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Environmental Toxicology of Hydrogen Sulfide

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Keywords

contact process; emission; exposure; occupational health; Princess Alice; public health; sewer gas; smoking; sour gas; suicide

1. Introduction

The passenger-carrying paddle steamer Princess Alice was sunk in a collision on the River Thames in 1878 with the loss of over 640 lives and, curiously, may represent one of the largest mass poisoning episodes in history [1, 2]. Raw discharge from the London sewers had been released into the Thames (standard practice at the time) and some survivors reported the unusually foul nature of the water. The extraordinarily high death toll of the Princess Alice accident (> 80%) is in stark contrast to the similarly violent sinking of the pleasure craft Marchioness on the Thames a century later in 1989, where only 51 of 130 people on board were lost (< 40% fatalities) [3, 4]. The Board of Trade inquiry and the Coroner's inquest at the time of the Princess Alice disaster were primarily concerned with establishing blame for the collision and determining if there were any criminal charges to be filed. That there may have been significant deaths caused by hydrogen sulfide (H₂S) inhalation, possibly accelerated by the victims thrashing at the surface, was not given much serious consideration [1, 2]. Nevertheless, it was only nine years after the Princess Alice disaster occurred that the necessary investment was made to treat and separate the sewage before releasing it into the Thames [5]. It has since become entrenched in sanitary engineering lore that many of the Princess Alice deaths were due to poisoning, probably by H₂S [6].

While it is now widely accepted that H₂S acts as a signaling molecule and exhibits some potentially beneficial therapeutic effects [7–15] at elevated levels H₂S is highly toxic. Gaseous H₂S continues to be one of the most common hazardous substances attributed to acute poisoning deaths in occupational settings [16]. However, there are still facets of H₂S toxicity that remain elusive – including, but not necessarily limited to, a comprehensive estimate of the prevalence of this poisonous gas emitted into the environment and any effects associated with such exposures, the mechanism(s) of its cellular toxicity, and lack of

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effective antidotes. Herein, we consider some of the knowledge gaps associated with H₂S in the environment and its toxic effects on the human body when inhaled.

2. Some Physical Properties of Hydrogen Sulfide

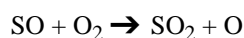
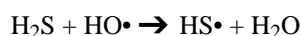
Hydrogen sulfide, H₂S (also known as hydrosulfuric acid, hydrogen sulfide, sewer gas, and stink damp, dihydrogen monosulfide, dihydrogen sulfide, sulfane, sulfurated hydrogen, and sulfur hydride) possessing the characteristic smell of rotten eggs. The gas is slightly heavier than air with a specific gravity of 1.19 at 15° C (the mean environmental temperature) and a molar mass of 34.08 g/mol. Among its hazardous traits, H₂S is corrosive, explosive (at 4.3–45% by volume in air) and flammable (260° C ignition temperature).

Although not as polar as water, the structure of H₂S, is similar to that of water, and it is also moderately soluble in water [17]. The p*K*_a for the reaction H₂S ⇌ H⁺ + HS⁻ is 7.04, with the second p*K*_a being inaccessible in water [18, 19]. Except where otherwise stated, data are provided for H₂S in the standard state (25°C, 101 kPa). Consequently, in aqueous media at pH 7.4 (prior to any biochemical modification and irrespective of the exposure route *in vivo*) hydrogen sulfide is ~30% H₂S and ~70% HS⁻ (hydrosulfide). Where any greater precision is unnecessary and in keeping with common practice in the biochemical/toxicological literature, this mixture in aqueous media and the form bound to metal ions is referred to as “sulfide” throughout.

2.1 Brief Environmental Chemistry of Hydrogen Sulfide

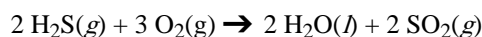
If released as a gas, hydrogen sulfide remains in the atmosphere for approximately one day in the summer and 42 days in winter, becoming converted to sulfur dioxide and sulfuric acid [20] in a reaction catalyzed by hydroxyl radical:

Equations 1. Conversion of hydrogen sulfide to sulfur dioxide in air by hydroxyl radical

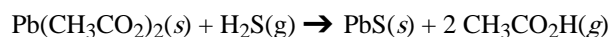


H₂S can also be intentionally removed from the air by combustion, producing elemental sulfur and/or SO₂ [21]:

Equations 2. Conversion of hydrogen sulfide to elemental sulfur and sulfur dioxide in air by combustion



In the presence of metal ions, hydrogen sulfide tends to react and form metal sulfides, the salts of hydrogen sulfide[18, 19]. Such a reaction is the basis for the lead(II) acetate paper test used to detect H₂S, with the moistened paper turning black due to formation of a PbS precipitate [21]:

Equation 3. Detection of hydrogen sulfide using lead acetate paper

H₂S partitions into water, forming solutions of hydrosulfuric acid (or sulfhydrylic acid). If sufficiently aerated, H₂S can be oxidized, forming elemental sulfur and water. Additional biological methods of H₂S removal have been explored to manage large-scale anthropogenic sources of H₂S in liquid form [22]. H₂S also enters soil when deposited from the air, due to surface spills, or other natural events [23]. Air, however, is the medium where most H₂S is found, and where it poses the greatest risk to people. These interconnected chemical processes can be thought of as a simplified form (or subset) of the global sulfur cycle (Figure 1).

2.2 Detection and Quantitative Analysis

While the human nose remains a more sensitive detector than most other equipment (see section 6) it is not an adequate monitoring system, since it can become desensitized and is not useful for assessment of accumulated doses. Many devices suitable for personnel exposure monitoring have and continue to be described (much of this in trade publications rather than peer-reviewed literature) but a survey of these is outside the scope of this review. Such devices, either individually worn, or mounted in work areas, tend to be based on principles of optical spectrometry, electrochemistry, or conductivity changes in films/nanomaterials [24–27]. Multiple colorimetric tests for H₂S have been known for some considerable time [25], but the lead acetate method (see section 2.1) with the reagent typically impregnated into tape within a cartridge, remains popular due to its sensitivity.

Methods suitable for analysis of environmentally-relevant samples began to be developed about half a century ago [28]. Nowadays, for many forensic purposes, straightforward gas chromatography-mass spectrometry (GC-MS) is quite adequate [29], but GC coupled to chemiluminescent detection of sulfur appears to offer some advantages for the analysis of biological materials [30]. There are many methods available for the quantitative determination of H₂S in fuel gases, but fewer in the case of air samples. Essentially dedicated instruments based on pulsed fluorescence detection of SO₂ generated from H₂S are commercially available and have found application to quantitation of emissions from point sources [31, 32]. Gas chromatography with flame photometric detection (GC/FPD) is the U.S. Environmental Protection Agency (EPA) recommended test method for H₂S in air [33]. Approaches to the analysis of water samples are more numerous and include chromatographic, iodometric, photometric and potentiometric procedures. In comparison, however, inductively coupled plasma-atomic emission spectrometry (ICP-AES) in conjunction with vapor generation techniques has been shown to be advantageous in terms of detection limit, throughput and lower reagent consumption/waste generation [34, 35].

All the above analytical methods are reliable, each with reasonably well-documented detection limit, linear range, reproducibility and known interferences. Where possible, they have been extensively checked against each other. As experimental sensitivity can always be increased by the collection and processing of larger sample volumes, selection of a particular method for any situation is largely a matter of cost, convenience, availability of equipment and practical experience of the personnel involved. The uncertainties evident in the analysis

presented below (sections 3 and 4) are, in all probability, essentially independent of the analytical instrumentation, but instead reside in the sampling protocols and incomplete data sets. Accurate identification and documentation of all potential sources, plus determination of the invariably temporal nature of their emissions, remain challenging hurdles to entirely reliable estimations of net environmental H₂S fluxes.

3. Emissions & Environmental Sources

As a key component of the sulfur cycle (Figure 1) H₂S can be produced naturally in the environment through the anaerobic breakdown of sulfate by bacteria, anthropogenically by way of a variety of industrial practices (see below) and by degradation of sulfur-containing protein in mammals [23, 36, 37]. Although not the focus of this particular review, H₂S is a member of the small group of currently recognized gasotransmitters (along with nitric oxide and carbon monoxide)[9, 11, 13, 23, 38].

Background H₂S air concentrations typically range between 0.11 ppb and 0.33 ppb, although concentrations in urban areas can be as high as 1 ppb. As expected, the closer one lives to sources of H₂S emissions, the higher the background levels tend to be (and can exceed 90 ppb) [23]. According to the literature reviewed by the World Health Organization several years ago [39], yearly H₂S emissions from all sources on land are from 53 to 100 million metric tons of sulfur, while oceanic emissions are between 27 and 150 million metric tons. Here we have also summarized source-based emission estimates for hydrogen sulfide as reported in the literature over the 10-year period 2004–14 (Table 1).

The results of this literature review (Table 1) indicate that out of the 79 studies in the assessment, and the 132 results included [40], animal feeding operations (AFOs) were the most commonly studied sources (n = 31). This data reflects the propensity for H₂S poisonings relative to AFOs and the consequent regulatory activities. While typically the maximal concentration measurements taken within AFO operations were the highest among the studies reviewed (8.66E+03 mg/m³), AFOs did not always contribute the highest fluxes into the air (6.30E+07 mg/hour); natural geothermal activity and anthropogenic energy production were one to two orders of magnitude greater. This observation is likely due to the indoor nature of AFO sources, which can tend to accumulate H₂S rather than emit the gas at rates comparable to less enclosed sources. As of 2016, there were in the region of a quarter of a million AFOs in the U.S. and less than one thousand fossil fuel burning power plants (50 MW capacity, or greater) suggesting that the net fluxes of H₂S from all AFO and all energy production sources might be roughly comparable. Given the smaller number of geothermally active sites, the net contribution from these is likely lower. Only the two studies in the “other” category described releases into water, although it should be noted that the search terms used to conduct the review could have given preferential treatment to air monitoring over water measurements (for instance, “releases” was not a search term). The apparent lack of any studies assessing H₂S levels from a variety of other types of sources, such as fires, paper mills and tanneries, is noteworthy.

3.1 Naturally Produced H₂S

In the environment, H₂S is often produced by sulfate-reducing bacteria through the anaerobic digestion of organic material. It is also expected that some plants may use and emit H₂S [41, 42]. Significant environmental sources of the gas include places where the breakdown of organic matter coupled with a lack of oxygen occurs, including swamps, hydrocarbon deposits, volcanoes, undersea vents, sulfur springs, and stagnant bodies of water. H₂S may also be present naturally in well-water [23, 39, 43].

Geothermal activity produces H₂S, along with other toxic compounds, when the gases within magma (CO₂, SO₂, N, H, CO, S, Ar, Cl, and F) combine with hydrogen and water [44]. Geothermal activity has been less studied than man-made and agricultural sources of H₂S in recent years. Yearly H₂S emissions from all sources on land and oceanic emissions are comparable, 53–100 million metric tons and 27–150 million metric tons of sulfur, respectively [39]. Thus, it seems reasonable to infer that geothermal emissions must represent the largest source of environmental H₂S as AFOs and other anthropogenic sources do not contribute to the oceanic emissions. This suggestion is supported by observations from many other studies [23]. Interestingly, high levels of H₂S in the atmosphere likely due to volcanic eruptions has been implicated in several mass extinctions throughout Earth's history [45, 46]. Small blooms of H₂S have also recently been detected in the Dead Sea and off of the coast of Namibia in the Atlantic Ocean [47].

3.2 Anthropogenic Sources of H₂S

In recent years, anthropogenic sources of H₂S emissions into the air have been studied significantly more often than natural sources (n = 69 vs. n = 10)[40], despite the propensity for natural sources to emit H₂S at high rates (Table 1). Among anthropogenic sources, H₂S can be found at elevated levels in or near sewage systems, animal containment, and slaughterhouses (generally categorized as AFOs). Industrial sources where H₂S can be present include oil and gas processing sites, geothermal power plants, coke ovens, food processing facilities, tanneries, and pulp/paper mills. While H₂S is primarily released in gaseous form, it can also be found in liquid waste related to industrialization [23, 39].

The amount of H₂S emitted into the atmosphere from human activity is difficult to quantify worldwide due to a lack of comprehensive data and/or reporting. For example, H₂S emissions in the U.S. were exempt from reporting to the EPA's Toxic Release Inventory (TRI) between 1991 and 2011. According to the TRI, in 2012 most hydrogen sulfide air releases in the U.S. were the result of three industrial sectors: pulp and paper (64% by weight), chemicals (17%), and petroleum refining (8%)[48]. Contrastingly, the most significant source of H₂S emissions in western Canada is the oil and gas industry, due to geologic formations that are naturally high in H₂S [49]. Overall, total known hydrogen sulfide releases in the U.S. (into air, water, and through underground injection) range between 26 and 27 million pounds per year (Table 2).

Animal feeding operations (AFOs) are agricultural enterprises where animals are kept and raised in confined situations resulting in high concentrations of H₂S in the air. While AFOs do not emit H₂S at rates on par with geothermal activity, with approximately 257,000 AFOs

in the US alone, their sheer numbers can still contribute significant amounts into the air[51]. The substantial influx of AFO studies in recent years is likely due to that fact and the prioritization of quantification of air emissions from AFOs by the United States Department of Agriculture's Initiative for Future Agriculture and Food System Program and, consequently, funding from the National Research Initiative Program [52]. In order to accurately quantify total H₂S contributions to the atmosphere from AFOs, all AFO operations and their H₂S management methods need to be tracked and monitored over time.

Energy production was another area identified[40] that exhibits the potential to emit H₂S at high rates, although monitoring results were highly variable within this sector. H₂S forms naturally within geologic formations that support oil and gas production as high-sulfur kerogens decay. When sulfur (and H₂S) content are high in wells, they are referred to as "sour gas" wells. While this gas may not pose an issue at all drilling sites, where it does can have serious consequences. In Kaixian County, China, for example, 64,000 residents had to be evacuated and 243 were killed when an accidental sour gas well blowout occurred in 2003 [53]. The Saskatchewan government recently tested 43 facilities in southeast Saskatchewan that were leaking sour gas, finding average concentrations of 30,000 ppm, well above levels that can kill livestock and people [54]. Wells and refineries where H₂S may be present also exist in the U.S. Out of Michigan's 10,652 producible oil wells, for example, 1,360 saw H₂S levels exceeding 300 ppm [55]. The hazards posed by high emission rates from oil and gas sites is compounded by the fact that, in the U.S., no OSHA monitoring program exists at this time, though such programs have been proposed in the past. Skrtic [43] discusses these continuing gaps in much further detail.

3.3 Major Commercial Uses

For commercial purposes, H₂S is used to produce sulfur through the Claus process (Equations 4) and, subsequently, sulfuric acid (H₂SO₄) by the Contact Process (Equations 5). Sulfuric acid is one of the most highly traded chemical commodities in the world due to its role in producing phosphate (60% of worldwide demand) and other fertilizers (10%) [56].

Equations 4. Claus process (industrial production of elemental sulfur from H₂S).

Overall: $2\text{H}_2\text{S} + \text{SO}_2 = 3\text{S} + 2\text{H}_2\text{O}$

- Thermal Step:
 - $2\text{H}_2\text{S} + 3\text{O}_2 \rightarrow 2\text{SO}_2 + 2\text{H}_2\text{O}$ ($H = -4147.2\text{ kJ mol}^{-1}$)
- Catalytic Step:
 - $2\text{H}_2\text{S} + \text{SO}_2 \rightarrow 3\text{S} + 2\text{H}_2\text{O}$ ($H = -1165.6\text{ kJ mol}^{-1}$)

Equations 5. Contact process (industrial production of sulfuric acid).

- $\text{S}_{(s)} + \text{O}_2 \rightarrow \text{SO}_{2(g)}$
- $2\text{SO}_{2(g)} + \text{O}_{2(g)} \rightleftharpoons 2\text{SO}_{3(g)}$ ($H = -196\text{ kJ mol}^{-1}$)
- $\text{H}_2\text{SO}_{4(l)} + \text{SO}_{3(g)} \rightarrow \text{H}_2\text{S}_2\text{O}_7(l)$
- $\text{H}_2\text{S}_2\text{O}_7(l) + \text{H}_2\text{O}_{(l)} \rightarrow 2\text{H}_2\text{SO}_{4(l)}$

H₂S is beneficial in a variety of other sectors. It is used to make sodium sulfide and sodium hydrosulfide. These compounds are then used in the production of dyes, pesticides, and even pharmaceuticals. H₂S also has roles to play in metallurgy, laboratory settings, and agriculture [23]. The nuclear energy sector utilizes H₂S in large quantities to separate “heavy water,” containing the hydrogen isotope deuterium, from regular water [21].

Natural gas purification and petroleum refining supply approximately 60% of the sulfur and SO₂ used in the production of sulfuric acid [56]. In petroleum refining, H₂S is a result of the hydrotreating process, where sulfur compounds found in the crude oil are removed by reaction with hydrogen gas [48, 50].

3.4 H₂S Suicides

On a smaller scale, emergency medical personnel may be exposed to high levels of the gas when responding to H₂S suicides, also called “detergent suicides”[57, 58]. The procedure involves mixing hydrochloric acid (found in commercial pool and toilet bowl cleaners) with either lime sulfur (found in common pesticides) or bath sulfur (available in Japan) in an enclosed space to generate toxic levels of H₂S gas [57, 59, 60].

The trend started in Japan in 2007 and has since moved abroad, as methods for generating H₂S from household chemicals were publicized on the Internet; in 2008 alone, 500 men, women, and children committed suicide in Japan using this method. Increasingly, more people in the U.S. have followed suit. Prior to 2008, there were no records of Americans committing suicide using intentionally-generated H₂S gas. Between 2008 and 2010, however, 30 such suicides occurred. Even if alerted to the presence of toxic gas, the temptation for would-be rescuers to assist collapsed individuals is great and five emergency responders were injured during rescue efforts in that period [61]. There also has been a report of suicide by H₂S inhalation in an apartment building where residents not in the immediate vicinity of the release site were affected [58, 61].

These and other developments have recently led to a growing concern that H₂S might find application as a terrorist weapon [59]. Disturbingly, despite this known health risk to the public, emergency personnel and certain other workers, there is no FDA-approved antidote and/or reliable protocol for treating acute hydrogen sulfide poisoning currently available.

4. H₂S Regulation in the U.S

In the United States, hydrogen sulfide is regulated in a variety of ways by the U.S. Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) and the Occupational Safety and Health Administration (OSHA). The exposure limits recommended by OSHA are enforceable by law, but only in the workplace. OSHA sets limits in industries where H₂S is found over the threshold quantity of 1,500 pounds (680.38 kg) [62]. Additional national organizations such as the Agency for Toxic Substances and Disease Registry (ATSDR), National Institute for Occupational Safety and Health (NIOSH), and the American Conference of Governmental Industrial Hygienists (ACGIH) also provide recommended exposure limits. Data regarding occupational and ambient exposures are fraught with complications and contradictions, however, since actual H₂S emission levels

and concentrations within a mixture of sulfurcontaining gases are usually unknown [23, 39]. Acute exposure guidelines (Table 3) have been developed by several regulatory and non-governmental organizations primarily based on experimental animal studies.

At a national level, H₂S was originally on the proposed hazardous air pollutants (HAPs) list of the Clean Air Act Amendments of 1990 with 188 other pollutants that are known, or suspected, to cause serious adverse health and/or environmental effects. Instead of ambient air quality standards, HAPs are regulated at the source nationally by limiting industrial emissions. The levels permitted are driven by the most effective technological controls available. Successful petitioning resulted in the removal of H₂S from the HAPs list in 1991 [71]. Hydrogen sulfide is, however, found on the U.S. EPA's list of Extremely Hazardous Substances [43] as determined by the Emergency Planning and Community Right-To-Know Act in the event of accidental releases [72]. Additionally, starting in 2011, U.S. companies were required to report their emissions of H₂S to the Toxic Release Inventory (TRI) a system for tracking toxic chemicals that may pose environmental and health risks. There had previously been a TRI reporting stay for hydrogen sulfide enacted in 1995 that was then lifted in 2011 [73].

H₂S does not fall under the regulatory authority of the EPA for National Ambient Air Quality Standards, but the EPA does have a reference concentration for chronic inhalation (RfC) at 2×10^{-3} mg/m³ (1.4 ppb). The EPA also has the regulatory authority to institute regulations on specific H₂S sources if it so chooses, such as oil and gas wells. It is assumed that daily exposures of H₂S above this level over a lifetime will have deleterious effects. No parallel reference dose for chronic oral exposure (RfD) exists at this time [51]. In lieu of national limits on H₂S, individual states in the U.S. can choose to limit exposures, although their standards vary significantly. See Appendix B in Skrtic 2006 [43] for state ambient hydrogen sulfide standards.

5. Exposure Pathways

Inhalation is the main route of exposure for hydrogen sulfide, with dermal/eye contact, injection, or ingestion being plausible but less likely routes. Humans can typically smell H₂S at low concentrations in the air, between 0.0005 and 0.3 ppm, lower than our most sensitive H₂S monitoring equipment [23]. Because H₂S in gaseous form is heavier than air, the highest risk of exposure for people is in enclosed spaces at, or just below, ground level. In common with many toxicants, the most well-documented arena for understanding hydrogen sulfide risks is in the occupational setting. According to available data from OSHA and the Bureau of Labor Statistics (BLS), H₂S is one of the most dangerous gases in the workplace, second only among toxic gases to carbon monoxide. From 2004–14, approximately 83 workers lost their lives, and 120 were sickened and missed work due to exposure to H₂S while on the job. The majority of both fatal and nonfatal workplace incidents involved exposures to males, not females [62, 74–79]. Beyond summary statistics, it is difficult to interpret trends from the (incomplete) U.S. data available on occupational fatalities and injuries due to H₂S exposures. However, workers in industries such as petroleum production and refining, sewer and wastewater treatment, agricultural silos and pits, textile

manufacturing, pulp and paper processing, food processing, hot asphalt paving, and mining are considered those most at-risk [78–80].

Favorable conditions for high H₂S production and accumulation — such as hot weather, confined spaces, and low wind — are likely better indicators than one's job, especially for assessing risk outside of occupational settings. For the American public also, hydrogen sulfide remains a significant inhalation hazard. In 2012, there were an estimated 809 non-occupational exposures resulting in 5 deaths as logged in the National Poison Data System [81]. In 2013 there was an increase in both exposures and deaths (855 and 10 respectively) second only to carbon monoxide with regard to deaths (n = 60)[82]. The elderly, asthma sufferers and children with otherwise compromised respiratory systems are at higher risk of the compound's negative effects since H₂S targets the respiratory tract [23, 39].

It is not reliably known what fraction of H₂S to which a person may be exposed can be absorbed into the body and become systemically distributed as H₂S/HS⁻ in the bloodstream [83–85]. H₂S/HS⁻ appears to be primarily detoxified through oxidation in the liver, and also by methylation [86]. However, urinary thiosulfate, the last product of mammalian mitochondrial sulfide oxidation, is the most commonly used biomarker for H₂S exposure [87].

The toxic effects of H₂S can vary greatly based on the level, route and duration of the exposure. For discussion purposes, we find it convenient to consider three main types of exposure: acute, post-acute, and chronic (Figure 2) – based on descriptions in the peer-reviewed literature and lower-range regulatory limits (Table 3). These exposure characteristics and their effects are neither rigorously delimited, nor generally accepted, as most authors do not distinguish between acute and what we shall call “post-acute” effects. In our view, the distinction is important because “post-acute” effects occur more than about 10–15 min after sub-lethal acute exposure, once H₂S/HS⁻ has already disappeared from the circulation, but in the time frame during which victims of H₂S poisonings present at the emergency clinic (Frawley et al., 2017, manuscript in revision).

6. Human Health Effects

There is, of course, a body of work describing H₂S as a modulator of physiological functions [38, 39, 88, 89]. It has been implicated in the regulation of blood pressure, neurotransmission, antiinflammatory action, aiding digestion, and other activities [7, 12, 14, 15, 23, 90]. Investigations looking into the role that H₂S may play in suspended animation [91, 92] may have experienced a loss of interest as the effect in question appears diminished in larger animals [93]. To date, however, the majority of well-documented health effects arising from exposure to hydrogen sulfide remain negative, especially at levels above 1 ppm in air. Most hydrogen sulfide toxicity studies have either involved retrospective analysis of acute, uncontrolled incidents where the exact concentration and any pre-existing conditions of the victims were not known or more controlled research studies with animals, whose results were then extrapolated to humans. The consensual viewpoint is that the respiratory tract and nervous system are especially sensitive to the effects of H₂S exposure [23, 94]. The

general symptoms exhibited by individuals exposed to varying levels of gaseous H₂S are summarized below (Table 4).

At all levels – acute, post-acute, and chronic – the effects of H₂S inhalation still presents many unknowns, although markedly more gaps exist within post-acute and chronic exposures. Effects following dermal exposure and ingestion, as well as genotoxicity and reproductive effects, are even less well understood [23, 94].

6.1 Acute Exposures (> 300 ppm, rapid onset)

Hydrogen sulfide odor becomes detectable at concentrations as low as .0005 ppm, but the sense of smell is lost after 2–15 minutes at 100 ppm [23, 94], rendering the odor of the gas an ineffective hazard warning. In situations involving extremely high H₂S levels in air, potential victims run the risk of experiencing “knockdown,” or passing out in the area. Knockdown severely diminishes survival rates due to trauma sustained during the fall and/or inability to escape. Collapsed victims also endanger responders as they entice would-be rescuers into locations with dangerously high toxicant levels.

In cases of severe acute toxicity, i.e. > 500 ppm H₂S, unconsciousness and death may result almost immediately [63, 94], probably through cardiopulmonary paralysis. Interestingly, it is not uncommon for individuals receiving a high dose of the toxicant for a very short duration to experience knockdown, but then spontaneously (and rapidly) recover, requiring no medical intervention and exhibiting no long-term sequelae [23]. Such observations have been well-replicated in laboratory animals [97].

6.2 Post-Acute Exposures (> 100 ppm, slower onset)

Having received lower hydrogen sulfide doses over more prolonged durations rather than acute cases, victims often present at the clinic more than 30 min after exposure, exhibiting symptoms such as difficulty in breathing, noncardiogenic pulmonary edema, cyanosis and, ultimately coma/death. In such cases, death may be delayed for hours to days and a variety of subsequent neurological disorders, if developed, require weeks to present [23, 78, 98, 99]. Levels of H₂S up to approximately 10 ppm for short periods (a couple of hours) can certainly be tolerated well by healthy adults. In the 1–300 ppm range, however, there is a paucity of available quantitative data on the effects [100], but sometimes, no symptoms have been observed even during controlled exposure trials [23].

6.3 Chronic Exposures (< 1 ppm, for at least days)

The effects of low-level or long-term exposure to ambient levels of hydrogen sulfide (< 1 ppm) in air are more difficult to estimate because the mechanism(s) for chronic toxicity is(are) not well understood. At such levels and duration, based heavily on anecdotal evidence, expected symptoms of exposure could include visual complications, olfactory fatigue, nausea, respiratory irritation, and possible headaches due to the sensitivity of those systems to H₂S exposure [23, 101–103].

Few places, however, provide a better natural experiment for determining health effects from chronic H₂S exposure than Rotorua, New Zealand, where a population of 60,000 people

lives near an active geothermal field. The most reliable background levels of H₂S in this area indicate a median concentration of 30 µg/m³ (20 ppb) [104]. While initial indications were that there might be cardiovascular, nervous system and respiratory diseases stemming from this chronic low level-H₂S exposure [105] some 15 years later, further studies have so far failed to identify any negative sequelae apparent in the potentially susceptible population [106–111].

7. Conflicting Observations Regarding the Chemical Toxicology of H₂S

7.1 Lessons from occupational accidents

The available (anecdotal) evidence from acute human (occupational) mass exposures to H₂S gas suggests approximately 20% of victims should require no treatment. But there will be ~5% fatalities and about three-quarters of the victims can be expected to arrive alive at the clinic exhibiting coma, disequilibrium, respiratory insufficiency and/or pulmonary edema [94, 112, 113]. Amongst sewer workers exposed in enclosed spaces below ground level, fatalities can be expected to be higher, but there are still survivors [114–116]. Based on their experience with workers in Canadian sour gas wells (the epicenter of H₂S poisonings in North America) Burnett *et al.*[112] assert that “increased attention to cardiopulmonary resuscitation at the exposure site and during transportation to hospital is necessary to reduce the mortality from H₂S exposure.” Neurological sequelae to sulfide poisoning have been reported [23, 94, 113, 117, 118], but these remain rare. Interestingly, discounting minor symptoms like dizziness and headaches that resolve themselves, no long-term neurological (or other) effects were evident in any of the 221 cases documented in the Canadian study[112]. A satisfactory animal model of human H₂S exposure reproducibly leading to neurological sequelae following a single toxicant dose remains elusive [119]. Thus, there is a nagging suspicion that most of the reported neurological consequences of H₂S exposures in humans necessitating treatment might be due to other factors such as brain anoxia, or head injury sustained during knockdown, rather than any more direct effect of the toxicant.

Where autopsies have been performed in a timely fashion, it has been noted that the internal organs of human H₂S poisoning victims have been discolored – the blood and sectioned brain, in particular, appearing distinctly green. This green color is due to the formation of sulfhemoglobin [120–123] in which the porphyrin ring has been covalently modified (Figure 3) [124–126]. Significantly, at this time, these established characteristics of human poisonings have not been observed together in any of the reported animal models of which we are aware. For instance, mice given LD₄₀ doses of NaSH by injection either die in less than 4 min or fully recover within 15 min [97]. Furthermore, purified mouse hemoglobin can readily be manipulated to undergo the same conversion to sulfhemoglobin as the human protein. However, the animals have so far never exhibited any evidence of sulfhemoglobin formation, irrespective of whether the toxicant is given by single-shot intraperitoneal injection, slow tail-vein infusion, or by inhalation (A.A. Cronican, K.L. Frawley, L.L. Pearce & J. Peterson, unpublished observations). This situation is not helpful with regard to the development of effective therapies and there are no currently approved antidotes/protocols to treat poisoning by sulfide (H₂S/HS⁻), only suggested supportive countermeasures [23, 127, 128].

Some authors in the early literature (before the structures were properly identified) have confused the terminology. For example, what is now known as either methemoglobin-sulfide, or sulfidomethemoglobin (metHbSH, where HS⁻ is a ligand to the heme iron) some early authors [114] referred to as sulfhemoglobin (SHb). Here we reserve the latter term for the covalently modified macrocyclic structure shown in Figure 3.

7.2 H₂S catabolic biochemistry

Despite some thoughtfully discussed cautionary arguments [129–131], the reader will be aware that a significant literature continues to rapidly emerge regarding the possible function of H₂S as a “gasotransmitter” [10, 13, 38, 132, 133]. Taking a pragmatic stance, we may assert this body of work to be outside the scope of the present review and confounding, rather than clarifying, with regard to some important questions relevant to H₂S toxicity. Any signaling functions of H₂S must take place at orders of magnitude lower concentration than the relevant levels in toxicity scenarios – considerations of mass action alone probably ensuring that different small-molecule bioinorganic reactions are involved in these two circumstances. For example, there presently seems to be a concurring opinion [38, 134–139] that the catabolic elimination of H₂S in mammals is catalyzed almost exclusively by the sulfide oxidase system localized within mitochondria. This may well be the case under more-or-less normal physiological circumstances, but probably not at the elevated H₂S levels to be experienced during poisonings and, perhaps, some other pathological conditions. The first enzyme of the sulfide oxidase system, sulfide quinone reductase, abstracts a hydrogen atom from H₂S and passes two electrons to the electron-transport system via ubiquinone. Of course, the terminal acceptor for these two electrons is oxygen at the active (ligand-binding) site of cytochrome *c* oxidase (complex IV). Now we have an instructive conundrum, for if the primary molecular target for the toxicant sulfide is, as widely accepted (see below) the ligand-binding site of cytochrome *c* oxidase, then sulfide unavoidably inhibits its own elimination (Figure 4).

There are, however, several lines of evidence that contradict the notion that sulfide need necessarily inhibit its own elimination completely. First, mice rendered unconscious (near death) by infusion of NaSH solutions into the tail vein over 5–10 min recover within seconds of stopping the infusion (Frawley et al., 2017, manuscript in revision) much faster than recovery from equivalently toxic levels of the similarly acting toxicant sodium cyanide. Second, the observation at autopsy of sulfhemoglobin formation in humans [120–123] is clear evidence for at least one other alternate competitive metabolic pathway for sulfide. Third, a literature has emerged describing the presence of dimethylsulfide (CH₃SCH₃) in exhaled breath [140, 141] another pathway for elimination of sulfide. This has been confirmed/discovered in individuals with elevated levels due to “extra-oral halitosis”; that is, not due to bacterial production of dimethylsulfide in the oral cavity, but from internal sources [142, 143]. These recent observations regarding dimethylsulfide generation in humans echo the earlier literature in which the “methylation pathway” was generally recognized as a detoxification route, albeit subordinate to the sulfide oxidase system [86, 144]. Finally, it appears that sulfide (H₂S/HS⁻) can only be detected in the bloodstream of both rats and sheep for a matter of seconds when administered intravenously at sub-lethal, but measurably toxic, levels [145–148]. In short, there are almost certainly multiple

pathways through which sulfide can be eliminated from mammals, though these remain poorly delineated at this time. This ought not to be surprising as sulfide is both a good ligand and reductant [129] – that is, some of its biochemistry may not necessarily be enzyme catalyzed.

7.3 Molecular pathology

While sulfide can clearly react with multiple biomolecules and there are tissue-specific variations in the toxic response, the crucial molecular target in acute cases is generally accepted to be cytochrome *c* oxidase (complex IV) of the mitochondrial electron-transport system (ETS)[23, 97, 127, 128, 149–151]. Sulfide is certainly a potent inhibitor of complex IV, but it is less well known that it also reacts with the enzyme resulting in catalytic turnover [89, 149, 152, 153]. Therefore, while these reactions remain poorly understood, they do provide yet another potential route for catabolic elimination of sulfide when enzyme inhibition is sub-maximal. As molecular H₂S can freely diffuse through membranes, it readily crosses the blood-brain barrier to inhibit mitochondrial ETSs within the central nervous system. In unanesthetized laboratory animals, this results in clear behavioral signs of intoxication 2 min post-injection and can lead to death from respiratory paralysis within ~3 min [23, 97], or cardiac failure after ~7 min [147, 148]. At this time, it is not clear how to reconcile the observation that free H₂S/HS⁻ seemingly only persists for a matter of seconds in the bloodstream [145–148] yet onset of symptoms associated with complex IV inhibition by H₂S/HS⁻ begins at 2 min after the toxicant dose. We remind the reader at this point that significant numbers of human victims of H₂S inhalation arrive at the clinic with cardiopulmonary symptoms 30 min or more after exposure and frequently succumb hours later [51, 94, 112, 154].

7.4 Pulmonary considerations

Prior to the emergence of any gasotransmitter activity, there were insightful, concise reviews of H₂S toxicity published [87, 154–156] that still provide an excellent entry point to this literature, as well as some lengthier scholarly documents [94, 144, 157]. A few key points worth reiterating include that while there are some relatively mild and mostly resolvable ocular conditions associated with chronic H₂S exposures, the neurological sequelae reported in humans following more acute exposures may primarily be caused by brain anoxia or head trauma suffered during a collapse, both secondary to the direct toxic effects of H₂S. The observed symptoms of acute gaseous exposures are hyperpnea, then unconsciousness (“knockdown”), followed by apnea and finally, death, frequently accompanied by pulmonary edema. The lung appears to be especially sensitive as hyperpnea and apnea are observed in laboratory animals administered sulfide solutions by injection [158], while edema only seems to follow H₂S inhalation [87, 154, 156, 159]. Recent work with the cysteine dioxygenase knockout mouse, which accumulates sulfide, has confirmed that the lung (and pancreas) is (are) more susceptible to toxicity from endogenously elevated sulfide than liver, or kidney [160]. Also, in various other animal models, sulfide has been demonstrated to contribute to the development and progression of lung inflammation and injury [161]. Bizarrely and to the contrary, however, sulfide is apparently ameliorative in the case of lipopolysaccharide-induced acute lung-injury (ALI) in rats [162] and in burn/smoke-induced ALI in sheep[8]. Both Olson [130, 131] and Haouzi [163] have written extensively about the

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practicalities of manipulating sulfide in biological samples and the difficulty in distinguishing physiological from pharmacological processes, particularly at the uncertain sulfide levels obtained in tissues irrespective of the method of administration. Of course, one should expect that many of the paradoxical observations in the present literature could be resolved with improved knowledge of the underlying sulfide biochemistry. In this regard, quantitative understanding of the small molecule bioinorganic chemistry underpinning much of the field appears especially lacking. So, for example, while some authors argue that oxygen-dependent redox processes are involved in sulfide cytotoxicity observed in cultured cells [164, 165], other groups have pointed out that in the case of intact animals [97] and human patients [156] any effects of supplemental oxygen are indistinguishable from normal recovery. While less than helpfully informative, it is probably not disingenuous to describe the current status of the relevant redox biochemistry [133, 138] as complicated at best.

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There is perhaps some hypersensitivity exhibited by individuals with pre-existing conditions such as asthma [23, 87], but in comparison to other common chemical reagents like ammonia and volatile organic acids, H₂S is a modest lachrymator/pulmonary irritant. Accidental releases of sulfide being more likely to elicit eruptions of puerile humor from one's laboratory colleagues than more serious consequences. Given such experiences, it is possible that the severity of inhaled H₂S as an irritant has sometimes been overstated – maybe originating in attempts to explain some of the observed physiological responses to exposure predating any understanding that one or more sulfide species might be signaling molecules. During inhalation, the sulfide fluxes experienced by the lung tissues are going to be significantly greater than both the systemic levels and, also, the fluxes that the lung tissues themselves would experience following toxicant administration by alternate methods. Thus, development of pulmonary edema following H₂S inhalation, the most notable issue in human fatalities [112], reflects this locally elevated exposure, but probably involves responses other than a mere reaction to an irritant. Typically, clinical presentations of pulmonary edema are secondary to either elevated pulmonary capillary pressure from left-side heart disease (cardiogenic) or injury and an increased permeability of the lung microvasculature, frequently associated with sepsis (noncardiogenic)[166, 167]. Endothelial barrier function is seemingly always compromised, while the epithelial barrier is usually, but not always affected [167]. The less-often-encountered syndromes neurogenic pulmonary edema and high-altitude pulmonary edema each show both cardiogenic and noncardiogenic features [167–169]. It has been clear for decades that H₂S-induced pulmonary edema is associated with vascular permeability due to the high protein content of the extravasated fluid [84, 170, 171] – but a further similarity between this and any of the other noncardiogenic syndromes essentially remains open to question.

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Multiple types of calcium and potassium ion channels (at least) are susceptible to modulation by H₂S, especially within the cardiovascular system [172–174]. These emerging effects of H₂S exhibit a complicated interdependence with those of nitric oxide, the relationship being demonstrably evident in endothelial and smooth muscle cells [172, 175–177]. Since the details of these interactions in physiological circumstances are still emerging, any associated pathological biochemistry is even less well delineated, but there is promising scope here for the discovery of a mechanism to explain H₂S-induced pulmonary edema and, thus, potential therapeutic targets. There has been some recent focus on the lung

epithelial sodium channel as a target for treating H₂S-induced acute pulmonary edema [178–180]. Unfortunately, there is cause for pessimism with regard to this suggestion because multicenter clinical trials with epithelial sodium channel activators/stimulators for the treatment of patients with pulmonary edema have, thus far, proven disappointing [181]. In proof-of-concept laboratory experiments with animals, where the poisoning protocols were quite unlike human cases, it has been shown that hydroxocobalamin [182] and its biological precursor, cobinamide [183], offer some protection against injected NaSH. However, in keeping with the reported observation that free sulfide is eliminated from the bloodstream very quickly [145, 146], the hydroxocobalamin had to be given within ~2 minutes of the toxicant. Cobinamide was given during administration of the toxicant dose – neither of these protocols being of much practical value in relation to human poisonings.

8. Concluding Remarks

Hydrogen sulfide represents a public health risk worthy of continued attention, especially from an occupational perspective [16] – but the monitoring infrastructure currently in place could be improved. Incomplete databases and inadequate research regarding the health effects of H₂S across the range of levels to be found in the environment, as well as the potential for the gas to be used for malicious purposes – either by individuals or on a mass scale – is concerning. Future research efforts should be focused on better monitoring of known H₂S emissions, along with improving the documentation of exposures and their subsequent health impacts, identification of new potential sources and, most importantly, clarifying the mechanistic pathways by which H₂S exerts its toxic effects. Currently, in the absence of any FDA-approved (or off-label) therapeutics, the only available option for treating sulfide intoxication is supportive care and speculative application of antidotes for cyanide, which have thus far exhibited only limited efficacy. The lack of a clear mechanistic understanding of acute sulfide toxicity presents a significant barrier to the rational development of effective antidotes and protocols for their therapeutic application.

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- Hydrogen sulfide remains a significant occupational hazard.
- Major environmental sources of hydrogen sulfide in the U.S. are the result of three industrial sectors: pulp and paper (64% by weight), chemicals (17%), and petroleum refining (8%).
- High emission rates from oil and gas sites remain a hazard and are compounded by the fact that, in the U.S., no OSHA monitoring program exists at this time.
- Details of the mechanism(s) of hydrogen sulfide toxicity are incomplete.
- There are currently no FDA-labeled antidotes and no recommended treatment options for sulfide poisoning beyond supportive care.

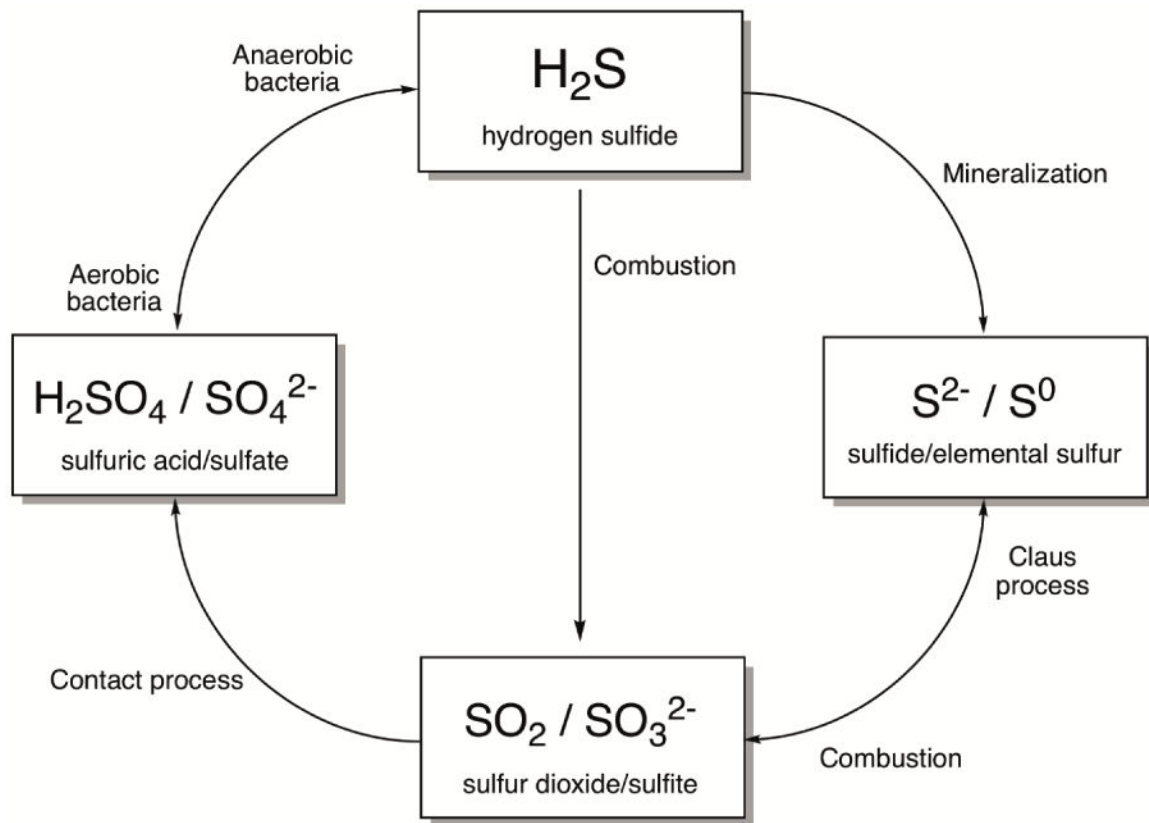


Figure 1.
Participation of hydrogen sulfide in the global sulfur cycle.

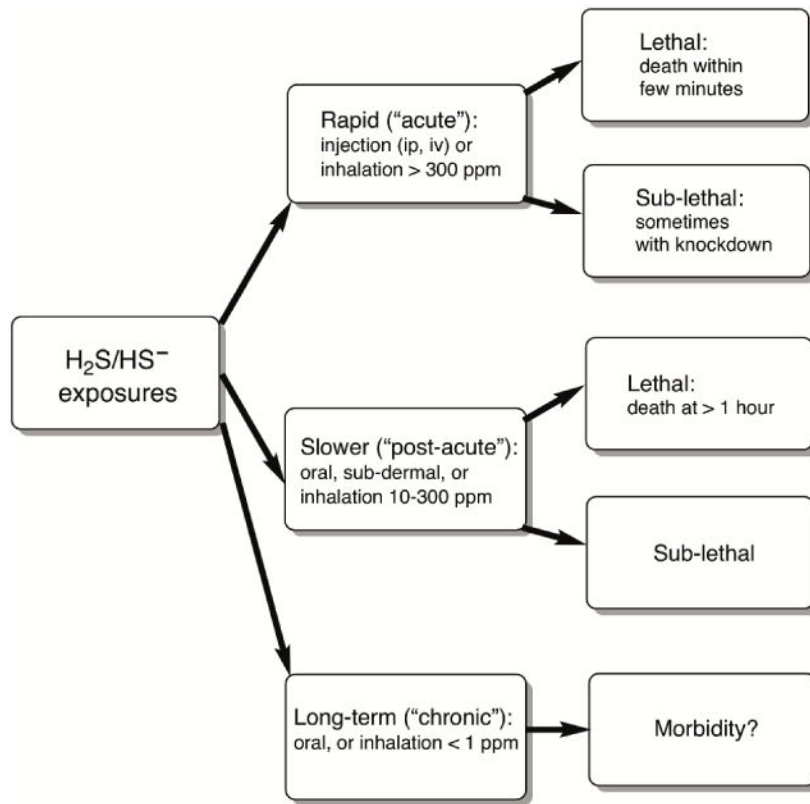


Figure 2.
Categories of Lethal and Sub - lethal H₂S Poisonings

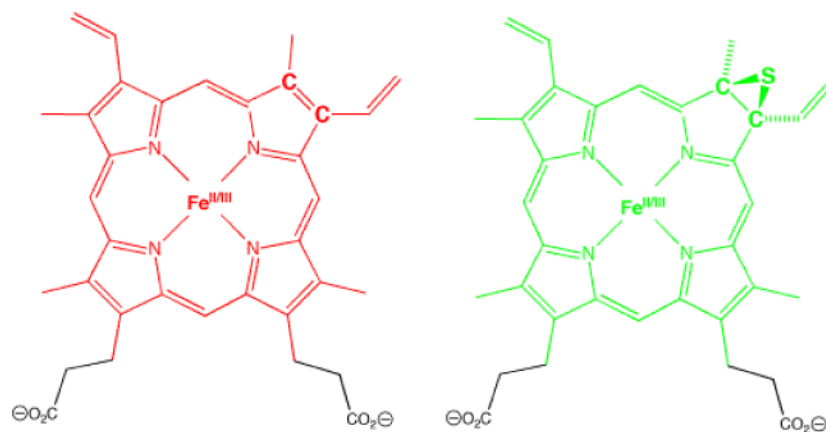


Figure 3. Structures of Native Red Heme (Iron-Protophyrin IX, on left) and the Kinetically Stable Form [124] of the Green Sulheme (on right).

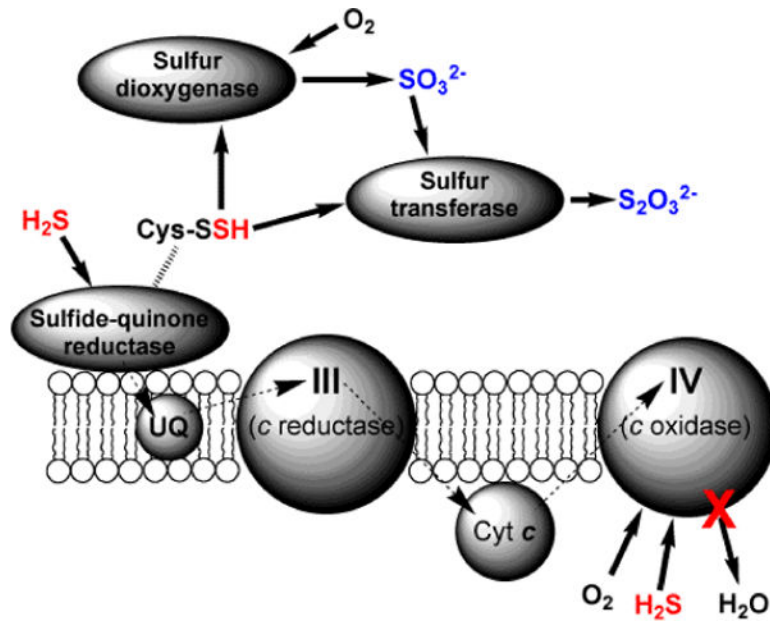


Figure 4.
The Association between H₂S Catabolism and the Mitochondrial Electron-Transport System.

Table 1

Meta-analysis of hydrogen sulfide source categories with maximum measurements collected by studies conducted between 2004–14, shown in descending order by study incidence and broken down by maximum measurement types (concentration, flux, flux density).

Source Categories (# of studies)	Maximum Measurements Reported ^a		
	Concentration (mg/m ³)	Flux (mg/hour)	Flux Density (mg/m ² /hour) ^b
AFO (n=31)	8.66E+03	6.30E+07	2.12E+04
Wastewater (n=20)	1.31E+03	8.91E+06	1.07E+01
Decomposition (n=10)	3.13E+03	1.44E+05	8.97E-03
Geothermal (n=9)	9.45E+01	3.78E+08	9.95E+03
Energy Production (n=7)	5.18E+02	2.57E+09	–
Other (n=2)	4.50E+03 ^c	–	–

(–) no measurements reported

^aDue to significant variance between data collection methods and data reported across the studies, only the measured maxima are used for comparison purposes.

^bAdditional flux densities were reported on animal feeding operation (AFO) sources using variable units (e.g. pigs or birds, but not by area), so their measurements have not been included in this comparison table.

^cTotal sulfur in water, plant emissions and sulfur-bituminous concrete emissions.

Table 2

Yearly Industrial Releases (lbs) for Hydrogen Sulfide, U.S., 2012–14[48, 50].

	2012 (% of total)	2013 (% of total)	2014 Emissions (% of total)
Total On-site Disposal or Other Releases	26,175,250 (99.96%)	26,920,643 (99.8%)	25,965,719 (99.8%)
Fugitive Air Emissions	9,815,319 (37%)	9,958,673 (37%)	9,083,805 (35%)
Point Source Air Emissions	10,754,996 (41%)	11,931,036 (44%)	11,486,797 (44%)
Surface Water Discharges	497,709 (2%)	513,188 (2%)	543,028 (2%)
Underground Injection Class I Wells	4,700,126 (18%)	4,153,417 (15%)	4,490,400 (17%)
Total Off-site Disposal or Other Releases	11,631 (0.04%)	46,021 (0.2%)	54,339 (0.2%)
Off-site RCRA Subtitle C Landfills and Other Landfills	3,834 (0.01%)	13,136 (0.05%)	9,078 (0.03%)
Total On- and Off-site Disposal or Other Releases	26,186,881 (100%)	26,966,663 (100%)	26,020,057 (100%)

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Table 3

Airborne hydrogen sulfide exposure limits established by various U.S. and international public safety organizations.

Agency	Exposure Level Types	REL (ppm)	Reference	
ACGIH	TLV-TWA	1	OSHA [63]	
	TLV-STEL	5		
AIHA	ERPG 1 ^a	0.1	AIHA [64]	
	ERPG 2	30		
	ERPG 3	100		
ATSDR	MRL-Acute	0.07	ATSDR [23]	
	MRL-Intermediate	0.02		
	MRL-Chronic	n/a		
DOE	PAC-1	0.51	DOE [65]	
	PAC-2	27		
	PAC-3	50		
EPA	RfC	0.001	EPA [51]	
	AEGL-1: 10 min	0.75	NRC [66]	
		30 min		0.60
		60 min		0.51
		4 hr		0.36
		8 hr		0.33
	AEGL-2: 10 min	41		
		30 min		32
		60 min		27
	4 hr	20		
		8 hr		17
	AEGL-3: 10 min	76		
		30 min		59
		60 min		50
		4 hr		37
8 hr		31		
DFG	MAK	5	DFG [67]	
IARC	Carcinogenicity classification	n/a	IARC [68]	
NIOSH	IDLH	100	NIOSH [69]	
	REL: 10-min	10		
OSHA	PEL (8-hour TWA) – general industry	n/a	OSHA [63]	
	PEL Ceiling	20		
	PEL Peak: 10 min	50		
WHO	TWA: 24 hr	0.10	WHO [70] b	

Agency	Exposure Level Types	REL (ppm)	Reference
Range: 1 ppb – 100 ppm			

^aERPGs estimate the concentrations at which most people will begin to experience health effects if they are exposed to a hazardous airborne chemical for 1 hour. (Sensitive members of the public are not covered by these guidelines; they may experience adverse effects at concentrations below the ERPG values.) A chemical may have up to three ERPG values, each of which corresponds to a specific tier of health effects:

ERPG-3 is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects.

ERPG-2 is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual’s ability to take protective action.

ERPG-1 is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing other than mild transient health effects or perceiving a clearly defined, objectionable odor.

^bWhile not discussed in WHO’s 2010 report on select air pollutants, the World Health Organization did publish air quality guidelines on H₂S in this report from 2000.

Abbreviations & Definitions (alphabetical): ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline level; AEGL-1 = nondisabling threshold limit; AEGL-2: disabling threshold limit; AEGL-3: lethality threshold limit; AIHA = American Industrial Hygiene Association; ATSDR = Agency for Toxic Substances and Disease Registry; DFG = Deutsche Forschungsgemeinschaft; DOE = U.S. Department of Energy; ERPG = emergency response planning guideline; IDLH = immediately dangerous to life and health; IARC = International Agency for Research on Cancer; MAK = maximum workplace concentration across an 8-hour day, 40- hour work week; MRL = minimum risk level (inhalation factors, not oral, have been derived); MRL-Acute = MRL for acute-duration inhalation exposure (14 days); MRL-Chronic = MRL for chronic-duration inhalation; MRLIntermediate = MRL for intermediate-duration inhalation exposure (15–364 days); NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; NRC = National Research Council; OSHA = Occupational Safety and Health Administration; PAC-1 = All protective action criteria correspond to 60-minute AEGL values. PAC-1 is for mild, transient health effects; PAC-2 = irreversible or other serious health effects that could impair the ability to take protective action; PAC-3 = life-threatening health effects; PEL = permissible exposure limit; PEL Peak: 10 min = acceptable maximum peak above ceiling over an 8-hour shift for 10 minutes once only if no other measured exposure occurs; PPM = parts per million; REL = recommended exposure limit; RfC = daily inhalation exposure limit over a lifetime that does not present risk of deleterious effects; TLV-STEL = threshold limit value – short-term exposure limit; TLV-TWA = threshold limit value – time weighted average.

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Table 4

Pathophysiological responses to hydrogen sulfide at various concentrations in air.

Concentrations (ppm)	Expected Effects/Symptoms
0.00011–0.00033	Typical background concentrations (OSHA)
0.0005	Lowest concentration detectable by human olfactory senses (ATSDR)
0.01–1.5	Odor threshold (when rotten egg smell is first noticeable to some). Odor becomes more offensive at 3–5 ppm. Above 30 ppm, odor described as sweet or sickeningly sweet (OSHA)
2–5	Prolonged exposure may cause nausea, tearing of the eyes, headaches or loss of sleep. Airway problems (bronchial constriction) in some asthma patients (OSHA)
20	Possible fatigue, loss of appetite, headache, irritability, poor memory, dizziness (OSHA)
50 – 100	Slight conjunctivitis (“gas eye”) and respiratory tract irritation after 1 hour cause digestive upset and loss of appetite (ANSI and OSHA)-hour exposure. May
100	Coughing, eye irritation, loss of sense of smell after 2–15 minutes. Altered respiration, pain in the eyes and drowsiness after 15–30 minutes followed by throat irritation after 1 hour. Several hours of exposure results in gradual increase in severity of these symptoms and death may occur within the next 48 hours (ANSI and OSHA)
100 – 150	Loss of smell (olfactory fatigue or paralysis) (OSHA)
200 – 300	Marked conjunctivitis and respiratory tract irritation after 1 hour of exposure (ANSI and OSHA). Pulmonary edema may occur from prolonged exposure (OSHA)
500 – 700	Staggering, collapse in 5 minutes (OSHA). Serious damage to the eyes. Loss of consciousness and possibly death in 30 minutes - 1 hour (ANSI and OSHA)
700 – 1000	Rapid unconsciousness, “knockd own” or immediate collapse within 1 to 2 breaths, cessation of respiration and death within minutes (ANSI, ATSDR, and OSHA)
1000 – 2000	Unconsciousness at once, with early cessation of respiration and death in a few minutes. Death may occur even if individual is removed to fresh air at once (ANSI and OSHA)

Sources: [23, 95, 96]

Abbreviations: ppm, parts per million; ANSI, American National Standards Institute; ATSDR, Agency for Toxic Substances and Disease Registry; OSHA, Occupational Safety and Health Administration