Intravenous (IV) access should be established as soon as possible and IV sodium nitrite administered once the decision is made to induce methemoglobinemia. The generally accepted adult dose of sodium nitrite is 10 mL of a 3% solution; the pediatric dose is 0.33 mL/kg up to 10 mL but may be adjusted based on hemoglobin level. Because sodium nitrite is a potent vasodilator, it should not be administered rapidly, but given over 2–5 min. The thiosulfate portion of the cyanide antidote kit is not useful in H_2S poisoning. Sulfide is present in the blood only transiently, and methemoglobin therapy is *not* indicated in most patients. If a patient has persistent acidosis, shock, cardiotoxicity, or coma despite optimal supportive care, the authors recommend induction of methemoglobinemia given the above animal and case-based human evidence supporting possible benefit.

Hydroxocobalamin and Cobinamide

Hydroxocobalamin, a precursor of Vitamin B_{12}, and cobinamide, a Vitamin B_{12} analog, both have a high affinity for sulfides and have been investigated as possible antidotes for H_2S poisoning. Animal models suggest a reduction in lethality and amelioration of cardiac depression with hydroxocobalamin treatment [47, 48]. A single fatal human case report notes a reduction in blood sulfide levels after hydroxocobalamin treatment [49]. One rabbit model shows increased survival and binding of sulfide to cobinamide [50]. However, in these animal models, sulfide is continuously infused, generating a constant supply of H_2S that may complex with an antidote before entering cells. Neither hydroxocobalamin nor cobinamide has yet proven clinically useful in human H_2S poisoning. Again, this may be due to the extreme rapidity with which free hydrogen sulfide leaves the circulation and enters tissues, once victims are removed from exposure. Any complex-forming antidote that cannot be administered almost immediately is likely to be of limited value [51–53]. Given the current absence of evidence supporting antidotal effects of hydroxocobalamin and cobinamide in humans, the authors recommend against their use in hydrogen sulfide poisoning (Grade III Evidence).

Hyperbaric Oxygen

Hyperbaric oxygen is a theoretical therapy for H_2S poisoning. A few case reports and

retrospective series have described using hyperbaric oxygen for H_2S poisoning. In these cases, positive outcomes were reported (Grade III Evidence) [54, 55]. However, these data are uncontrolled and subject to publication bias. The pillar of evidence-based treatment for human hydrogen sulfide poisoning remains supportive care, once the patient has been removed from the source of exposure. Hyperbaric oxygen therapy is rarely immediately available and logistically often interferes with the provision of supportive care. It is therefore the authors' opinion that hyperbaric oxygen should not be used in human H_2S poisoning. Current evidence that does not demonstrate a clear benefit and there is a high likelihood that hyperbaric oxygen treatment will delay other beneficial aspects of care.

Prehospital Treatment

A study of 250 cases of exposure to H_2S in the Alberta oil fields found that with increased awareness and improved prehospital treatment, the fatality rate was reduced from 6% to 2.8%, unconsciousness on hospital arrival decreased from 13% to 2%, and hospital admission rates decreased from 51% to 22%. Prehospital treatment also resulted in an overall decrease in workers' compensation claims [34].

Prevention

Safety officers, industrial hygienists, and workers in those industries should learn the hazards of H_2S and the proper response in the event of an accident. Safe evacuation and prompt medical attention are important. Real-time gas detecting devices are available and should be used to monitor levels of H_2S before entry into a potentially contaminated zone.

Common Errors in Hydrogen Sulfide Poisoning

Failure to consider hydrogen sulfide in cases of rapid knockdown, multiple victim poisonings at a single site, or unexplained poisoning in a confined space

Failure to account for olfactory fatigue to hydrogen sulfide gas

Failure to protect emergency personnel during attempted rescue of poisoned patients

Failure to consider hydrogen sulfide in cases of seizure, coma, or metabolic acidosis

Failure to assess for trauma secondary to sudden unconsciousness

Failure to treat on the basis of clinical presentation rather than reported or suspected exposure

Failure to perform ocular decontamination

Evidence-Based Recommendations for Practice

Clinical Recommendation	Evidence rating
Supportive care should include decontamination and oxygen supplementation	III
Methemoglobin induction with sodium nitrite may be considered for severely poisoned patients that remain symptomatic in medical care	III
Patients severely poisoned by H_2S should be evaluated for concomitant trauma	III

Key Points in Hydrogen Sulfide Poisoning

1. Hydrogen sulfide causes a rapid knockdown effect.
2. Decontamination is essential.
3. Safe removal from exposure and supportive care is the mainstay of therapy.
4. Trauma frequently accompanies H_2S poisoning and must be evaluated and treated.
5. Induction of methemoglobinemia with IV sodium nitrite may be antidotal.
6. Vitamin B_{12} and its analogs currently lack human evidence for effectiveness.
7. Hyperbaric oxygen therapy currently lacks human evidence for effectiveness.

References

1. Mowry JB, Spyker DA, Cantilena Jr LR, McMillan N, Ford M. 2013 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st annual report. Clin Toxicol (Phila). 2014;52(10):1032–283.
2. Guidotti TL. Hydrogen sulfide: advances in understanding human toxicity. Int J Toxicol. 2010; 29(6):569–81.
3. Kage S, Ikeda H, Ikeda N, Tsujita A, Kudo K. Fatal hydrogen sulfide poisoning at a dye works. Legal Med (Tokyo, Japan). 2004;6(3):182–6.
4. Fuller DC, Suruda AJ. Occupationally related hydrogen sulfide deaths in the United States from 1984 to 1994. J Occup Environ Med/Am Coll Occup Environ Med. 2000;42(9):939–42.
5. Guidotti TL. Occupational exposure to hydrogen sulfide in the sour gas industry: some unresolved issues. Int Arch Occup Environ Health. 1994;66(3):153–60.
6. ATSDR. Health Consultation, Puna Geothermal Venture Pahoa (Puna District). Hawaii: Hawaii County; 1997. www.atsdr.cdc.gov/HAC/PAH/PUNA/pgv.html. Accessed 23 Jan 2015.
7. Bates MN, Garrett N, Graham B, Read D. Cancer incidence, morbidity and geothermal air pollution in Rotorua, New Zealand. Int J Epidemiol. 1998;27(1):10–4.
8. Kamijo Y, Takai M, Fujita Y, Hirose Y, Iwasaki Y, Ishihara S. A multicenter retrospective survey on a suicide trend using hydrogen sulfide in Japan. Clin Toxicol (Phila). 2013;51(5):425–8.
9. Reedy SJ, Schwartz MD, Morgan BW. Suicide fads: frequency and characteristics of hydrogen sulfide suicides in the United States. West J Emerg Med. 2011; 12(3):300–4.
10. Truscott A. Suicide fad threatens neighbours, rescuers. CMAJ. 2008;179(4):312–3.
11. ATSDR. Toxicological profile for hydrogen sulfide. Atlanta: US Department of Health and Human Services, Public Health Service, Agency for Toxic Health Substances and Disease Registry; 2006.
12. Barr LA, Calvert JW. Discoveries of hydrogen sulfide as a novel cardiovascular therapeutic. Circ J. 2014; 78(9):2111–8.
13. Wang R. Physiological implications of hydrogen sulfide: a whiff exploration that blossomed. Physiol Rev. 2012;92(2):791–896.
14. Yang W, Yang G, Jia X, Wu L, Wang R. Activation of KATP channels by H_2S in rat insulin-secreting cells and the underlying mechanisms. J Physiol. 2005; 569(Pt 2):519–31.
15. Caliendo G, Cirino G, Santagada V, Wallace JL. Synthesis and biological effects of hydrogen sulfide (H_2S): development of H_2S-releasing drugs as pharmaceuticals. J Med Chem. 2010;53(17):6275–86.
16. Kimura Y, Goto Y, Kimura H. Hydrogen sulfide increases glutathione production and suppresses oxidative stress in mitochondria. Antioxid Redox Signal. 2010;12(1):1–13.
17. American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Fairfax: AIHA Press; 2007.
18. Reiffenstein RJ, Hulbert WC, Roth SH. Toxicology of hydrogen sulfide. Annu Rev Pharmacol Toxicol. 1992;32:109–34.
19. Beauchamp Jr RO, Bus JS, Popp JA, Boreiko CJ, Andjelkovich DA. A critical review of the literature on hydrogen sulfide toxicity. Crit Rev Toxicol. 1984; 13(1):25–97.
20. Policastro MA, Otten EJ. Case files of the University of Cincinnati fellowship in medical toxicology: two patients with acute lethal occupational exposure to hydrogen sulfide. J Med Toxicol. 2007;3(2):73–81.
21. Haggard HW, Henderson Y, Charlton TJ. The influence of hydrogen sulfide on respiration. Am J Physiol. 1922;61:289–97.
22. Warenycia MW, Smith KA, Blashko CS, Kombian SB, Reiffenstein RJ. Monoamine oxidase inhibition as a sequel of hydrogen sulfide intoxication: increases in brain catecholamine and 5-hydroxytryptamine levels. Arch Toxicol. 1989;63(2):131–6.
23. Snyder JW, Safir EF, Summerville GP, Middleberg RA. Occupational fatality and persistent neurological sequelae after mass exposure to hydrogen sulfide. Am J Emerg Med. 1995;13(2):199–203.
24. Occupational Safety and Health Administration. Hydrogen sulfide: hazards. https://www.osha.gov/SLTC/hydrogensulfide/hazards.html. Accessed 23 Jan 2015.
25. Burnett WW, King EG, Grace M, Hall WF. Hydrogen sulfide poisoning: review of 5 years' experience. Can Med Assoc J. 1977;117(11):1277–80.
26. Lambert TW, Goodwin VM, Stefani D, Strosher L. Hydrogen sulfide (H_2S) and sour gas effects on the eye. A historical perspective. Sci Total Environ. 2006;367(1):1–22.
27. Milby TH, Baselt RC. Hydrogen sulfide poisoning: clarification of some controversial issues. Am J Ind Med. 1999;35(2):192–5.
28. Haouzi P. Ventilatory and metabolic effects of exogenous hydrogen sulfide. Respir Physiol Neurobiol. 2012;184(2):170–7.
29. Parra O, Monso E, Gallego M, Morera J. Inhalation of hydrogen sulphide: a case of subacute manifestations and long term sequelae. Br J Ind Med. 1991; 48(4):286–7.
30. Duong TX, Suruda AJ, Maier LA. Interstitial fibrosis following hydrogen sulfide exposure. Am J Ind Med. 2001;40(2):221–4.
31. Gregorakos L, Dimopoulos G, Liberi S, Antipas G. Hydrogen sulfide poisoning: management and complications. Angiology. 1995;46(12):1123–31.
32. Zhang Z, Huang H, Liu P, Tang C, Wang J. Hydrogen sulfide contributes to cardioprotection during ischemia-reperfusion injury by opening K ATP channels. Can J Physiol Pharmacol. 2007;85(12): 1248–53.
33. Shen Y, Shen Z, Luo S, Guo W, Zhu YZ. The cardioprotective effects of hydrogen sulfide in heart

diseases: from molecular mechanisms to therapeutic potential. Oxid Med Cell Longev. 2015;2015:925167.
34. Arnold IM, Dufresne RM, Alleyne BC, Stuart PJ. Health implication of occupational exposures to hydrogen sulfide. J Occup Med. 1985;27(5):373–6.
35. Gabbay DS, De Roos F, Perrone J. Twenty-foot fall averts fatality from massive hydrogen sulfide exposure. J Emerg Med. 2001;20(2):141–4.
36. Adelson L, Sunshine I. Fatal hydrogen sulfide intoxication. Report of three cases occurring in a sewer. Arch Pathol. 1966;81(5):375–80.
37. Audeau FM, Gnanaharan C, Davey K. Hydrogen sulphide poisoning: associated with pelt processing. N Z Med J. 1985;98(774):145–7.
38. Breysse PA. Hydrogen sulfide fatality in a poultry feather fertilizer plant. Am Ind Hyg Assoc J. 1961;22:220–2.
39. Perry Jr GF. Occupational medicine forum. J Occup Environ Med/Am Coll Occup Environ Med. 1995;37:656–8.
40. Kage S, Takekawa K, Kurosaki K, Imamura T, Kudo K. The usefulness of thiosulfate as an indicator of hydrogen sulfide poisoning: three cases. Int J Legal Med. 1997;110(4):220–2.
41. Smith L, Kruszyna H, Smith RP. The effect of methemoglobin on the inhibition of cytochrome c oxidase by cyanide, sulfide or azide. Biochem Pharmacol. 1977; 26(23):2247–50.
42. Smith RP, Gosselin RE. The influence of methemoglobinemia on the lethality of some toxic anions. II. Sulfide. Toxicol Appl Pharmacol. 1964;6:584–92.
43. Smith RP, Gosselin RE. On the mechanism of sulfide inactivation by methemoglobin. Toxicol Appl Pharmacol. 1966;8(1):159–72.
44. Chenuel B, Sonobe T, Haouzi P. Effects of infusion of human methemoglobin solution following hydrogen sulfide poisoning. Clin Toxicol (Phila). 2015;53(2):93–101.
45. Beck JF, Bradbury CM, Connors AJ, Donini JC. Nitrite as antidote for acute hydrogen sulfide intoxication? Am Ind Hyg Assoc J. 1981;42(11):805–9.
46. Stine RJ, Slosberg B, Beacham BE. Hydrogen sulfide intoxication. A case report and discussion of treatment. Ann Intern Med. 1976;85(6):756–8.
47. Truong DH, Mihajlovic A, Gunness P, Hindmarsh W, O'Brien PJ. Prevention of hydrogen sulfide (H_2S)-induced mouse lethality and cytotoxicity by hydroxocobalamin (vitamin B(12a)). Toxicology. 2007;242(1–3):16–22.
48. Haouzi P, Chenuel B, Sonobe T. High-dose hydroxocobalamin administered after H_2S exposure counteracts sulfide-poisoning-induced cardiac depression in sheep. Clin Toxicol (Phila). 2015;53(1):28–36.
49. Fujita Y, Fujino Y, Onodera M, et al. A fatal case of acute hydrogen sulfide poisoning caused by hydrogen sulfide: hydroxocobalamin therapy for acute hydrogen sulfide poisoning. J Anal Toxicol. 2011;35(2):119–23.
50. Brenner M, Benavides S, Mahon SB, et al. The vitamin B12 analog cobinamide is an effective hydrogen sulfide antidote in a lethal rabbit model. Clin Toxicol (Phila). 2014;52(5):490–7.
51. Dulaney Jr M, Hume AS. Pyruvic acid protects against the lethality of sulfide. Res Commun Chem Pathol Pharmacol. 1988;59(1):133–6.
52. Haouzi P, Chenuel B, Sonobe T, Klingerman CM. Are H_2S-trapping compounds pertinent to the treatment of sulfide poisoning? Clin Toxicol (Phila). 2014; 52(5):566.
53. Klingerman CM, Trushin N, Prokopczyk B, Haouzi P. H_2S concentrations in the arterial blood during H_2S administration in relation to its toxicity and effects on breathing. Am J Physiol Regul Integr Comp Physiol. 2013;305(6):R630–8.
54. Asif MJ, Exline MC. Utilization of hyperbaric oxygen therapy and induced hypothermia after hydrogen sulfide exposure. Respir Care. 2012;57(2):307–10.
55. Lindenmann J, Matzi V, Neuboeck N, Ratzenhofer-Komenda B, Maier A, Smolle-Juettner FM. Severe hydrogen sulphide poisoning treated with 4-dimethylaminophenol and hyperbaric oxygen. Diving Hyperb Med. 2010;40(4):213–7.