CYANIDE AND HYDROGEN SULFIDE: A REVIEW OF TWO BLOOD GASES, THEIR ENVIRONMENTAL SOURCES, AND POTENTIAL RISKS

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ABSTRACT

The uncontrolled releases of blood gases have been to blame for historic public health catastrophes, but they also play vital roles in modern day industrial processes and within the body. Cyanide, specifically hydrogen cyanide (HCN), and hydrogen sulfide (H_2S) are two such blood gases of interest. Accurate assessments of the risks each pose are essential to capitalizing on their positive contributions to society and preventing further incidents. While these two compounds have been studied for many years, new research is shedding light on their potential sources, emission rates, risks, and antidotal mechanisms; emerging science centered on the endogenous role of H_2S has enthused many researchers regarding the potential application of this blood gas in preventing or treating maladies, yet caution must be exercised in such endeavors as we still do not fully understand the mechanisms by which H_2S is toxic to humans. Recent studies have pointed to the risk of exposure to elevated levels of cyanide in foods, but also from anthropogenic sources such as fire smoke, marijuana smoke, and releases from mining sites. This study reviews recent literature surrounding H_2S and cyanide sources and human health effects, including discussions on their sources, emission rates, and mechanisms of toxicity, in order to better understand their public health significance. Finally, recommendations for better management of these two blood gases to reduce risk are presented, including remarks on systematic air monitoring and antidote needs, public health preparedness considerations, and the potential risks that hydrogen sulfide and cyanide pose on a global scale.

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PREFACE

My thanks and sincerest regards go to Drs. Jim Peterson and Linda Pearce for their patience and leadership; I have learned far more from them than the content of this study. The guidance and support of my additional committee members, Drs. Ravi Sharma and Bruce Pitt, were invaluable throughout my coursework, research, and dissertation preparation, as well.

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1.0 INTRODUCTION

Hydrogen sulfide (H_2S) and cyanide - hydrogen cyanide (HCN) specifically - are toxic compounds that share many interesting qualities and are found readily in the environment and industrial settings. Given the widespread distribution of H_2S and cyanide and/or their precursors, together with the highly toxic nature of the agents themselves, it is appropriate in the public health community to be proactive and continually diligent when characterizing and managing the hazards associated with their release and usage. The overall objective of this research is to review and compare the toxicity, effects, and scenarios where people may be exposed to dangerous levels of these two "blood gases" in order to help manage the risks they pose. Accordingly, this first chapter introduces the concept of blood gases and their public health relevance. Chapter 2 consists of an in-depth study of one particular blood gas, H_2S, wherein sources, regulation, suspected effects, and conflicting chemical toxicity observations are summarized. A systematic review of H_2S emissions and concentrations literature published from 2004 – 2014 is included in this chapter. A summary focusing primarily on emission sources and "normal" environmental levels of cyanide is presented in Chapter 3 up to the end of December 2012, as the chapter was then published by this author and colleagues in *Toxicology of Cyanides and Cyanogens: Experimental, Applied and Clinical Aspects* (Malone et al., 2015). Finally, Chapter 4 discusses overall gaps in the state of the science, where future research and public health endeavors should be aimed to prevent or mitigate potential adverse impacts from H_2S and cyanide, and broader issues that could cause or be affected by the release of these two compounds on a global scale. As an introduction to these concepts, let us first review how cyanide and H_2S are classified by the medical community.

1.1 BLOOD GASES

Among professionals within clinical medicine, the term "blood gases" refers to a spectrum of measurements taken of dissolved gases in arterial blood used to determine how well the body is taking in oxygen, expiring carbon dioxide, and preserving the acid-base balance in extra-cellular fluid. This arterial blood gas (ABG) test helps to give medical personnel an idea of the overall health of a patient by determining the blood's acid-base balance (pH), partial pressure of oxygen (P_aO_2), partial pressure of carbon dioxide (P_aCO_2), oxygen saturation (S_aO_2), concentration of bicarbonate (HCO_3^-), and base excess and base deficit (CLSI, 2004). Beyond the indicators sought in the traditional ABG test, many other environmentally-relevant gases can be carried by the blood. Anesthesia, for example, relies heavily on the blood's ability to transport inert gases such as nitrous oxide throughout the body (Baker and Farmery, 2011). Environmental agents found outside of anesthesia but historically encompassed by the same terminology – such as hydrogen cyanide (HCN) and hydrogen sulfide (H_2S) – also play specific roles in the body, supporting or interfering with cellular respiration depending on their concentrations. HCN and H_2S, ubiquitous and highly toxic blood gases that may also reasonably be described as "cellular toxicants" or "mitochondrial poisons," are the foci of the following study.

1.2 GASEOUS SIGNALING MOLECULES

Blood gases suspected of playing role(s) in the body at low levels are referred to as *gaseous signaling molecules*, a category in which both HCN and H_2S belong (Borowitz et al., 1997, Wang, 2002). These gaseous molecules are used to transmit chemical signals at a cellular level or beyond,

and can be produced endogenously or brought in from external sources. Additional gaseous signaling molecules currently include ammonia (NH_3), carbon dioxide (CO_2), carbon monoxide (CO), carbon suboxide (C_3O_2), ethylene (C_2H_4) (in plants), methane (CH_4), nitric oxide (NO), nitrous oxide (N_2O), oxygen (O), and sulfur dioxide (SO_2) (Cooper, 2000, Cummins et al., 2014, Heitman and Agre, 2000, Hogg et al., 1996, Kenney et al., 2015, Kerek, 2000, Levitt et al., Lin et al., 2009, Liu et al., 2010, NHLBI, 2012, Rennke and Denker, 2007, Stryer, 1995, Wu and Wang, 2005). Within the category of gaseous signaling molecules is an even more specialized and emerging field called *gasotransmitters*.

1.3 GASOTRANSMITTERS

Only certain gaseous signaling molecules fall into the subcategory of gasotransmitters, although the distinction between the two terms has been blurred within the literature. For example, Mustafa et al. (2009) define a gasotransmitter as a "…gaseous messenger molecule involved in any signaling process." Polhemus and Lefer (2014) describe NO, CO, and H_2S as "endogenous gasotransmitters" or "signaling molecules," or explain that they "are all produced endogenously via enzymes." In contrast, Tinajero-Trejo et al. (2013) describe gasotransmitters more specifically, as "small gaseous molecules that play key roles in biology… All these gases penetrate membranes, are poisons in excess, are endogenously generated and have important biological targets, especially metalloproteins." For the purpose of this study, let us define gaseous signaling molecules as any that can be produced within or outside of the body, while gasotransmitters are small molecules of gas produced endogenously that freely permeate membranes; they can evoke endocrine, paracrine, and autocrine effects; their production is regulated by the body; they have well defined functions

at physiologically relevant concentrations; when the body absorbs this gas from the environment, the functions can be mimicked; and they likely target specific cellular and molecular mechanisms (Wang, 2002).[1] Gasotransmitters are distinct from more classic messenger molecules such as hormones and neurotransmitters in that gasotransmitters chemically modify intracellular proteins, thereby affecting cellular metabolism more directly and immediately (Mustafa et al., 2009). Understanding the core functioning differences between these molecules may not only help understand their benefits, but may also support antidote development to protect against overexposure (e.g. in the case of H_2S).

Originally, NO was the only known gasotransmitter, playing roles in the cardiovascular, immune, and nervous systems (Tinajero-Trejo et al., 2013). Recent research has since placed CO and H_2S into that category, as well (Wang, 2002, Marks et al., 1991). CO serves as a neurotransmitter and helps to regulate certain cardiovascular and immune systems (Mann, 2010, Marks et al., 1991), while H_2S is suspected to affect the cardiovascular system and to help regulate metabolism within cells and in the body more generally (Wang, 2002). Despite the fact that cyanide can be produced endogenously and activates several biological functions (Borowitz et al., 1997), it is not considered a gasotransmitter by the larger scientific body or by some of the more specific definitions put forth in the literature – further supporting the need for more research into these compounds and how gasotransmitters are defined.

The specialized roles that cyanide and H_2S play as gaseous signaling molecules increase the risks they pose as environmental pollutants to humans. Put simply, the body is sensitive to low levels of these compounds, so higher levels produced exogenously may prove deadly. While

[1] For more information, see the European Network on Gasotransmitters, which was formed in 2011 to promote research around gasotransmitters (http://www.gasotransmitters.eu).

toxicity due to consumption or dermal absorption of cyanide or H_2S can occur, inhalation is the most perilous exposure route for both of these agents in terms of efficacy. (Worldwide, however, cyanide exposure is more likely to occur through ingestion.) High levels of H_2S and cyanide in the air can occur in a variety of situations, such as during mining operations, but fire smoke containing HCN is more of a concern in the case of cyanide. Two antidote kits are approved for use in the case of acute cyanide poisoning: Cyanokit™ (hydroxocobalamin) and Nithiodote (containing the sodium salts of nitrite and thiosulfate). Concerns exist as to their efficacy, however (Cambal et al., 2011, Cambal et al., 2013), and while research is ongoing, there is no approved antidote for H_2S (Jiang et al., 2016, ATSDR, 2014a).

Quantifying inhalation risks posed by cyanide and H_2S is complicated by the fact that few recent studies have been conducted that wholly document emissions, and the levels that people may be exposed to these compounds in a variety of situations. These inhalation threats, along with additional information, are discussed separately for each compound in chapters 2 and 3. Chapter 3 on cyanide also discusses risks due to ingestion from dietary sources. Finally, Chapter 4 brings together H_2S and cyanide to discuss directions of future research, emergency response risks, education needs, and global issues that should be considered on a broader scale.

2.0 ENVIRONMENTAL TOXICOLOGY OF HYDROGEN SULFIDE

2.1 INTRODUCTION

In 1878, the passenger-carrying paddle steamer Princess Alice was sunk in a collision on the River Thames, with the loss of over 640 lives, and curiously, may actually represent one of the largest mass poisoning episodes in history (Thurston, 1965, Lock, 2013). 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% of passengers and crew) 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) (DETR, 2001). The Board of Trade enquiry and 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; the investigation did not consider that there may have been significant deaths caused by hydrogen sulfide (H_2S) inhalation, possibly accelerated by the victims thrashing at the surface (Thurston, 1965, Lock, 2013). 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 (Cooper, 2001) and, certainly, it is entrenched in sanitary engineering lore that many of the Princess Alice deaths were due to poisoning, probably by H_2S (Dobraszczyk, 2014).

Our understanding of H_2S sources and effects have vastly improved since 1878. Within the body it is believed that H_2S can be beneficial at very low levels (Dongó et al., 2011, Esechie et al., 2009, Yang et al., 2008). Above endogenous levels, however, H_2S can be harmful; to this day in

the U.S. and likely elsewhere, H_2S remains one of the most common hazardous substances attributed to poisoning deaths on the job (Frame and Schandl, 2015). Although scientists of multiple disciplines have studied this ubiquitous compound for many years, there are still facets of H_2S that remain elusive – including but not limited to a comprehensive estimate of the prevalence of this poisonous gas emitted into the environment and effects associated with such exposures, the mechanism(s) of its cellular toxicity, and effective antidote(s). The knowledge and research gaps associated with H_2S in the environment and its subsequent effects on the human body (especially when inhaled) are discussed herein.

2.2 PHYSICAL PROPERTIES OF HYDROGEN SULFIDE

Hydrogen sulfide is known by many names: hydrosulfuric acid, hydrogen sulphide, sulfinated hydrogen, sewer gas, and stink damp, dihydrogen monosulfide, dihydrogen sulfide, sulfane, sulfurated hydrogen, sulfur hydride and hydrosulfuric acid. H_2S is a colorless gas, slightly heavier than air, possessing the characteristic smell of rotten eggs. Among its many hazardous traits, H_2S is corrosive, explosive, and flammable. Table 1 below further describes the various properties of hydrogen sulfide:

Table 1. Physical properties of hydrogen sulfide

Trait	Properties[a]
Chemical formula	H_2S
CAS registry	7783-06-4
Molecular weight	34.08 g/mol
Odor	Rotten eggs[b]
Appearance	Colorless
Physical state (STP)	Gas
Melting point (°C)	-85.49
Boiling point (°C)	-60.33
Solubility (water)	3.98 – 4.1 g/L (20℃)

Table 1 Continued

Solubility (organic solvents)	Glycerol, gasoline, kerosene, carbon disulfide, crude oil; certain polar organic solvents (methanol, acetone, propylene carbonate, sulfolane, tributyl phosphate, various glycols, & glycol ethers)
Log K_{ow}	Not applicable
Log KOW Henry's law constant (25℃)	9.8 x 10^{-3} atm • m^3/mol

a. Reference: ATSDR (2014a)
b. Detectable only at low levels

Although not as polar as water, the molecular structure of H_2S, is similar to that of water and is also moderately soluble (Oviedo, 2010). The pK_a for the reaction $H_2S \leftrightarrows H^+ + HS^-$ is 7.04, and the second pK_a is unaccessible in water (Harris, 2010, Butcher, 2010, Housecroft and Sharpe, 2012)[2]. Consequently, at pH 7.4 (and irrespective of the exposure route *in vivo*) hydrogen sulfide is ~30% H_2S and ~70% HS^- (hydrosulfide) prior to any biochemical modification. 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.

If released as a gas, H_2S remains in the atmosphere for approximately 1 day in the summer and 42 days in winter, becoming changed to sulfur dioxide (SO_2) and sulfuric acid (H_2SO_4) during this process (Bottenheim and Strausz, 1980). Converting H_2S to SO_2 requires the introduction of a hydroxyl radical (Equation 1).

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

$$H_2S + HO\bullet \rightarrow HS^+ - H_2O$$
$$HS + O_2 \rightarrow HO\bullet + SO$$
$$SO + O_2 \rightarrow SO_2 + O$$

[2] Except where otherwise stated, data in this text are provided for H_2S in its standard state (at 25 °C, 100 kPa).

H_2S can also be intentionally removed from the air via combustion, producing elemental sulfur or SO_2 through the following chemical reactions (Rayner-Canham and Overton, 2009):

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

$$2\ H_2S(g) + O_2(g) \rightarrow 2\ H_2O(l) + 2\ S(s)$$
$$2\ H_2S(g) + 3\ O_2(g) \rightarrow 2\ H_2O(l) + 2\ SO_2(g)$$

In the presence of metal ions, hydrogen sulfide can react and form metal sulfides – or the salts of hydrogen sulfide (Pouliquen et al., 2000). This reaction allows lead(II) acetate paper to be used to detect H_2S, as the moistened paper turns black in color due to a PbS precipitate when the gas is present (Rayner-Canham and Overton, 2009):

Equation 3. Detection of hydrogen sulfide using lead acetate paper

$$Pb(CH_3CO_2)_2(s) + H_2S(g) \rightarrow PbS(s) + 2\ CH_3CO_2H(g)$$

H_2S released into water it is referred to as hydrosulfuric acid or sulfhydric acid. If sufficiently aerated, H_2S can be oxidized, forming elemental sulfur and water. Additional biological methods of H_2S removal have been explored to manage large-scale anthropogenic sources of H_2S in liquid form (Zhang et al., 2008). H_2S can also enter soil when deposited from the air or due to surface spills or natural events (Pouliquen et al., 2000, Sittig, 2002). Air is the medium where most H_2S is found, and where it is of most risk to people. Significant data gaps still exist when describing its particular fate and transport, however, as well as transformation rates within the broader sulfur cycle.

2.3 EMISSIONS & ENVIRONMENTAL SOURCES

Figure 1 is a simplified representation of the global sulfur cycle and where hydrogen sulfide is found therein.

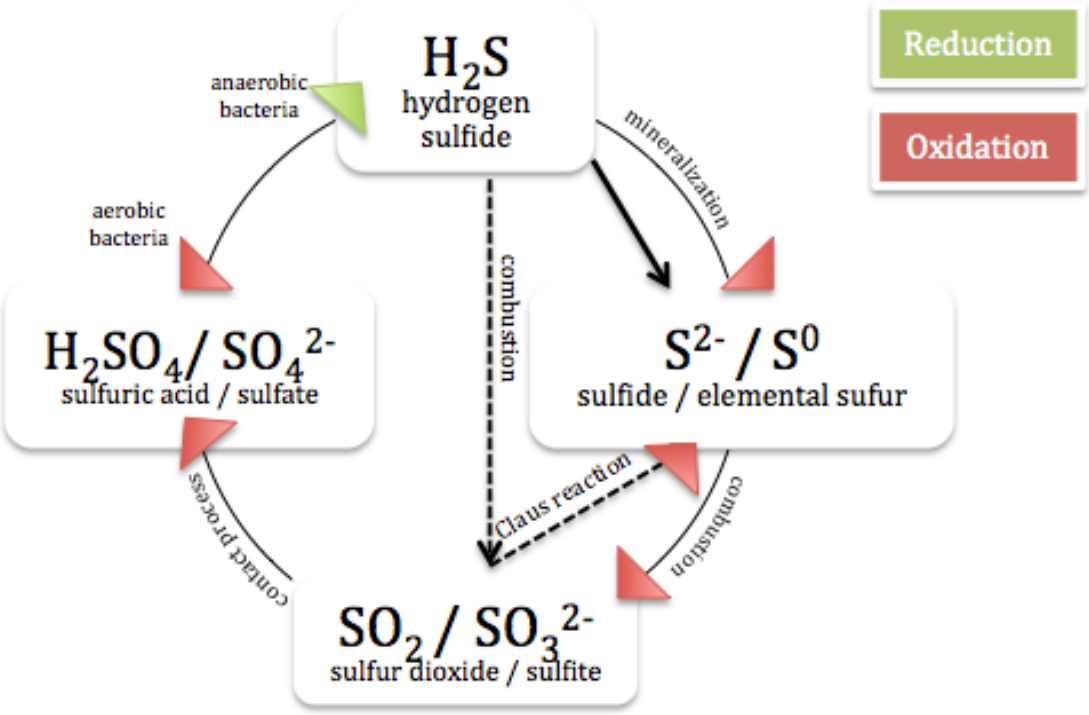


Figure 1. Global sulfur cycle

Hydrogen sulfide is a small part of the much larger cycle – so human activity is not likely to be able to significantly affect it. H_2S can be produced naturally in the environment through the anaerobic breakdown of organic matter by sulfate-reducing bacteria, anthropogenically by various industrial practices, and by normal biological processes within the body (Sivert et al., 2007, ATSDR, 2014a, Ober, 2006). Although not the focus of this chapter, production of H_2S in the body is a result of digesting protein-containing food. As previously discussed, H_2S is also part of a group of currently recognized gasotransmitters (along with NO and CO) (Wang, 2002). Although concentrations in urban areas can be as high as 1 ppb based on data prior to 1993 (US EPA, 1993), background H_2S air concentrations typically range between 0.11 ppb and 0.33 ppb. As to be expected, the closer a person lives to sources of H_2S emissions, the higher the background levels

tend to be (and can exceed 90 ppb) (Fulton et al., 2003, Horton et al., 2009, Inserra et al., 2004, White et al., 1999).

Current assessments on yearly H_2S emissions are based on data collected several years ago; terrestrial sources are estimated to account for 53 to 100 million metric tons of sulfur, while ocean emission rates are between 27-150 million metric tons (Hill et al., 1972, WHO, 2003). Natural sources, such as geothermal activity, are estimated to contribute most (90-95%) of the worldwide H_2S emissions (Beauchamp et al., 1984, US EPA, 1993). To provide a more a recent estimate of H_2S releases into the environment and their sources, emissions and concentrations data in published literature were aggregated in the following study.

2.3.1 Research Aggregation Methods

To quantify hydrogen sulfide sources based on size and the breadth of recently published research, we catalogued original research published from 2004-2014 that reported on either emissions or concentrations of H_2S from various sources under baseline (non-experimental) conditions. The search terms entered into both Google Scholar and the University of Pittsburgh's journal database (PittCat) were as follows: *allintitle: H2S OR "hydrogen sulfide" OR "hydrogen sulphide" AND concentration OR concentrations OR emission OR emissions*. Most articles were in English (>95%) as a result of the search terms, an acknowledged limitation of the study design, but non-English texts were reviewed where translation services permitted.

In total, 217 studies were initially returned in the search. The following exclusions were then used to filter out non-valid studies:

- Review articles, so as to prevent counting data twice (n=5)
- Studies that did not monitor natural or baseline H_2S concentrations or emissions (e.g. they controlled all conditions) (n=114);
- Non-peer-reviewed studies (unless official governmental/industry report/manual) (n=4); and
- Monitoring data not supplied, e.g. Conference proceedings that did not list direct measurements, or articles where results were not listed in the abstract and where full text was not available either openly or through PittCat (University of Pittsburgh) interlibrary loan requests (n=18).

After these exclusions, 76 valid studies remained. Most of these studies reported multiple results, and in those cases the peak, median, and/or average of concentrations and/or emissions were logged where available. We then grouped the monitoring results (n=130) by H_2S source; converted fluxes (n=16), flux densities (37), and concentrations of H_2S (n=77) into consistent units where possible[3]; and evaluated the aggregate trends.

2.3.2 Results

A systematic review of all valid studies that provided estimates for H_2S releases recorded as concentrations, flux, and flux density in the academic literature from 2004-14 have been

[3] Twenty (20) flux density results were reported in various animal units (AU) (e.g. mg of H_2S emitted per pig per hour). Due to monitoring technique variability (passive vs. active) and the broad range of animals that were studied, no attempt was made to convert these 20 flux densities into units comparable to the other 110 monitoring results reviewed. The Flux Density (AU) are all related to AFO emissions and reported *as is* in Appendix A, but they are not represented in the max emissions / concentrations summarized in Table 2.

summarized by general emission source below (Table 2). The complete tabulated dataset is presented in the appendix.

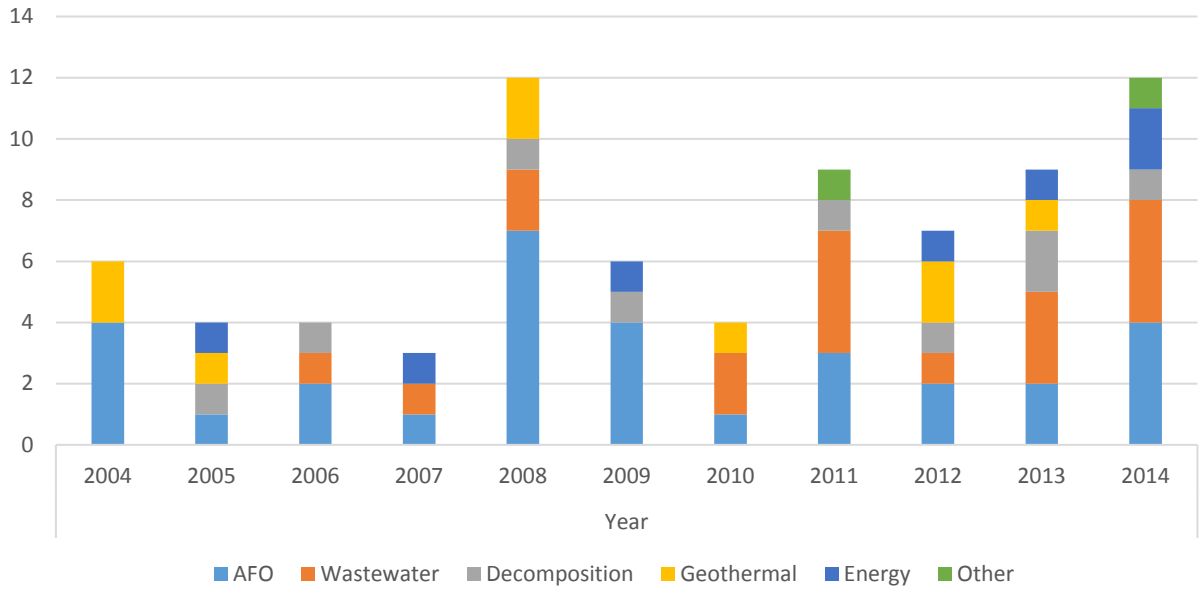


Figure 2. H_2S study sources by year, 2004-14

The years 2008 and 2014 saw the highest publishing rates on the topic of H_2S emissions and concentrations among the studies reviewed (Figure 2). Out of the 76 studies included in the assessment, animal feeding operations (AFOs) were the most commonly studied sources (n=31). In decreasing order, the next most commonly monitored sources by study were industrial or residential wastewater (n=18), decomposition of organic material (n=9), natural geothermal sources (n=9), energy production (n=7), and "other" (n=2) (Figure 3).

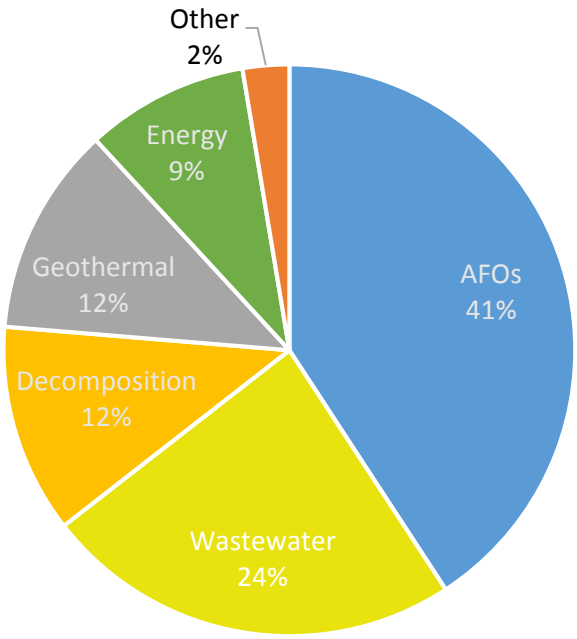


Figure 3. Topics (percentage) of the H_2S studies included in the study (n=76)

The emission source for each study was defined using the following distinctions:

AFOs – Animal Feeding Operations – Studies assessed H_2S emissions from any type of agricultural enterprises where animals are kept and raised in confined situations. Most of these studies investigated collective manure releases of the gas, but animals' H_2S emissions directly were also included on occasion. Swine AFOs were the most commonly studied source in this category (n=23), much more so than poultry (n=4) or cattle (n=4).

Decomposition – Studies (n=9) where the focus was on measuring H_2S emissions from decomposing organic matter, such as in wetlands, sedimentary mud, compost piles, and landfills.

Energy – Monitoring near intentional energy production activities (n=7), including oil and gas drilling and geothermal power plants.

Geothermal – Measured naturally-occurring H_2S geothermal activity (n=9) from volcanoes, geothermal fields, or marine environments.

Wastewater – H_2S levels/emissions from wastewater treatment plants and/or sewer systems (n=18).

Other – When studies fell outside of the other five categories listed above (n=2), they were classified as "Other." The first of these studies monitored concentrations of H_2S in water, as well as plant emissions, and the second looked at sulfur-bituminous concrete emissions.

While AFOs were the most studied source, the concentration and flux measurements of AFO operations were not the highest among the studies reviewed (Table 2); natural geothermal activity and anthropogenic energy production were two to three orders of magnitude greater for those measurement categories, respectfully. The standings listed in the table below remain essentially the same when assessing only the air monitoring results - the only difference being that animal feeding operations would contribute to the highest concentrations by source.

Table 2. Meta-analysis of hydrogen sulfide source categories with maximum measurements collected by studies conducted between 2004-14

Source Categories (# of studies)	Maximum Measurements Reported Within Each Category[a]		
	Concentration (mg/m^3)	Flux (mg/hour)	Flux Density (mg/m^2/hour)
AFO (n=31)	8.66E+03[b]	6.30E+07	**2.12E+04**[c]
Wastewater (n=18)	1.53E+03[d]	8.91E+06	1.07E+01
Decomposition (n=9)	**6.41E+05**[d]	1.44E+05	8.97E-03
Geothermal (n=9)	**3.79E+06**[d]	**3.78E+08**	**9.95E+03**
Energy Production (n=7)	5.18E+02	**2.57E+09**	-
Other (n=2)	4.50E+03[e]	-	-

Shown in descending order by study incidence and broken down by maximum measurement types. Top two sources for each measurement classification are bolded.
(-) no measurements reported in studies reviewed.
a. For comparison in air (e.g. if concentrations of sulfide in water were excluded), AFOs presented the highest concentrations.
b. Due to significant variance between data collection methods and data reported across the studies, only the maximum measurements are used for comparison purposes.
c. Additional flux densities were reported on AFO sources using variable units (e.g. pigs or birds but not by area). Their measurements are not included in this comparison table, but they can be found in the appendix.
d. The studies represented in these maximum concentrations reported total sulfur or dissolved sulfide, not H_2S.
e. The next highest maximum concentration in the Other category is significantly lower: 18.4 mg/m^3.

Only 5 results out of 130 included in the study reported H_2S levels/emissions directly in water (the rest monitored air). The search terms used to conduct the review could have favored studies that monitored air rather than water (e.g. “releases” was not a search term).

2.3.3 H_2S Produced Naturally in the Environment

In the environment, H_2S is often produced by sulfate-reducing bacteria through the anaerobic digestion of organic material. Additionally, some plants may use and emit H_2S as part of their primary functionality and not as decaying biomass (Wickenhauser et al., 2005, Jin and Pei, 2015). Significant environmental sources of this potent gas into the air 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. Small blooms of H_2S have recently been detected in the Dead Sea (Oren et al., 2004) and off of the coast of Namibia in the Atlantic Ocean due to fertilizer runoff and the breakdown of organic matter (Ward, 2006, Brüchert et al., 2009). Monitoring results of this source resulted in the second highest concentration measurements in the study (and actually exceeded the original study’s monitoring equipment’s measurement capability) (Brüchert et al., 2009). H_2S may also be present naturally in well water, often due to the activity of sulfate-reducing bacteria (Barton and Fauque, 2009). Overwhelmingly, though, air is the medium where H_2S is most likely to be present at levels that pose direct risks to public health.

Geothermal activity causes H_2S emissions to be released into the air, along with other toxic compounds, when the gases within magma (CO_2, SO_2, N, H, CO, S, Ar, Cl, and F) combine with hydrogen and water (Shinohara et al., 2002). While less studied than agricultural sources in recent years, naturally occurring geothermal activity did, in fact, register the highest concentrations of

H_2S into ambient air, and the second highest fluxes and flux densities (Table 2). This finding is supported by observations from many other studies (ATSDR, 2014a). Interestingly, high levels of H_2S in the atmosphere likely due to volcanic eruptions have been implicated in several mass extinction events throughout Earth's history (Knoll et al., 2007, Kump et al., 2005). Because of the capacity for natural sources like geothermal activity to emit H_2S at high rates, additional monitoring should be conducted to prevent accidental human overexposure and to help quantify worldwide yearly emissions more precisely, which would aid primary and secondary public health prevention efforts.

2.3.4 Anthropogenic Sources of H_2S

In recent years, anthropogenic sources of H_2S concentrations and emissions into the air have been studied significantly more often than natural sources (62 vs. 14 study topics), despite the propensity for natural sources to emit H_2S at high rates (Table 2). Although speculation, this trend could likely be due to the higher cost and complexity associated with measuring certain natural sources, such as aboveground and undersea volcanic activity. Among anthropogenic sources, H_2S can be found at elevated levels in or near sewage systems, and within animal containment buildings and slaughterhouses (generally categorized as AFOs). Industrial sources where H_2S can be present include oil and gas processing sites, geothermal power plants, coke ovens, food processing facilities, tanneries, and pulp/paper mills (Skrtic, 2006, Burstyn et al., 2007, Peralta et al., 2014, Chénard et al., 2004, Colomer et al., 2012, Vasarevičius, 2011, Rimatori et al., 1996, Svendsen, 2001). It is of note that H_2S emissions can be abated by at least 99% from geothermal power plants using either the Stretford process or various incineration and injection methods (Reed and Renner, 1995, Baldacci et al., 2005), but each plant's compliance will differ. Distinguishable from this

study and highlighted by Table 2 is the lack of recent studies assessing H_2S levels from a variety of known or potential H_2S sources (such as fires and tanneries) and flux densities from energy production operations. While H_2S is primarily released in gaseous form, it can also be found in liquid waste related to industrialization. Releases into water generally do not impact the waterway for very long, though, as H_2S quickly evaporates from water (except for in undisturbed, anoxic conditions) (Patterson and Runnells, 1992, ATSDR, 2014a).

The amount of H_2S emitted into the atmosphere from human activity is difficult to quantify worldwide due to a lack of comprehensive data and/or reporting. For example, H_2S emissions in the U.S. were exempt from reporting into the EPA's Toxic Release Inventory (TRI) between 1991 and 2011 (discussed further in Section 2.5). Additionally, the list of industries represented in the TRI is not exhaustive. According to the TRI, however, in 2012 most H_2S air releases in the U.S. were the result of three industrial sectors: pulp and paper (64% by weight), chemical (17%), and petroleum refining (8%) (US EPA, 2014). Contrastingly, the most significant source of H_2S emissions in western Canada is the oil and gas industry, due to geologic formations naturally high in H_2S (also called *sour gas*) (Hessel et al., 1997). Overall, total known H_2S releases in the U.S. (into air, water, and through underground injection) based on data from 2012-14 range between 26 and 27 million pounds per year (Table 3).

Table 3. Yearly TRI On-site and Off-site Reported Disposed of or Otherwise Released (in pounds), for All industries, for Hydrogen Sulfide, U.S., 2012-14[a]

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

a. H_2S emissions were not required to be reported to TRI from 1991-2011. Source: US EPA (2015)
b. Sub-category emissions will not add up to 100% of total, as not all release categories captured in the TRI are included in this table.

Animal feeding operations (AFOs) are agricultural enterprises where animals are kept, raised, and slaughtered in confined situations. Based on this study, AFOs are emitting relatively high quantities of H_2S (peak 6.30E+07 mg/hr) and are areas where elevated concentrations of H_2S can be found in the air at any given time (8.66E+03 mg/m^3). This characteristic is especially so during summer months and when manure mixing occurs indoors. While AFOs do not emit H_2S at rates (flux) on par with geothermal activity (3.78E+08 mg/hr) or energy production (2.57E+09 mg/hr), with approximately 257,000 AFOs in the United States alone (US EPA, 2003b), their sheer numbers can still contribute significant amounts into the air and/or expose workers to unsafe levels of H_2S. The substantial influx of AFO studies in recent years identified in this study may be due to a number of factors. Firstly, air and sludge monitoring at animal feeding operations may simply

be easier to conduct than other sources. The facilities are not mobile, and their emissions are fairly predictable – in stark contrast to volcanic eruptions, for example. Access to these sites may also be easier to obtain compared with oil and gas drilling sites or other industrial operations. Additionally, the quantification of air emissions from AFOs by the United States Department of Agriculture's Initiative for Future Agriculture and Food System Program seems to have been prioritized lately and, consequently, there is funding from the National Research Initiative Program (Li et al., 2008). As stated previously, however, AFOs according to Toxic Release Inventory estimates are not the top contributors of H_2S into the environment in the U.S., so it is possible that AFO monitoring priorities are askew compared with other sources. In order to accurately quantify total H_2S contributions to the atmosphere from AFOs, all AFO operations and their H_2S management methods should be tracked and monitored consistently over time.

Energy production was another area within this study that may emit H_2S at high rates, having recorded the highest flux measurement of all studies reviewed (2.57E+09 mg/hour). Energy production included two different types of studies – one on oil and gas extraction and processing, and the other focused on geothermal energy production. The highest flux measurement was cited from a geothermal power study (Peralta et al., 2014), however monitoring methods (active vs. passive) and results were highly variable within this little-studied category (n=7). More studies need to be conducted if one wanted to statistically compare H_2S from these two energy-generation sources.

An aspect of oil and gas drilling not adequately represented in the present studies reviewed is the issue of "sour gas" incidents. H_2S forms naturally within geologic formations that support oil and gas production as high-sulfur kerogens decay. When sulfur (and H_2S) content are high in wells, they are referred to as sour gas wells, and this situation can present serious consequences in

the event of a major uncontrolled release or blowout. In 2003 in Kaixian County, China, for example, 64,000 residents had to be evacuated and 243 died when an accidental sour gas well blowout occurred in 2003 (Yang et al., 2006). The Saskatchewan government recently tested 43 facilities in southeast Saskatchewan, Canada that were leaking sour gas, finding average concentrations of 30,000 parts per million (ppm) (Leo, 2015), well above levels that can kill nearby livestock, wildlife and people (500 ppm – See Table 5). Wells and refineries where H_2S may be present also exist in the U.S. Out of Michigan's 10,652 producible oil wells, for example, 1,360 saw H_2S levels exceeding 300 ppm (Michigan DEQ, 2016). Data prior to 1993 indicate that there are at least 14 major areas in 20 different U.S. states where H_2S is commonly found in natural gas deposits (US EPA, 1993). Sour gas must be processed before it can be shipped to market, presenting secondary exposures during transportation and processing. The hazards posed by high emission rates from oil and gas infrastructure are compounded by the fact that in the U.S. no Occupational Safety and Health Administration (OSHA) monitoring program exists at this time, though such systems have been proposed in the past. Skrtic (2006) discusses these regulatory gaps in much further detail. In addition to the recommendations presented by Skrtic, future research should also consider concomitant monitoring of other air pollutants that may be present with H_2S – such as particulate matter, volatile organic compounds (VOCs), and various sulfur compounds – in order to understand risk factors more comprehensively and in the event of major sour gas incidents.

2.3.5 Commercial Uses of H_2S

For commercial purposes, H_2S is used to produce SO_2 and then eventually sulfur, one of the most commercially important elements on the market today (King et al., 2013). The conversion is

accomplished using a modification of the Claus reaction, originally developed in 1883 (Equation 4) (GPSA, 2004). The main use of sulfur is as a reactant in the production of sulfuric acid (H_2SO_4), and the process by which this occurs is called the Contact process (Equation 5) (Ryan and Norris, 2014).

Equation 4. Overall Claus reaction (industrial production of elemental sulfur from H_2S)

$$3H_2S + 1\ ½\ O_2 = 3/x\ S_x + 3H_2O \qquad (\Delta H\ @\ 77°F \approx -264{,}400\ \text{Btu})$$

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

$$S_{(s)} + O_2 \rightarrow SO_{2(g)}$$
$$2SO_{2(g)} + O_{2(g)} \rightleftharpoons 2SO_{3(g)} \quad (\Delta H = -196\ \text{kJ mol}^{-1})$$
$$H_2SO_{4(l)} + SO_{3(g)} \rightarrow H_2S_2O_{7(l)}$$
$$H_2S_2O_{7(l)} + H_2O_{(l)} \rightarrow 2H_2SO_{4(l)}$$

Sulfuric acid is one of the most highly traded chemical commodities in the world due to its role in producing phosphate fertilizer (60% of worldwide total consumption) and other types of fertilizers (10%) according to data from 2009 (King et al., 2013). H_2S is beneficial in a variety of other sectors, such as the production of sodium sulfide and sodium hydrosulfide. These compounds are then used in the production of dyes, pesticides, and even pharmaceuticals. H_2S also plays role in metallurgy, laboratory settings, and agriculture (Beck et al., 1981a, Grant and Schuman, 1993, Sittig, 2002). The nuclear energy sector utilizes H_2S in large quantities to separate "heavy water," which contains more of the hydrogen isotope deuterium, from regular water (Rayner-Canham and Overton, 2009).

Since significant quantities of sulfur and by extension hydrogen sulfide are needed for all of the industries mentioned previously, one must wonder where such volumes originate. Natural gas purification and petroleum refining supply approximately 60% of the sulfur and SO_2 used for the production of sulfuric acid (King et al., 2013). H_2S is a result of the petroleum refining's hydrotreating process, where sulfur compounds found in the crude oil are combined with hydrogen

gas (OSHA, 1999). The 2015 U.N. Paris Agreement on climate change calls for a reduction in global greenhouse gas emissions worldwide, and by extension a transition away from burning fossil fuels including petroleum products (UNFCCC, 2015). When it becomes legally binding in 2017 and enters into force in 2020, the Agreement could have serious implications for commercial enterprises within the 195 member countries that rely on large quantities of H_2S for their operations.

2.4 EMERGING THREAT: DETERGENT SUICIDES

An emerging arena where H_2S exposures are becoming a risk, but for which the academic literature is still lacking, is in the case of "detergent suicides." The process involves mixing hydrochloric acid (found in commercial pool cleaners 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 H_2S gas (Adkins, 2010, Bott and Dodd, 2013, Morii et al., 2010).

The detergent suicides trend started in Japan in 2007 and has since moved abroad, as methods for generating H_2S 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 H_2S gas. Between 2008-2010, however, 30 H_2S suicides were identified. Due to the relative rarity of this issue, without being aware of or prepared for the toxic levels of H_2S in the air near the victim, five emergency responders were injured during rescue efforts in that time period (Reedy et al., 2011). There have also been reports of suicide by H_2S inhalation where residents and hotel guests not in the immediate vicinity of the release site

were affected (Reedy et al., 2011, Morii et al., 2010, Truscott, 2008). Such an increase in recent years of a previously rare inhalation hazard indicates a growing risk to the proximate populations and emergency responders from detergent suicides. Suicides by way of H_2S gas have also led to a growing concern that H_2S might find application as a terrorist weapon (Adkins, 2010). Despite such health risks to residents, workers, and emergency personnel, there is no FDA-approved antidote and/or reliable protocol for treating acute hydrogen sulfide poisoning in either H_2S or HS^- form on the market today. This issue is discussed in further detail in Section 4.2.

2.5 H_2S REGULATION IN THE U.S.

In the United States, H_2S is regulated in a variety of ways by the U.S. Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA) (for workplace-specific exposures). 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. These regulatory and recommended exposure limits are discussed in further detail below.

While laboratory animal studies of hydrogen sulfide have aided in the development of regulatory exposure guidelines, occupational and ambient exposures are fraught with complications and contradictions. Detailed H_2S emission quantities and the compound's concentration within a mixture of sulfur-containing gases are often unknown (WHO, 2003, ATSDR, 2014a). Standards for exposure to hydrogen sulfide are primarily based on experimental animal studies, as exact concentrations can rarely be quantified in incidents involving humans.

This trend is backed by the case reports that are associated with the fatal and non-fatal occupational injuries listed in Table 6 through Table 9. Acute exposure guidelines, however, have been developed by several regulatory and non-governmental organizations (Table 4). These guidelines vary wildly, with recommended exposure limits ranging from 1 ppb – 100 ppm depending on the potential exposure duration.

At a national level, H_2S was originally (improperly) included 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 industry emissions, and the levels permitted are driven by Maximum Achievable Control Technology standards. Successful petitioning resulted in the removal of H_2S from the HAPs list in 1991 (Bell et al., 2013), and it is still absent from the HAPs list.

H_2S is, however, found on the U.S. EPA's list of Extremely Hazardous Substances as determined by the Emergency Planning and Community Right-To-Know Act (EPCRA) in the event of accidental releases of 100 pounds or more (US EPA, 1986). OSHA sets limits in industries where H_2S is found over the threshold quantity of 1,500 pounds (680.38 kg) (OSHA, 2013). Additionally, starting in 2011, U.S. companies were required to report their emissions of H_2S 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 (hold) for hydrogen sulfide enacted in 1994 that was then lifted in 2011. Starting in 2013, industries that exceed the yearly thresholds of 25,000 pounds of H_2S for manufacturing (intentional or coincidental), 25,000 pounds for processing, or 10,000 pounds for "otherwise use" are required to report their emissions into TRI (for reporting years 2012 and beyond) (US EPA, 2011).

H_2S does not fall under the regulatory authority of the U.S. EPA for National Ambient Air Quality Standards (NAAQS), but the EPA does have a reference concentration for chronic inhalation (RfC) at $2x10^{-3}$ mg/m^3 (1.4 ppb). It is assumed that daily exposures of H_2S above this level over a lifetime will have deleterious effects. No parallel reference dose for chronic oral exposure (RfD) exists at this time. (US EPA, 2003a). The EPA has the regulatory authority to institute regulations on specific H_2S sources if it so chooses. In lieu of national limits on H_2S, individual U.S. states can choose to limit exposures, although their standards vary significantly. See Appendix B in Skrtic (2006) for a table that covers state-based ambient hydrogen sulfide standards.

Table 4. Airborne hydrogen sulfide exposure limits established by various U.S. and international public safety organizations (CAS 7783-06-4; UN 1053)

Agency	Exposure Level Types	REL (ppm)	Reference
ACGIH	TLV-TWA	1	OSHA (2012)
	TLV-STEL	5	
AIHA	ERPG 1[a]	0.1	AIHA (2013)
	ERPG 2	30	
	ERPG 3	100	
ATSDR	MRL-Acute	0.07	ATSDR (2014a)
	MRL-Intermediate	0.02	
	MRL-Chronic	n/a	
DOE	PAC-1	0.51	DOE (2016)
	PAC-2	27	
	PAC-3	50	
EPA	RfC	0.001	US EPA (2003a)
	AEGL-1: 10 min	0.75	NRC (2010)
	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	

Table 4 Continued

DFG	MAK	5	DFG (2013)
IARC	Carcinogenicity classification	n/a	IARC (2013)
NIOSH	IDLH	100	NIOSH (2016)
	REL: 10-min	10	
OSHA	PEL (8-hour TWA) – general industry	n/a	OSHA (2012)
	PEL Ceiling	20	
	PEL Peak: 10 min	50	
WHO	TWA: 24 hr	0.10	WHO (2000)[b]
REL Range: 1 ppb – 100 ppm			

a. ERPGs 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.

b. While not discussed in WHO's 2010 report on select air pollutants, the World Health Organization did publish air quality guidelines on H_2S in this report from 2000 – a guideline that was omitted from ATSDR (2014a).

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; MRL-Intermediate = 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.

2.6 EXPOSURE PATHWAYS

Inhalation is the main route of exposure for H_2S, although dermal/eye contact, injection, and ingestion are also plausible routes. As such, this section focuses on effects from inhaling H_2S

unless otherwise noted. Humans can typically smell H_2S at low concentrations in the air, between 0.0005 and 0.3 ppm (Guidotti, 1994, Ruth, 1986), a range that pushes the limits of our most sensitive H_2S monitoring equipment. Because H_2S in gaseous form is heavier than air, the highest risk of exposure for people is in enclosed spaces and along the ground, such as near oil and gas wells, underground, near manure pits, and in sewage systems (Gregorakos et al., 1995, Praxair, 2015). The elderly, asthma sufferers, and children with compromised respiratory systems are at higher risk of the compound's negative effects since H_2S targets the respiratory tract (ATSDR, 2014a, Kilburn, 2012, Jäppinen et al., 1990, Campagna et al., 2004, Dorman et al., 2004, Lopez et al., 1988b).

It is not known what ratio of H_2S that a person is exposed to is actually absorbed into the body (Khan et al., 1990, Prior et al., 1990, Prior et al., 1988). Once H_2S is brought into the body, however, it is absorbed by the blood and then distributed systemically. Bisulfide (HS^-), an inorganic anion, is produced as molecular hydrogen sulfide dissociates. It is believed that H_2S exerts its toxic effects on humans by inhibiting cytochrome *c* oxidase when the HS^- anion binds to ferric heme (Dorman et al., 2002, Hill et al., 1984), possibly along with other currently-undetermined mechanisms of toxicity subsidiary to cytochrome *c* oxidase inhibition (Cronican et al., 2015). In doing so, cellular respiration slows and eventually stops.

H_2S is primarily detoxified through oxidation in the liver, and also by methylation (Ammann, 1987). Bisulfide is excreted from the body within 30 minutes, having converted to SX species, although the specific type is not yet known. "Post-acute" effects (*i.e.* anything occurring more than about 10-15 minutes after exposure) are probably not due to HS^-, but perhaps a subsidiary reacting with oxygen (L.L. Pearce & J. Peterson, unpublished observations). Urinary

thiosulfate is the most commonly used biomarker for H_2S exposure, however (Milby and Baselt, 1999).

Effects of H_2S can vary greatly based on the level and speed of the exposure. In the following sections and figure we have broken down exposure types in to three main categories: acute (>100 ppm), post-acute (1-100 ppm), and chronic (<1 ppm) (Figure 4). Exposure ranges listed in this figure are based on levels reported in the literature and lower-range regulatory limits in Table 4. However, these values should not be considered absolute. There is still much unknown about the effects of post-acute and chronic exposures and their cutoff values. The consequences of these types of exposure are further discussed in the following section, categorized where possible as effects from acute, post-acute, and chronic exposures.

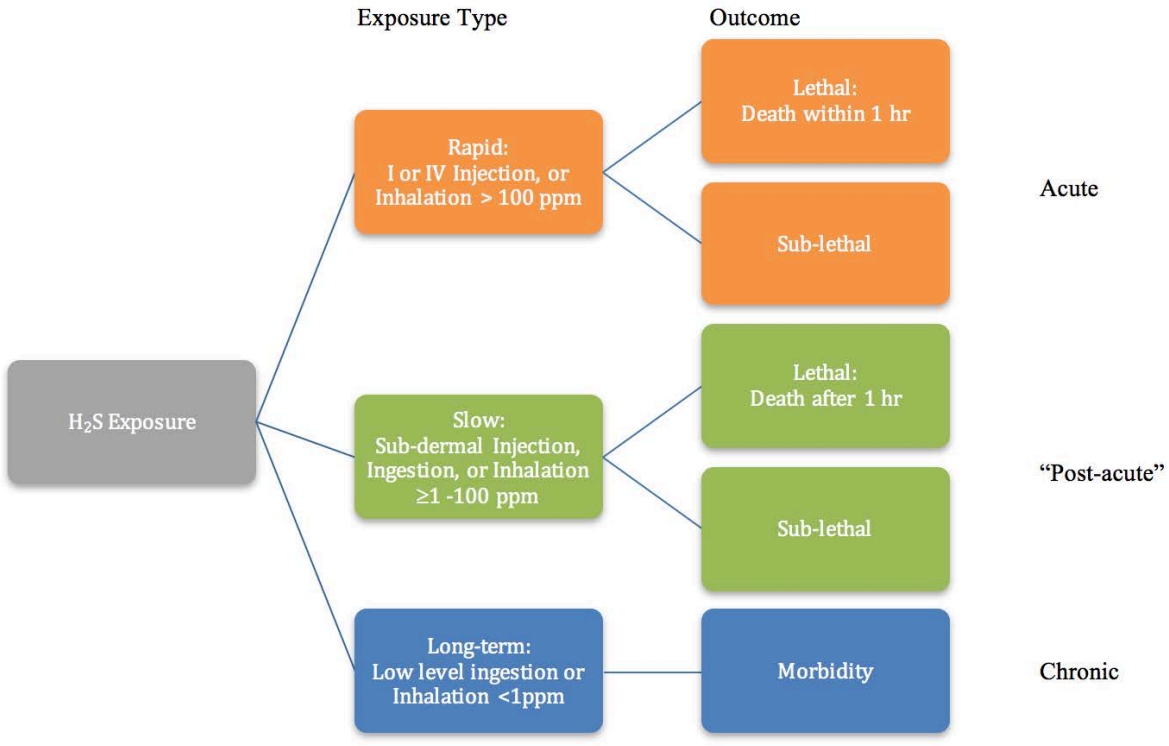


Figure 4. Types of lethal and sub-lethal H_2S poisonings

2.7 HUMAN HEALTH EFFECTS

While the adverse effects and emissions of hydrogen sulfide are the foci of this chapter, it is interesting to note that at low levels H_2S may serve as a modulator in the body (Abe and Kimura, 1996, Nicholls et al., 2013, WHO, 2003). H_2S is suspected to help regulate blood pressure, neurotransmission, inflammation reduction, and aiding digestion, among others (Dongó et al., 2011, Yang et al., 2008, ATSDR, 2014a, Szabo, 2007). There are also some studies that examined the role that H_2S may play in suspended animation (Blackstone et al., 2005, Volpato et al., 2008), but the effects are generally found to subside in studies investigating the possible link between suspended animation and H_2S in larger animals (Asfar et al., 2014).

To date, the majority of documented health effects from exposure to hydrogen sulfide are negative, especially at levels above 1 ppb in the air. Over time, the health effects due to acute H_2S exposures have become better understood, while the concentrations considered to be neurotoxic have changed. At the beginning of the 19th century, for example, concentrations of 700–1000 ppm in the air were considered to be dangerous (Ramazzini, 1713). More recently, this understanding changed to 0.6 ppm in 1987 (Gaitonde et al., 1987), and damaging to the brain at concentrations of 30–80 ppm (CIIT, 1983). However, most human hydrogen sulfide toxicity studies have involved acute, uncontrolled incidents where the exact concentration and any pre-existing conditions are not known. (Refer to the many data gaps presented in Table 6 through Table 9.) Controlled research studies almost always involve animals, whose results were then extrapolated to humans, but extrapolating toxicity carries uncertainty factors in assessing risk. The general consensus is that the respiratory track and nervous system are especially sensitive to the effects of H_2S exposure (Arnold et al., 1985, Beauchamp et al., 1984, ATSDR, 2014a, Guidotti, 2010, Kilburn et al., 2010). Duration of exposure and the level of H_2S in the environment both play important roles in resulting

health effects. Despite these unknowns, in Table 5 we have attempted to aggregate the expected symptoms – from offensive odors to death – of exposure to various levels of airborne H_2S.

Table 5. Conditions and physiological responses to hydrogen sulfide at various concentrations in the 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 exposure. May cause digestive upset and loss of appetite (ANSI and OSHA)
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, "knockdown" 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: (ANSI, 1972, ATSDR, 2014a, OSHA, 2014)	
Abbreviations: PPM, parts per million; ANSI, American National Standards Institute; ATSDR, Agency for Toxic Substances and Disease Registry; OSHA, Occupational Safety and Health Administration	

In the following three sections we summarize known and potential health effects due to acute, post-acute, and chronic exposure to H_2S in humans. See ATSDR (2014a) for details about effects from a broad set of exposures such as ingestion, as well as a review of results from animal studies, which were not the main focus of this chapter.

2.7.1 Acute Exposure Effects (>100 ppm, rapid onset)

Hydrogen sulfide's odor becomes detectable in concentrations as low as .0005 ppm, but an individual's sense of smell is lost after 2-15 minutes at/near 100 ppm (Ruth, 1986, Beauchamp et al., 1984), effectively rendering odor ineffective at risk prevention. In situations presenting with extremely high H_2S levels in the air, people also run the risk of experiencing "knockdown," or passing out in the area. This hazard severely diminishes survival rates due to the inability to escape and may also endanger potential rescuers (ATSDR, 2014a).

In cases of severe acute toxicity, a person is exposed to extremely high levels of hydrogen sulfide (above 500 ppm) for a short time period either through an injection or inhalation. At these levels, unconsciousness and death may result almost immediately. Cause of death is typically respiratory failure or arrest, with symptoms such as difficulty breathing, noncardiogenic pulmonary edema, coma, and cyanosis (OSHA, 2012, Parra et al., 1991, Krekel, 1964, Deng and Chang, 1987, ATSDR, 2014a, Adelson and Sunshine, 1966). If the victims survive the initial knock down, they may exhibit various neurological and respiratory sequelae following exposure (Kilburn, 1993, Snyder et al., 1995, Tvedt et al., 1991a, Tvedt et al., 1991b, Hessel et al., 1997). In other cases, there are reports where individuals exposed to high levels exhibit no long-term symptoms (Ravizza et al., 1982, Deng and Chang, 1987, Krekel, 1964, Osbern and Crapo, 1981), but the reason remains unknown.

As with many other compounds, the most well documented arena for understanding hydrogen sulfide risks at high levels is through occupational exposures. According to available data from OSHA and the Bureau of Labor Statistics (BLS), H_2S 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 H_2S while on the job. The majority of both fatal and nonfatal workplace incidents involved exposure to males, not females (Bureau of Labor Statistics, 2016a, Bureau of Labor Statistics, 2016b, Bureau of Labor Statistics, 2016c, Bureau of Labor Statistics, 2016d). See Table 6 to Table 9 for details regarding fatal and nonfatal injuries where hydrogen sulfide was identified as either the primary or secondary source, 2004-2014. Note the many data gaps, where rows do not add up to the totals listed by BLS. This issue is compounded by the fact that reliable exposure data are often not available when such incidents occur, either on the job or in communities living near H_2S sources.

Table 6. Hydrogen sulfide as primary or secondary source in fatal workplace injuries, 2004-2010

Characteristic	2005	2006	2007	2008	2009	2010
Total[1]	5	9	14	6	7	9
Occupation (SOC)[2]						
Management, business, science, and arts occupations	-	-	5	-	-	-
Management, business, and financial occupations	-	-	5	-	-	-
Management occupations	-	-	5	-	-	-
Other management occupations	-	-	5	-	-	-
Natural resources, construction, and maintenance occupations	-	6	7	-	5	6
Construction and extraction occupations	-	-	4	-	5	-
Extraction workers	-	-	-	-	3	-
Installation, maintenance, and repair occupations	-	-	-	-	-	3
Production, transportation, and material moving occupations	-	-	-	3	-	-
Primary source[3]						
Chemicals and chemical products	5	7	13	6	6	9
Other chemicals	5	7	13	6	6	9
Sulfur and sulfur compounds	5	7	13	6	6	9
Hydrogen sulfide	5	7	13	6	6	9
Secondary source[4]						
Structures and surfaces	-	-	9	-	-	5

Table 6 Continued

Structures	-	-	9	-	-	5
Mines, caves, tunnels	-	-	5	-	-	-

[1] The Census of Fatal Occupational Injuries (CFOI) has published data on fatal occupational injuries for the United States since 1992. During this time, the classification systems and definitions of many data elements have changed. Please see the CFOI Definitions page (http://www.bls.gov/iif/oshcfdef.htm) for a more detailed description of each data element and their definitions.

[2] Occupation data from 2003 to 2010 are based on the Standard Occupational Classification system, 2000. Occupation data from 2011 to the present are based on the Standard Occupational Classification system, 2010.

[3] Based on the BLS Occupational Injury and Illness Classification System (OIICS) in effect for 1992 to 2010 data. The primary source of injury identifies the object, substance, or exposure that directly produced or inflicted the injury. For most transportation incidents, the primary source identifies the vehicle in which the deceased was an occupant. For most falls, the primary source identifies the surface or object contacted.

[4] Based on the BLS Occupational Injury and Illness Classification System (OIICS) in effect for 1992 to 2010 data. The secondary source of injury, if any, identifies the object, substance, or person that generated the source of injury or that contributed to the event or exposure. For vehicle collisions, the deceased's vehicle is the primary source and the other object (truck, road divider, etc.) is the secondary source. For most homicides, the "bullet" is the primary source and the "assailant" is the secondary source. For most falls, the secondary source identifies the equipment or surface from which the worker fell.

Note: Data for all years are revised and final. Totals for major categories may include subcategories not shown separately. Dashes indicate no data reported or data that do not meet publication criteria. N.e.c. means "not elsewhere classified." CFOI fatal injury counts exclude illness-related deaths unless precipitated by an injury event. There were no fatal occupational injuries from H_2S exposure in 2004, so that column was not included in this table.

Source: Bureau of Labor Statistics (2016a). The public-facing version of the BLS database was down at the time of this inquiry, so the data above were provided directly by the BLS on 4-7-16.

Table 7. Hydrogen sulfide as primary or secondary source in fatal workplace injuries, 2011-2014

Characteristic	2011	2012	2013	2014
Total[1]	10	3	10	10
Occupation (SOC)[2]				
Natural resources, construction, and maintenance occupations	8	-	8	6
Farming, fishing, and forestry occupations	-	-	1	-
Supervisors, farming, fishing, and forestry workers	-	-	1	-
First-line supervisors/managers of farming, fishing, and forestry workers	-	-	1	-
First-line supervisors of farming, fishing, and forestry workers	-	-	1	-
Construction and extraction occupations	5	-	5	6
Other construction and related workers	3	-	1	-
Septic tank servicers and sewer pipe cleaners	3	-	1	-
Septic tank servicers and sewer pipe cleaners	3	-	1	-

Table 7 Continued

Extraction workers	-	-	-	-
Derrick, rotary drill, and service unit operators, oil, gas, and mining	-	-	-	1
Service unit operators, oil, gas, and mining	-	-	-	1
Installation, maintenance, and repair occupations	-	-	2	-
Other installation, maintenance, and repair occupations	-	-	2	-
Miscellaneous installation, maintenance, and repair workers	-	-	2	-
Helpers--installation, maintenance, and repair workers	-	-	2	-
Production, transportation, and material moving occupations	-	3	2	4
Production occupations	-	3	-	-
Transportation and material moving occupations	-	-	2	4
Material moving workers	-	-	2	-
Laborers and material movers, hand	-	-	-	-
Cleaners of vehicles and equipment	-	-	-	1
Pumping station operators	-	-	2	-
Wellhead pumpers	-	-	2	-
Primary source 2011[3]				
Chemicals and chemical products	9	3	9	9
Other chemicals	9	3	9	9
Sulfur and sulfur compounds	9	3	9	9
Hydrogen sulfide	9	3	9	9
Parts and materials	-	-	1	-
Building materials	-	-	1	-
Pipes, ducts, tubing	-	-	1	-
Metal pipes, tubing	-	-	1	-
Tools, instruments, and equipment	1	-	-	1
Ladders	1	-	-	1
Ladders fixed	-	-	-	1
Movable ladders	1	-	-	-
Straight ladders	1	-	-	-
Secondary source 2011[4]				
Chemicals and chemical products	1	-	1	1
Other chemicals	1	-	1	1
Sulfur and sulfur compounds	1	-	1	1
Hydrogen sulfide	1	-	1	1
Structures and surfaces	9	1	9	9

Table 7 Continued

Confined spaces[5]	9	1	9	9
Mines, caves, tunnels	-	-	-	2
Sewers, manholes, storm drains	-	-	-	2
Pipeline interiors	-	-	2	-
Tank, bin, vat interiors	4	-	2	3
Septic tank or water tank interiors	4	-	-	-
Oil storage tank interiors	-	-	-	1
Hopper interiors	-	-	-	2
Confined spaces on vehicles	1	1	2	4
Tanker truck interiors	-	1	2	3
Other confined spaces	-	-	1	-

[1] The Census of Fatal Occupational Injuries (CFOI) has published data on fatal occupational injuries for the United States since 1992. During this time, the classification systems and definitions of many data elements have changed. Please see the CFOI Definitions page (http://www.bls.gov/iif/oshcfdef.htm) for a more detailed description of each data element and their definitions.

[2] Occupation data from 2003 to 2010 are based on the Standard Occupational Classification system, 2000. Occupation data from 2011 to the present are based on the Standard Occupational Classification system, 2010.

[3] Based on the BLS Occupational Injury and Illness Classification System (OIICS) 2.01 implemented for 2011 data forward. The primary source of a fatal occupational injury is the object, substance, person, bodily motion, or exposure that most directly led to, produced, or inflicted the injury or illness.

[4] Based on the BLS Occupational Injury and Illness Classification System (OIICS) 2.01 implemented for 2011 data forward. The secondary source of a fatal occupational injury is the object, substance, person, or exposure, other than the source, if any, which most actively generated the source or contributed to the injury or illness.

[5] May differ from the definition of confined spaces as defined by Occupational Safety and Health Administration.

Note: Data for 2014 are preliminary. Data for all other years are revised and final. Totals for major categories may include subcategories not shown separately. Dashes indicate no data reported or data that do not meet publication criteria. N.e.c. means "not elsewhere classified." CFOI fatal injury counts exclude illness-related deaths unless precipitated by an injury event.

Source: Bureau of Labor Statistics (2016b). The public-facing version of the BLS database was down at the time of this inquiry, so the data above were provided directly by the BLS on 4-7-16.

Table 8. Number of nonfatal occupational injuries and illnesses involving days away from work (1) by selected worker and case characteristics, All U.S., private industry, 2004 - 2010

Characteristic	All sources of injury/ illness	Hydrogen sulfide (code 0972XX)						
		2004	2005	2006	2007	2008	2009	2010
Total:		-	30	20	-	20	-	-
Sex								
Men	563850	-	30	20	-	20	-	-
Women	365610	-	-	-	-	-	-	-
Number of days away from work								

Table 8 Continued

Cases involving 1 day	134080	-	20	-	-	-	-	-
“” 2 days	101560	-	-	-	-	-	-	-
“” 3-5 days	167010	-	-	-	-	-	-	-
“” 6-10 days	109690	-	-	-	-	-	-	-
“” 11-20 days	104220	-	-	-	-	-	-	-
“” 21-30 days	60030	-	-	-	-	-	-	-
“ 31 or more days	256590	-	-	-	-	-	-	-
Median days away from work [5]	8	-	1	180	-	5	-	-
Industry sector								
Goods producing industries [2]	223020	-	20	20	-	-	-	-
Natural resources and mining [2] [3]	20930	-	-	-	-	-	-	-
Agriculture Forestry Fishing and Hunting [2]	14010	-	-	-	-	-	-	-
Mining [3]	6910	-	-	-	-	-	-	-
Construction	74950	-	-	-	-	-	-	-
Manufacturing	127140	-	-	-	-	-	-	-
Service providing industries	710170	-	-	-	-	-	-	-
Trade Transportation and Utilities [4]	284630	-	-	-	-	-	-	-
Wholesale Trade	58060	-	-	-	-	-	-	-
Retail Trade	131380	-	-	-	-	-	-	-
Transportation and Warehousing [4]	89540	-	-	-	-	-	-	-
Utilities	5650	-	-	-	-	-	-	-
Information	19330	-	-	-	-	-	-	-
Financial activities	27480	-	-	-	-	-	-	-
Finance and Insurance	10500	-	-	-	-	-	-	-
Real Estate and Rental and Leasing	16980	-	-	-	-	-	-	-
Professional and business services	75890	-	-	-	-	-	-	-
Professional Scientific and Technical Services	18140	-	-	-	-	-	-	-
Management of Companies and Enterprises	7160	-	-	-	-	-	-	-
Administrative and Support and Waste Management and Remediation Services	50590	-	-	-	-	-	-	-
Education and health services	186830	-	-	-	-	-	-	-
Educational Services	10440	-	-	-	-	-	-	-
Health Care and Social Assistance	176380	-	-	-	-	-	-	-
Leisure and hospitality	88740	-	-	-	-	-	-	-
Arts Entertainment and Recreation	15050	-	-	-	-	-	-	-
Accommodation and Food Services	73700	-	-	-	-	-	-	-
Other services	27260	-	-	-	-	-	-	-

Table 8 Continued

Other Services except Public Administration	27260	-	-	-	-	-	-	-
Public Administration	-	-	-	-	-	-	-	-
[1] Days away from work include those that result in days away from work with or without job transfer or restriction.								
[2] Excludes farms with fewer than 11 employees.								
[3] Data for mining (Sector 21 in the North American Industry Classification System -- United States 2007) include establishments not governed by the Mine Safety and Health Administration (MSHA) rules and reporting such as those in oil and gas extraction and related support activities. Data for mining operators in coal metal and nonmetal mining are provided to BLS by the Mine Safety and Health Administration U.S. Department of Labor. Independent mining contractors are excluded from the coal metal and nonmetal mining industries. These data do not reflect the changes Occupational Safety and Health Administration made to its recordkeeping requirements effective January 1 2002; therefore estimates for these industries are not comparable with estimates for other industries.								
[4] Data for employers in railroad transportation are provided to BLS by the Federal Railroad Administration U.S. Department of Transportation. These data do not reflect the changes Occupational Safety and Health Administration made to its recordkeeping requirements effective January 1 2002; therefore estimates for these industries are not comparable with estimates for other industries.								
[5] Median days away from work is the measure used to summarize the varying lengths of absences from work among the cases with days away from work. Half the cases involved more days and half involved less days than a specified median. Median days away from work are represented in actual values.								
NOTE: Because of rounding and data exclusion of nonclassifiable responses data may not sum to the totals. Dashes indicate data that do not meet publication guidelines. The scientifically selected probability sample used was one of many possible samples each of which could have produced different estimates. A measure of sampling variability for each estimate is available upon request -- please contact iifstaff@bls.gov or call (202) 691-6170.								
SOURCE: Bureau of Labor Statistics (2016c). The public-facing version of the BLS database was down at the time of this inquiry, so the data above were provided directly by the BLS on 4-7-16.								

Table 9. Number of nonfatal occupational injuries and illnesses involving days away from work (1) by selected worker and case characteristics, All U.S., private industry, 2011 - 2014

Characteristic	All sources of injury/ illness	Hydrogen sulfide (code 1771XX)			
		2011	2012	2013	2014
Total:		-	50	-	-
Sex					
Men	560970	-	30	-	-
Women	348720	-	-	-	-
Number of days away from work					
Cases involving 1 day	127140	-	-	-	-
“” 2 days	97830	-	-	-	-
“” 3-5 days	156810	-	-	-	-
“” 6-10 days	108230	-	-	-	-

Table 9 Continued

“” 11-20 days	103270	-	-	-	-
“” 21-30 days	57630	-	-	-	-
“” 31 or more days	265530	-	-	-	-
Median days away from work [5]	9	-	19	-	-
Industry sector					
Goods producing industries[2]	225180	-	50	-	-
Natural resources and mining [2] [3]	24730	-	40	-	-
Agriculture forestry fishing and hunting [2]	17050	-	-	-	-
Mining [3]	7680	-	-	-	-
Construction	74460	-	-	-	-
Manufacturing	125990	-	-	-	-
Service providing industries	691260	-	-	-	-
Trade transportation and utilities [4]	278700	-	-	-	-
Wholesale trade	59240	-	-	-	-
Retail trade	120640	-	-	-	-
Transportation and warehousing [4]	95040	-	-	-	-
Utilities	3780	-	-	-	-
Information	15730	-	-	-	-
Financial activities	26350	-	-	-	-
Finance and insurance	10010	-	-	-	-
Real estate and rental and leasing	16350	-	-	-	-
Professional and business services	77720	-	-	-	-
Professional scientific and technical services	19360	-	-	-	-
Management of companies and enterprises	5530	-	-	-	-
Administrative and support and waste management and remediation services	52830	-	-	-	-
Education and health services	175900	-	-	-	-
Educational services	11460	-	-	-	-
Health care and social assistance	164440	-	-	-	-
Leisure and hospitality	90920	-	-	-	-
Arts entertainment and recreation	15770	-	-	-	-
Accommodation and food services	75140	-	-	-	-
Other services	25940	-	-	-	-

Table 9 Continued

Other services except public administration	25940	-	-	-	-
Public administration	-	-	-	-	-
[1] Days away from work include those that result in days away from work with or without job transfer or restriction.					
[2] Excludes farms with fewer than 11 employees.					
[3] Data for mining (Sector 21 in the North American Industry Classification System -- United States 2007) include establishments not governed by the Mine Safety and Health Administration (MSHA) rules and reporting such as those in oil and gas extraction and related support activities. Data for mining operators in coal metal and nonmetal mining are provided to BLS by the Mine Safety and Health Administration U.S. Department of Labor. Independent mining contractors are excluded from the coal metal and nonmetal mining industries. These data do not reflect the changes Occupational Safety and Health Administration made to its recordkeeping requirements effective January 1 2002; therefore estimates for these industries are not comparable with estimates for other industries.					
[4] Data for employers in railroad transportation are provided to BLS by the Federal Railroad Administration U.S. Department of Transportation. These data do not reflect the changes Occupational Safety and Health Administration made to its recordkeeping requirements effective January 1 2002; therefore estimates for these industries are not comparable with estimates for other industries.					
[5] Median days away from work is the measure used to summarize the varying lengths of absences from work among the cases with days away from work. Half the cases involved more days and half involved less days than a specified median. Median days away from work are represented in actual values.					
NOTE: Because of rounding and data exclusion of nonclassifiable responses data may not sum to the totals. Dashes indicate data that do not meet publication guidelines. The scientifically selected probability sample used was one of many possible samples each of which could have produced different estimates. A measure of sampling variability for each estimate is available upon request -- please contact iifstaff@bls.gov or call (202) 691-6170. For additional information about methodology and coding structures see the BLS Handbook of Methods chapter 9: http://www.bls.gov/opub/hom/homch9.htm.					
SOURCE: Bureau of Labor Statistics (2016d). The public-facing version of the BLS database was down at the time of this inquiry, so the data above were provided directly by the BLS on 4-7-16.					

Beyond summary statistics, it is difficult to interpret trends from the BLS data available on occupational fatalities and injuries due to H_2S. Generally, 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 (OSHA, 2016a). Favorable conditions for high H_2S production - 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, hydrogen sulfide remains a significant inhalation hazard, as well. In 2012, there were an estimated 809 non-occupational

exposures resulting in 5 deaths as logged in the National Poison Data System (Mowry et al., 2013). In 2013 there was an increase to 855 exposures and 10 deaths, second only to carbon monoxide deaths (n=60) (Mowry et al., 2014). Even with the previously discussed data gaps, acute H_2S effects are the most well documented and well understood category of exposures.

2.7.2 Post-Acute Exposure (≥1-100ppm, slower onset)

A less documented set of exposures occurs at levels greater than 1 ppm but typically less than 100 ppm, or occur via ingestion. In these cases, death and a variety of neurological disorders may not occur right away but take hours, days, or weeks to present (Gregorakos et al., 1995, ATSDR, 2014a, Haahtela et al., 1992, Hirsch, 2002). Levels up to 10 ppm can be tolerated fairly well by healthy adults for a short period of time, but between 10 and 100 ppm has been documented to produce some effects in animal studies, such as pulmonary congestion, pulmonary edema, and olfactory neuronal loss (Cantox Environmental Inc., 2002, Dorman et al., 2004, Kohno et al., 1991, Khan et al., 1990). Data are several lacking in this exposure category, since at other times, no symptoms are reported even during controlled exposure trials with humans (Bhambhani Y and M., 1991, Bhambhani et al., 1997, Bhambhani et al., 1996, Bhambhani et al., 1994).

The variability of symptoms and effects of post-acute exposures is likely due to a combination of factors. A generally overlooked possibility is that H_2S might be temporarily converted into HS-X species (which are themselves non-toxic), but being metastable, these species may revert back to H_2S. If the victim is cut off from the source of the exposure and HS-X reconversion to H_2S is slow enough, acute symptoms may be avoided. We suspect that post-acute toxicity could, therefore, be mechanistically similar to acute, but development of symptoms is slowed down by the formation of meta-stable buffers (HS-X). Sulfhemoglobin potentially

represents one such “buffer” and is frequently evident at autopsy of sulfide poisoning victims (See Section 2.8.3 on Molecular Pathology).

2.7.3 Chronic Exposure (<1ppm)

The effects of low-level or long-term exposure to ambient levels of H_2S (<1 ppm) found in the air are more difficult to estimate than either acute or post-acute because the mechanism for chronic toxicity is not well understood and H_2S is not included in most ambient air monitoring programs. Hydrogen sulfide turnover in the body may be fast enough so as not to produce the symptoms we have come to except at higher levels. At chronic levels and duration, we expect symptoms of exposure to include visual complications, olfactory fatigue, nausea, respiratory irritation, and possible headaches due to the sensitivity of those systems to hydrogen sulfide exposure (ATSDR, 2014a, Legator et al., 2001, Deng and Chang, 1987, Thoman, 1969, Jäppinen et al., 1990). However, significantly more research and real-time air monitoring need to be conducted in this arena to begin to understand the chronic effects to expect at specific H_2S levels.

Few places provide a better natural experiment for determining health effects from chronic H_2S exposure than Rotorua, New Zealand, where a population of 60,000 people live near an active geothermal field. The most reliable background levels of H_2S in this area indicate a median ambient concentration of 30 $\mu g/m^3$ (20 ppb) (Bates et al., 1997). Even though their follow up study of 1,637 adult men and women who had resided in the area for at least three years proved inconclusive, there was some suggestive evidence that low levels of H_2S were protective against asthma incidence (Bates et al., 2013). More recent research by Bates on this population has found similarly conflicting results regarding the effects of chronic H_2S exposure on lung function or as a risk factor for asthma or chronic obstructive pulmonary disease (Bates et al., 2015).

Effects from dermal exposure and ingestion, as well as genotoxicity and reproductive effects are even less well understood (ATSDR, 2014a). At all levels – acute, post-acute, and chronic – the effects of H_2S inhalation still present many unknowns, although markedly more gaps exist within post-acute and chronic exposures.

2.8 CONFLICTING OBSERVATIONS REGARDING THE CHEMICAL TOXICOLOGY OF H_2S

2.8.1 Lessons from Occupational Accidents

The available (anecdotal) evidence from human (occupational) mass exposures to H_2S gas clearly suggests that approximately 20% of victims should require no treatment, but there will be ~5% fatalities and about 75% of the victims can be expected to arrive alive at the clinic exhibiting coma, disequilibrium, respiratory insufficiency and/or pulmonary edema (Snyder et al., 1995, Burnett et al., 1977, ATSDR, 2006c). Amongst sewer workers exposed in enclosed spaces below ground level, fatalities can be expected to be higher, but there are still survivors (Adelson and Sunshine, 1966, Knight and Presnell, 2005, Yalamanchili and Smith, 2008). Based upon their experience with workers in Canadian sour gas wells (the epicenter of H_2S poisonings in North America) Burnett *et al.* (1977) assert that "increased attention to cardiopulmonary resuscitation at the exposure site and during transportation to hospital is necessary to reduce the mortality from H_2S exposure." Neurological sequelae have been reported (Schneider et al., 1998, Snyder et al., 1995, Tvedt et al., 1991a, ATSDR, 2006c), but these remain quite rare and, interestingly, no such long-

term effects were evident in any of the 221 cases documented in the Canadian study (Burnett et al., 1977).

Where autopsies have been performed in timely fashion (since H_2S leaves the body quickly), it has been noted that the internal organs of human H_2S poisoning victims have been discolored – the blood and sectioned brain in particular appearing distinctly green due to the formation of sulfhemoglobin (Park et al., 2009, Adachi et al., 1986, Tatsuno et al., 1986, Milroy and Parai, 2011) in which the porphyrin ring has been covalently modified (Figure 5) (Carrico et al., 1978, Park et al., 1986, Bondoc et al., 1986). 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 LD_{40} doses of NaSH by injection either die in less than 4 minutes, or fully recover within 15 minutes (Cronican et al., 2015). Moreover, while purified mouse hemoglobin can readily be manipulated to undergo the same conversion to sulfhemoglobin as the human protein, 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 (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 H_2S/HS^-, only suggested supportive countermeasures (ATSDR, 2014b, ATSDR, 2006c, ATSDR, 2006a, ATSDR, 2012).

Some authors in the early literature (before these structures were properly identified) confused this terminology. For example, what we now call sulfidomethemoglobin (metHbSH) some early authors (*e.g.* Adelson and Sunshine (1966)) referred to as sulfhemoglobin (SHb). Here we reserve the latter term for the covalently modified macrocyclic structures shown in Figure 5.

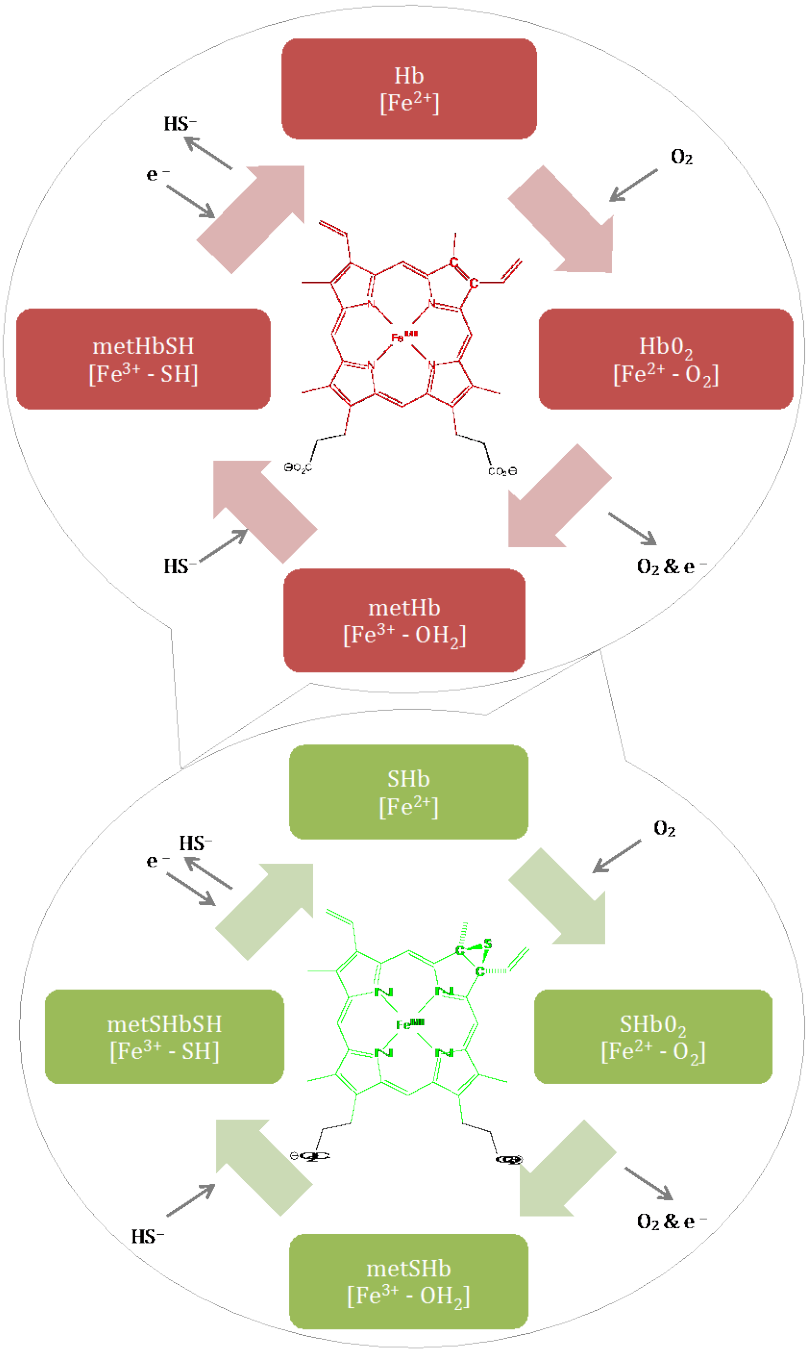


Figure 5. Hemoglobin cycle and interactions with H_2S

Table 10. Descriptive terminology for Figure 5

Term	Written Names	Characteristic
Hb	hemoglobin / deoxyhemoglobin	Red in color
HbO_2	oxyhemoglobin / monoxyhemoglobin	Red in color
metHb	methemoglobin	Red in color
metHbSH	methemoglobin sulfide / sulfido(met)hemoglobin	Red in color
SHb	sulfhemoglobin / sulfHb / deoxysulfHb	Green in color
$SHbO_2$	oxysulfhemoglobin	Green in color
metSHb	metsulfhemoglobin / sulfido(met)sulfhemoglobin	Green in color
metSHbSH	metsulfhemoglobin sulfide	Green in color

2.8.2 H_2S Catabolic Biochemistry

The reader will be aware that a significant literature continues to emerge regarding the function of H_2S as a "gasotransmitter" (Kolluru et al., 2013, Mancardi et al., 2011, Wang, 2010, Wang, 2002, Szabo et al., 2014, Xie et al., 2016), but this body of work is outside the scope of the present review and confounding, rather than clarifying, with regard to some important questions relevant to H_2S toxicity. Any signaling functions of H_2S take place at orders of magnitude lower concentrations 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 (Hildebrandt, 2011, Hildebrandt and Grieshaber, 2008, Kabil and Banerjee, 2010, Lagoutte et al., 2010, Szabo et al., 2014, Abou-Hamdan et al., 2015, Bouillaud and Blachier, 2011) that the catabolic elimination of H_2S in mammals is catalyzed almost exclusively by the sulfide oxidase system localized within mitochondria (Figure 6). This condition may well be the case under more-or-less normal physiological circumstances, but probably not at the elevated H_2S levels to be experienced during

poisonings and some other pathological conditions. The first enzyme of the sulfide oxidase system, sulfide quinone reductase, abstracts a hydrogen atom from H_2S and passes two electrons to the electron-transport chain 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 H_2S/HS^- is, as widely accepted (see below) the ligand-binding site of cytochrome *c* oxidase, then sulfide unavoidably inhibits its own elimination.

There are, however, several lines of evidence contradicting the notion that sulfide need necessarily inhibit its own elimination completely. Firstly, mice rendered unconscious (near death) by infusion of NaSH solutions into the tail vein over 5-10 minutes recover within seconds of stopping the infusion (L.L. Pearce & J. Peterson, unpublished observations) much faster than recovery from equivalently toxic levels of the similarly acting toxicant sodium cyanide. Secondly, the observation at autopsy of sulfhemoglobin formation in humans (Park et al., 2009, Adachi et al., 1986, Tatsuno et al., 1986, Milroy and Parai, 2011) is clear evidence for at least one other alternate competitive metabolic pathway for sulfide. Thirdly, a literature has emerged describing the presence of dimethylsulfide (CH_3SCH_3) in exhaled breath (Tangerman, 2009, Tangerman and Winkel, 2008) another pathway for elimination of sulfide. This occurrence 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 (Tangerman and Winkel, 2007, Tangerman and Winkel, 2010). Finally, it appears that H_2S/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 (Haouzi et al., 2014b, Sonobe et al., 2015, Haouzi et al., 2014a, Sonobe and Haouzi, 2015). 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 be surprising, as sulfide is both a good ligand and reductant; some of its biochemical toxicology may not be enzyme catalyzed.

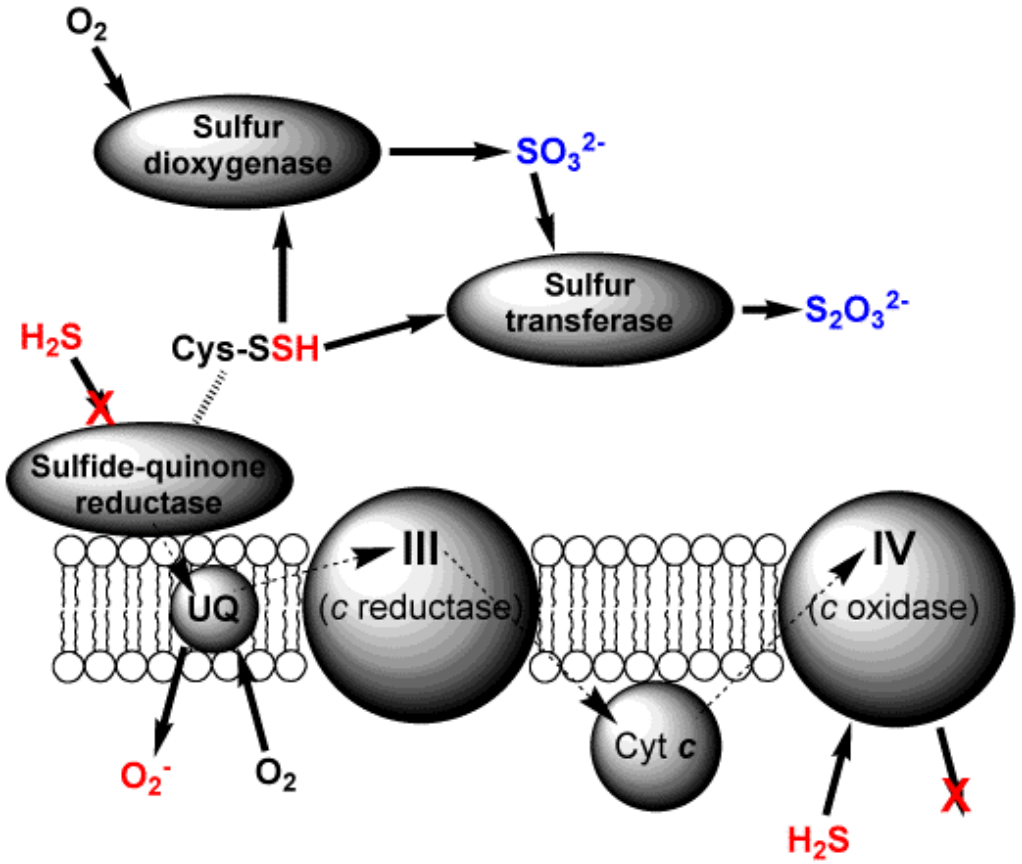


Figure 6. Inhibition of H_2S catabolism and ETC

2.8.3 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 chain (ETC) (ATSDR, 2014b, ATSDR, 2006c, Cooper and Brown, 2008, Dorman et al., 2002, Cronican et al., 2015, Guidotti, 1996, ATSDR, 2006a, ATSDR, 2012). 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 (Cooper and Brown, 2008, Hill et al., 1984, Nicholls and Kim, 1982, Nicholls et al., 2013). 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 H_2S can freely diffuse through membranes, it readily crosses the blood-brain barrier to inhibit mitochondrial ETCs within the central nervous system, which in unanesthetized laboratory animals results in clear behavioral signs of intoxication 2 minutes post-injection and can lead to death from respiratory paralysis within ~3 minutes (Cronican et al., 2015, ATSDR, 2006c), or cardiac failure after ~7 minutes (Sonobe et al., 2015, Sonobe and Haouzi, 2015).

At this time, it is not clear how to reconcile the observation that free H_2S/HS^- seemingly only persists for a matter of seconds in the bloodstream (Haouzi et al., 2014b, Sonobe et al., 2015, Haouzi et al., 2014a, Sonobe and Haouzi, 2015) yet onset of symptoms associated with complex IV inhibition by H_2S/HS^- occurs at 2 minutes after the toxicant dose. We remind the reader at this point that significant numbers of human victims of H_2S inhalation arrive at the clinic with cardiopulmonary symptoms 30 minutes or more after exposure and frequently succumb hours later (Burnett et al., 1977, ATSDR, 2006c, CSB, 2003, EPA, 2003, Guidotti, 1996).

2.8.4 Pulmonary Considerations

Prior to the emergence of any gasotransmitter activity, there were insightful concise reviews of H_2S toxicity published (Guidotti, 1996, Reiffenstein et al., 1992, Haggard, 1925, Milby and Baselt, 1999) that still provide an excellent entry point to this literature, as well as some lengthier scholarly documents (ATSDR, 2006c, Roth and Goodwin, 2003, Beauchamp et al., 1984). A few key points worth reiterating include that while there are some relatively mild and mostly resolvable ocular

conditions associated with chronic H_2S exposures, the neurological sequelae reported in humans following more acute exposures may primarily be caused by brain anoxia or head trauma suffered during collapse, both secondary to the direct toxic effects of H_2S. 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 (Almeida and Guidotti, 1999), while edema only seems to follow H_2S inhalation (Reiffenstein et al., 1992, Guidotti, 1996, Milby and Baselt, 1999, Lopez et al., 1989).

Recent work with the cysteine dioxygenase knockout mouse, which accumulates H_2S/HS^-, has confirmed that the lung (and pancreas) is (are) more susceptible to toxicity from endogenously elevated H_2S/HS^- than liver or kidney (Roman et al., 2013) and, also, in various other animal models, H_2S/HS^- has been demonstrated to contribute to the development and progression of lung inflammation and injury (Zhang and Bhatia, 2009). Bizarrely and to the contrary, however, H_2S/HS^- is apparently ameliorative in the case of lipopolysaccahride-induced acute lung-injury (ALI) in rats (Du et al., 2014) and in burn/smoke-induced ALI in sheep (Esechie et al., 2009). Olson and associates have written extensively (Olson, 2012, Olson et al., 2014) on the practicalities of manipulating H_2S/HS^- in biological samples and the difficulty in distinguishing physiological from pharmacological processes, particularly at the uncertain sulfide levels encountered.

Of course, one should expect that many of the paradoxical observations in the present literature could be resolved with improved knowledge of the underlying H_2S/HS^- 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 H_2S/HS^- cytotoxicity observed in

cultured cells (Eghbal et al., 2004, Truong et al., 2006), other groups have pointed out that in the case of intact animals (Cronican et al., 2015) and human patients (Reiffenstein et al., 1992) 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 (Kabil and Banerjee, 2010, Xie et al., 2016) as complicated, at best.

There is perhaps some hypersensitivity exhibited by individuals with pre-existing conditions such as asthma (ATSDR, 2006c, Milby and Baselt, 1999), but in comparison to other common chemical reagents like ammonia and volatile organic acids, H_2S is a modest lachrymator/pulmonary irritant – accidental releases being more likely to elicit eruptions of puerile humor from one's laboratory colleagues than more serious consequences. In view of such experiences, it is possible that the severity of inhaled H_2S 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 will 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 H_2S inhalation, the most notable lesion in human fatalities (Burnett et al., 1977), reflects this locally elevated exposure, but probably involves responses other than merely 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 increased permeability of the lung microvasculature, frequently associated with sepsis (noncardiogenic) (Murray, 2011, Ware and Matthay, 2005). Endothelial barrier function is seemingly always compromised, while the epithelial barrier is usually, but not

always affected (Murray, 2011). The less-often-encountered syndromes neurogenic pulmonary edema and high-altitude pulmonary edema each show both cardiogenic and noncardiogenic features (Bhagi et al., 2014, Murray, 2011, Šedý et al., 2015). It has been clear for decades that H_2S-induced pulmonary edema is associated with vascular permeability due to the high protein content of the extravasated fluid (Lopez et al., 1988a, Lopez et al., 1987, Prior et al., 1990) – but further similarity between this and any of the other noncardiogenic syndromes essentially remains open to question.

Multiple types of calcium and potassium ion channels (at least) are susceptible to modulation by H_2S, especially within the cardiovascular system (Dunn et al., 2016, Munaron et al., 2013, Martelli et al., 2013). These emerging effects of H_2S exhibit a complicated interdependence with those of nitric oxide, the relationship being demonstrably evident in endothelial and smooth muscle cells (Altaany et al., 2014, Dunn et al., 2016, Huang et al., 2015, Moccia et al., 2011). Since the details of these interactions in physiological circumstances are still emerging, any associated pathological biochemistry is unavoidably even less well delineated, but there is clearly promising scope here for discovery of a mechanism to explain H_2S-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 H_2S-induced acute pulmonary edema (Jiang et al., 2016, Jiang et al., 2014, Jiang et al., 2015). 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 (Fronius, 2013). In proof-of-concept laboratory experiments with animals, where the poisoning protocols were quite unlike human cases, it has been shown that hydroxocobalamin (Truong et al., 2007) and its biological precursor cobinamide (Brenner et al., 2014) offer some

protection against injected NaSH. However, in keeping with the reported observation that free H_2S/HS^- is eliminated from the bloodstream very quickly (Haouzi et al., 2014a, Haouzi et al., 2014b), the hydroxocobalamin had to be given within ~2 minutes of the toxicant, and the cobinamide was given during administration of the toxicant dose – neither protocol being of any practical value in relation to human poisonings.

2.9 H_2S CONCLUSION

Since the days of the Princess Alice disaster, we have come to understand a great deal more about the risks posed by hydrogen sulfide. On a global scale, the sulfur cycle shown is likely able to accommodate current emissions (or moderate man-made increases), since natural geothermal activity is the largest contributor to worldwide H_2S emissions based on this study and others. The compound's toxicity above endogenous gaseous signaling molecule levels, under-quantified emissions, the studies highlighted in sections 2.3 and 2.7, and the conflicting research findings documented in Section 2.8, however, make this compound a public health risk worthy of further study.

Take, for example, the many gaps presented in the BLS data in Table 6 through Table 9. One cannot compare worker injuries and fatalities across the four tables/years to identify potential trends due to the reporting discrepancies and blank records in the datasets. Regulators rely on timely, accurate, and consistent datasets to generate policies and procedures for protecting people, a structure that is considerably lacking for both H_2S exposures and emissions nationally. The need for further toxicity study is accentuated by the aging reports cited in the most recent ATSDR Draft Toxicological Profile for hydrogen sulfide and carbonyl sulfide, as well (ATSDR, 2014a). Of the

719 citations in the document's reference list, 408 (57%) were published more than 20 years ago. While this attribute does not invalidate the findings of the overall ATSDR report or each individual report found within, it does highlight the need for more up to date H_2S toxicity and emissions research, especially in light of advanced laboratory technologies in the last two decades.

The necessity to develop an antidote to H_2S acute and possibly post-acute exposures is another quite obvious research requisite highlighted in this study. Firstly, detergent suicides can and do fail, as well as expose bystanders and responders during the process. It is important, therefore, to avoid chronically-injured survivors. Secondly, the potential for this ubiquitous gas to be used for malicious purposes cannot be ignored by the field of public health. The use of chemical agents for terrorism purposes has been on the rise since 1968 (Figure 7) (RAND, 2016); it is imperative that emergency responders be prepared for targeted attacks using H_2S – a feat more easily accomplished if a working antidote were available.

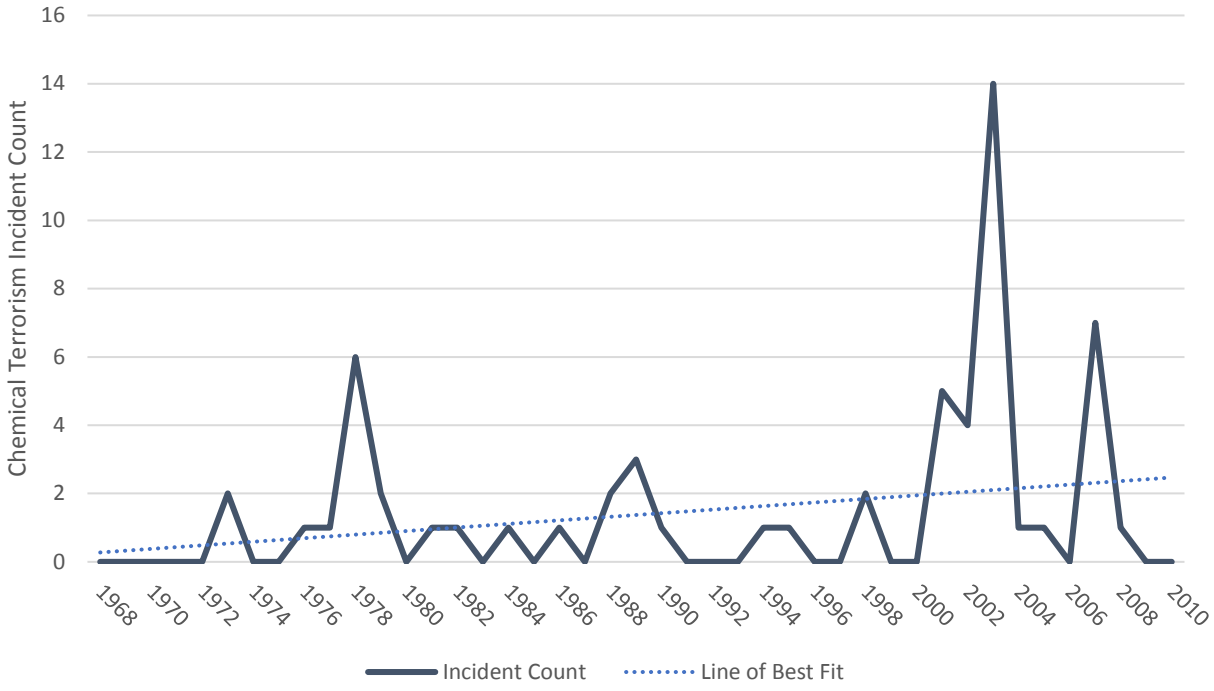


Figure 7. Count per year of worldwide terrorism incidents executed using chemical agents.

Data source: RAND Database of Worldwide Terrorism Incidents

And thirdly, H_2S continues to be one of the most dangerous gases in the workplace, despite the data gaps mentioned previously. As energy demand has and will likely continue to increase worldwide, there are growing political and industrial pressures to increase natural gas production for energy generation (US EIA, 2016b), especially from unconventional reserves such as shale gas and coalbed methane (US EIA, 2016a). Unfortunately, approximately 40% of untapped reserves may contain sour gas depending on the region explored (TOTAL, 2014, IEA, 2013), presenting a greater inhalation risk to fugitive H_2S emissions for workers and nearby residents than is already present. Having an antidote available on site in the event of an inadvertent exposure would be a valuable resource for any occupation, but especially so for remotely-located operations such as oil and gas drilling sites and AFOs. There does not seem to be a hydrogen sulfide candidate antidote under development at this time, however. Increased investment in research aimed at better understanding the mechanistic toxicology might provide the foundation for the rational design of antidotes, or at least suggest some leads.

H_2S presents serious risks in concentrated doses and confined spaces such as sewers and AFO buildings. On a global scale, however, the sulfur cycle (Figure 1) is able to accommodate current emissions (and any moderate anthropomorphic increase), since natural geothermal activity is the largest contributor to worldwide H_2S emissions based on this chapter's study and previous assessments (Beauchamp et al., 1984, Hill et al., 1972, US EPA, 1993). In summary, future research should focus on monitoring known and potential sources of H_2S emissions, improving the documentation of exposures and subsequent health impacts, clarifying the mechanistic pathways by which H_2S exerts its effects on the body, and developing a compound-specific antidote and/or treatments.

3.0 ENVIRONMENTAL TOXICOLOGY OF CYANIDE

3.1 INTRODUCTION

From a public health perspective, the available data (ATSDR, 2006b) indicate that the general population is primarily exposed to cyanide in two ways worldwide. Firstly, through inhalation of contaminated air, including tobacco smoke, and secondly, by ingestion of foods derived from cyanogenic plants. Air exposure is an essentially continuous, low-dose (*i.e.* chronic) process, with the exception of exposure during fires (See Fire Smoke section 3.6.1). Consumption of cyanogenic plant materials, especially by livestock (Merk Veterinary Manual, 2005), can result in symptoms of acute and chronic cyanide poisoning (ATSDR, 2006b). While the deliberate consumption of cyanide-laced foods and beverages can be an effective method for murder/suicide (Bebarta et al., 2011, Hall, 1979), accidental exposure from contaminated drinking water is of relatively low concern. The pK_a of HCN, ~9.24 at 25°C (Ghosh et al., 2006), ensures that the toxic anion (CN^-) readily becomes protonated in aqueous media around a neutral pH; subsequently, the uncharged HCN molecule is rapidly lost to the atmosphere. The physical properties of some important commercially available cyanide compounds are summarized in Table 1.

There are numerous routes by which cyanide may be released into the environment, but monitoring data suitable for quantifying the relative importance of the sources worldwide are scarce. Available data indicate that industrial manufacturing of cyanide may total approximately 2.3 million metric tones (2.5 million US tons) every year (Baskin et al., 2009). While the estimates vary between 0.5-12.9 x 10^{12} g of N/year emitted, the principal source of "environmental cyanide" (*i.e.* atmospheric HCN) is thought to be biomass burning (Crutzen and Carmichael, 1993, Flematti

et al., 2011, Li et al., 2003, Lupu et al., 2009), followed by - in no particular order - automobile emissions, volcanic activity and loss of industrial containment, especially in association with mining operations (ATSDR, 2006b). Deliberate releases of cyanide during activities such as "cyanide fishing" (Mak et al., 2005) and fumigation (ATSDR, 2006b) can be locally devastating to the wildlife targeted, but likely account for an insignificant addition to the total environmental cyanide burden.

The cyanide anion is a potent inhibitor of mitochondrial cytochrome *c* oxidase (respiratory complex IV) resulting in the observed acute toxicity towards the central nervous system and death by pulmonary failure (ATSDR, 2006b). Many other enzyme systems are also subject to inhibition, but only at significantly higher cyanide concentration (Ballantyne, 1987, Ballantyne and Salem, 2006). It is less widely appreciated that at lower cyanide concentrations, there are some intriguing non-toxic biological effects. For example, it has been independently verified in rats that cyanide salts are radioprotective (Schubert and Markley, 1963, Strelina, 1970, van der Meer et al., 1961) and metabolic cyanides appear to have multiple, beneficial effects in some plants (Xu et al., 2012). More recently, it has emerged that nitric oxide is able to reverse the inhibitory action of cyanide at cytochrome *c* oxidase (Cambal et al., 2011, Pearce et al., 2008), thereby affording protection in the form of an endogenous antidote. Presently, the extent to which our tolerance of normal environmental (and dietary) cyanide levels depends (or not) upon endogenous nitric oxide is presently unclear.

This chapter, covering the literature up to the end of December 2012, reviews the major cyanide sources/sinks in relation to the environment and human exposure, and, so far as may be possible, assesses the limits of what may be considered "normal" environmental cyanide levels.

3.2 ENVIRONMENTALLY RELEVANT CHEMISTRY OF CYANIDES

Table 11. Physical properties of common cyanide compounds

Property[a]	Hydrogen cyanide	Cyanogen chloride	Acetonitrile	Sodium cyanide	Potassium cyanide
Chemical formula	HCN	CNCl	CH_3CN	NaCN	KCN
CAS registry	74-90-8	506-77-4	75-05-8	143-33-9	151-50-8
Formula weight	27.03	61.47	41.05	49.01	65.12
Odor	Bitter almonds[b]	Pungent	Faint but distinct	Odorless if dry[c]	Odorless if dry[c]
Appearance[d]	Colorless	Colorless	Colorless	White	White
Physical state (STP)	Volatile liquid	Gas	Liquid / solvent	Solid / crystals	Solid / crystals
Melting point (°C)	-13.4	-6.0	-46.0	563.7	634.5
Boiling point (°C)	25.7	12.7-13.8	81.6	1496	Not available
Solubility (water)	Miscible	28 mg/L (25°C)	Miscible	480 g/L (10°C)	716 g/L (25°C)
Solubility (organic solvents)	Diethyl ether, ethanol	Diethyl ether, ethanol	Miscible	Ethanol, formamide[e]	Ethanol, methanol[e]
Log *K*ow	0.66	Not available	-0.34[f]	0.44	Not available
Henry's law constant	5.1×10^{-2} atm·m^3/ mol *Dimensionless:* 2.1	3.2×10^{-3} atm·m^3/ mol *Dimensionless:* 1.3	3.5×10^{-5} atm·m^3/ mol *Dimensionless:* 1.4×10^{-3}	Not applicable	Not applicable

[a]Data obtained from (ATSDR, 2006b) and references cited therein.
[b]Faint smell not detectable by everybody.
[c]Bitter almond smell of HCN apparent if wet.
[d]Pure compounds, aqueous solutions are colorless.
[e]Sparingly soluble in organic solvents.
[f]Data obtained from (International Programme on Chemical Safety, 1993) and references cited therein.

Hydrogen cyanide is the IUPAC-approved name for the molecular compound HCN, a colorless liquid having the odor of bitter almonds. Aqueous solutions and their vapors are now known as hydrocyanic acid, having previously been called prussic acid. The HCN molecule is soluble in alkaline aqueous media due to its ability to ionize to cyanide anion, (CN^-) and hydronium ion. However, the *pKa* of this weak acid is > 9, so that in mildly acidic-to-neutral natural waters the cyanide anion becomes protonated to the less soluble molecular acid – with a Henry's law constant favoring loss of HCN to the atmosphere (Ma et al., 2010) (Table 11).

Large amounts of HCN are produced industrially - approximately 750,000 tons were produced in 2001 in the U.S. - and it is a highly valuable precursor to many chemical compounds

ranging from polymers to pharmaceuticals (Wong-Chong et al., 2006). There are two common manufacturing routes both involving the reaction of methane and ammonia at elevated temperature over a platinum catalyst (Housecroft and Sharpe, 2008), but the first of these continues to be the more important:

Equation 6. Primary manufacturing route for producing HCN

$$2CH_4 + 2NH_3 + 3O_2 \longrightarrow 2HCN + 6H_2O$$

Equation 7. Secondary manufacturing route for producing HCN

$$CH_4 + NH_3 \longrightarrow HCN + 3H_2$$

A number of industrially important organic compounds are prepared by reaction of precursors with HCN including acetone → methyl methacrylate, used to form many resins and polymers, and butadiene → adiponitrile, the precursor to 1,6-diaminohexane use in the synthesis of Nylon 66 (Fox and Whitesell, 2004). (Acrylonitrile, a component of ABS plastics, is usually manufactured from propene and ammonia, not HCN.) The cyanide anion is a good nucleophile, which explains its use in organic chemistry as an attacking agent of partially positive carbons and its use in inorganic chemistry as a complexing agent for metal ions. Many industrial applications of cyanide make use of its complexing properties in various processes where metal surfaces are chemically modified, or metal mining operations. For example, the extraction of gold and silver during the refining of some ores utilizes the following chemistry (Housecroft and Sharpe, 2008):

Equation 8. Refining ores using a sodium cyanide solution to extract silver and gold

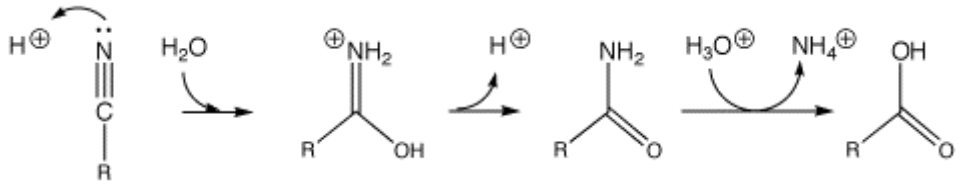
$$Ag_2S + 4\,NaCN + H_2O \longrightarrow 2\,Na[Ag(CN)_2] + NaSH + NaOH$$

$$4\,Au + 8\,NaCN + O_2 + 2\,H_2O \longrightarrow 4\,Na[Au(CN)_2] + 4\,NaOH$$

The organic chemistry of organo-cyanides, also referred to as nitriles, is in fact, somewhat similar to that of carboxylic acids. Both types of compounds have three carbon bonds to an electronegative atom and π bonding, which together render the carbon atom of the functional group

somewhat positive and thus electrophilic. Consequently, common pathways to the degradation of nitriles (Fox and Whitesell, 2004) involve the acid-catalyzed addition of water to form an immine, followed by rearrangement to the amide, addition of a second water molecule, rearrangement and elimination of ammonium ion.

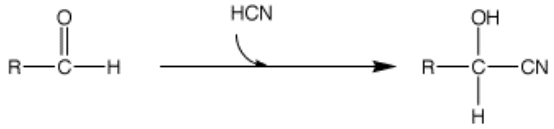
Equation 9. Common nitrile degradation pathways involve liberation of ammonium ion



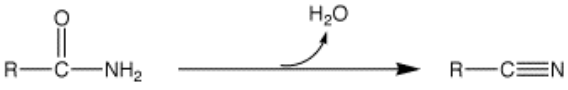
Thus, liberation of ammonia tends to be a feature of the environmental (and some biochemical) pathways to the degradation of nitriles, thereby linking environmental cyanide chemistry to the global nitrogen cycle.

Formation of nitriles is possible by several synthetic routes (Fox and Whitesell, 2004). For example, the addition of HCN to molecules containing carbonyl groups, forming hydroxynitriles, probably occurs in situations where inadequately contained cyanide waste comes into contact with organic matter (Equation 10). However, the dehydration of amides to nitriles is probably of greater biochemical importance (Equation 11):

Equation 10. Addition of HCN to carbonyl groups to form hydroxynitriles



Equation 11. Dehydration of amides to nitriles



The latter overall reaction is carried out by many plants in a series of steps to form cyanoglycosides (or cyanogenic glycosides) (Vetter, 2000). Cyanoglycosides contain a sugar ring connected by

bridging oxygen to a nitrile bearing carbon. Thousands of these are known, prime examples being linamarin and dhurrin (Figure 8), the most prevalent cyanogenic glycosides found in, respectfully, cassava root (Nhassico et al., 2008) and sorghum leaves (Busk and Møller, 2002).

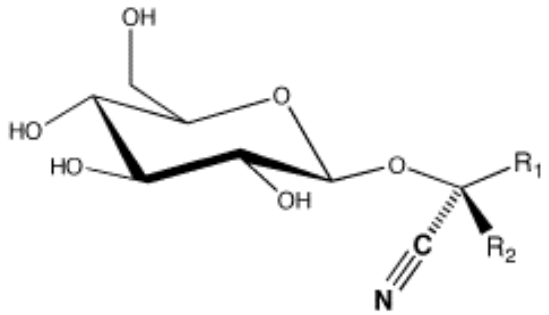


Figure 8. Linamarin (R1 ≡ R2 = –CH3) and dhurrin (R1 = p-hydroxyphenyl; R2 = –H)

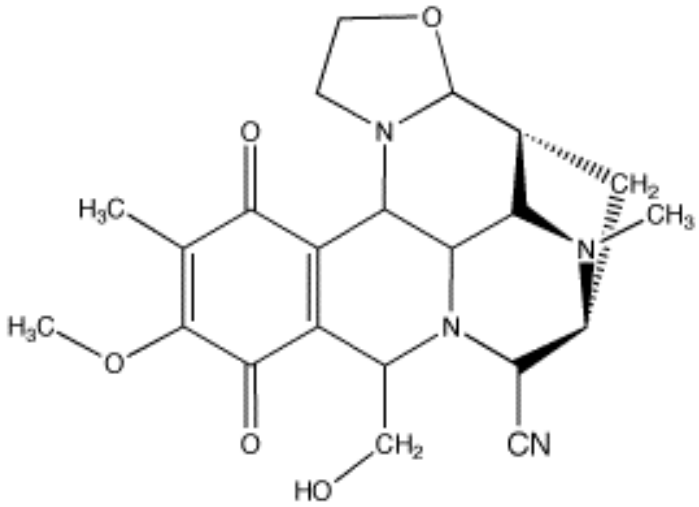


Figure 9. Cyanocycline A

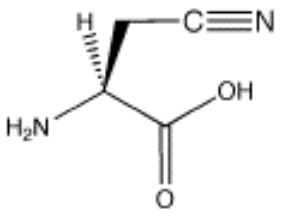
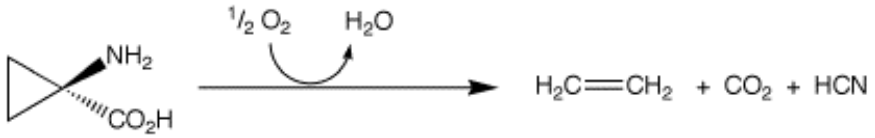


Figure 10. ß-cyanoalanine

Other examples of biological nitriles include those with anti-microbial and, in some cases, anti-tumor activities isolated from bacteria. For example, cyanocyclines, isolated from *Steptomyces*, composed of an isoquinoline residue fused to a diazabicyclic core (Figure 9) (Arora and Cox, 1988). In addition, HCN is often "fixed" or combined with the amino acid alanine (Figure 10) where it may subsequently add water to form an amino carbonate. In summary, plants (algae, bacteria, cyanobacteria, fungi, and higher green plants) exhibit quite a diverse set of anabolic pathways leading to formation of nitriles, and we only present a few examples here.

Interestingly, many plants also produce HCN in small quantities (Peiser et al., 1984). The plant hormone ethylene is generated by oxidation of aminocyclopropane carboxylic acid and HCN is released as a by-product:

Equation 12. Oxidation of aminocyclopropane carboxylic acid, releasing HCN

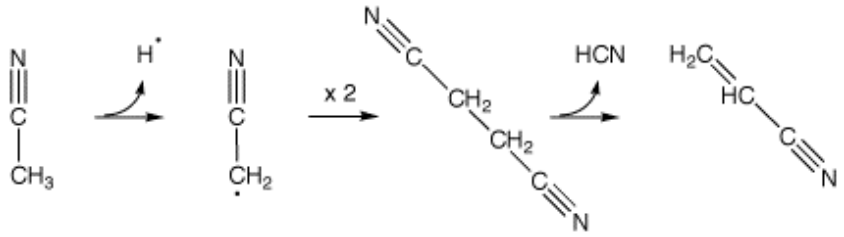


Some microbes synthesize HCN, but a significantly greater number tend to biodegrade cyanide using a variety of pathways employing oxidative, reductive, hydrolytic and group-exchange reactions (Ebbs, 2004). Pathways such as the cysteine → β-cyanoalanine → arginine conversion (Raybuck, 1992) can fix cyanide in the biosphere, but the vast majority lead to release of the nitrogen from cyanide as ammonium ion (Ebbs, 2004). Cyanate and thiocyanate (excreted by animals) are intermediates in some of the microbial pathways and, consequently, the biosphere may be thought of as a net converter of cyanide to ammonia thereby providing a link to the global nitrogen cycle. In most cases these reactions are carried out around neutral pH where cyanide is predominately protonated and the solubility of HCN is limited by Henry's law. However, recent studies searching for bacteria that could be useful in the remediation of highly-contaminated (*i.e.*

alkaline) soil have found and characterized a *Pseudomonas* strain of bacteria that degrades cyanide and its metal ion complexes at pH 11, while seemingly requiring only a carbon source (*e.g.* acetate) for cyanotrophic growth (Luque-Almagro et al., 2011a, Luque-Almagro et al., 2011b).

The combustion/pyrolysis of organonitriles and carbon-nitrogen containing polymers is complex. The production of HCN from these materials is dependent on time-dependent temperature and oxygen concentration variations during the course of a fire. Detailed molecular studies are scarce, but the mechanism of combustion/pyrolysis of acetonitrile (CH_3CN), an important solvent and by-product of acrylonitrile production, has been described in some detail (Britt, 2002). When oxygen is depleted and at temperatures below 1,000°C, there is substantial formation of HCN due to pyrolysis of acetonitrile by radical mechanisms including the following:

Equation 13. Pyrolysis of acetonitrile, forming HCN



When the relative amounts of fuel and oxygen are at least comparable, or oxygen is in excess, combustion of CH_3CN (producing CO and CO_2) results, and the oxidation of present HCN to NO occurs. The extent to which these reactions of acetonitrile can be used as a model for combustion/pyrolysis of other nitrogen containing molecules, including polymers, is not entirely clear. However, it does seem reasonable to infer that smoldering fires, where oxygen is depleted, have the potential to produce the significant amounts of HCN (Grabowska et al., 2012) – such as during the salvage phase of firefighting operations.

Similarly, in natural fires the most important contributor to atmospheric HCN levels is thought to be biomass burning (Li et al., 2003) with the greatest production of HCN from brush

fires occurring during the smoldering phases, and the most likely nitrogen source being amino acids (Lobert and Warnatz, 1993). A comparison of HCN production from the burning of different natural and synthetic materials is given in Table 12.

Table 12. HCN produced by combustion of a variety of materials[a]

Material	Temperature (C°)	Yield (g HCN produced/g sample combusted)
Acrylonitrile	750	0.030[b]
	> 1,000 (low O_2)	0.590[b]
Acrylic fiber	800	0.095–0.193[c]
Nylon	650 (well-ventilated)	0.005[d]
	650 (ventilation limited)	0.018[d]
	800	0.0076–0.0700[c, e]
	900 (well-ventilated)	0.011[d]
Polyurethane	650 (well-ventilated)	0.003[d]
	650 (ventilation limited)	0.001[d]
	900 (well-ventilated)	0.0003[d]
Urea-formaldehyde foam	800	0.015–0.042[c]
Rigid urethane foam	800	0.008[c]
Silk	n/a[g]	0.0222–0.0680[f]
	800	0.036[e]
Melamine	650 (well-ventilated)	0.001[d]
	900 (well-ventilated)	0.033[d]
Wool	350 (well-ventilated)	0.018[d]
	650 (well-ventilated)	0.002[d]
	900 (well-ventilated)	0.006[d]
	800	0.007–0.054[c, e]
	n/a	0.0126 – 0.0252[f]

[a]List not intended to be exhaustive.
[b]Data obtained from (Britt, 2002).
[c]Data obtained from (Sumi and Tsuchiya, 1973).
[d]Data obtained from (Simonson et al., 2000)
[e]Data obtained from (Hobbs and Patten, 1962)
[f]Data obtained from (Olsen et al., 1933)
[g]N/A: Temperature not indicated

Recent work on modeling the persistence of atmospheric HCN suggests that in both the stratosphere and the troposphere, the major degradation pathway is via a reaction with hydroxyl radical, followed by a cascade of reactions dependent on oxygen-derived species, where the ultimate products, CO_2 and NO_x, feed into the global carbon and nitrogen cycles, respectively:

Equation 14. Major degradation of atmospheric HCN via hydroxyl radical, releasing CO_2 and NO_X

In the stratosphere, HCN is thought to be a major trace gas at levels around 10 ppt and most likely degrades slowly with an average lifetime of 5-10 years per molecule (Kleinbo¨hl et al., 2006). After the initial reaction with hydroxyl radical the product degrades in a very complicated fashion. A minor degradation pathway by initial reaction with singlet oxygen may also be of some significance. In the troposphere, HCN also predominately reacts with hydroxyl radical, but the average residence time is less than six months per molecule. As the degradation pathway dependent on hydroxyl radical is slow, the major sink is consensually argued to be the ocean (Lupu et al., 2009, Li et al., 2003). Presumably, the sink strength is tied to microbial degradation – the algal and cyanobacterial populations of the ocean almost certainly being large enough to support this idea (Dzombak et al., 2006).

3.3 OCCUPATIONAL CONCERNS

Some of the cyanides commonly employed in industrial processes are either volatile themselves, or unavoidably converted to HCN upon contact with water (Table 11) – worrisome properties that facilitate dissemination of their toxic consequences. Despite this concern and the widespread/usage of cyanides (RTI International, 2006), commercial transport and industrial consumption of these compounds make very little contribution (TRI03, 2005) to the overall cyanide content of the environment based on available data. More importantly, incidents similar to the Bhopal disaster in

which the accidental release of methyl *isocyanate* from a manufacturing facility eventually resulted in 20,000 human causalities in India (Varma and Varma, 2005) have, to date, not occurred with cyanide compounds. In fact, where large-scale spills of cyanide have occurred and been well documented, wildlife has sometimes been decimated, but relatively few human fatalities have been reported (Table 13).

Workers may be exposed to cyanide on the job if they use cyanide compounds. According to the National Occupational Exposure Survey, in 2006 the number of workers exposed to cyanides in the U.S. totaled 165,295 (ATSDR). Dermal and inhalation are the main routes of exposure for this population (Baskin et al., 2009). While measured data are limited, the professions where a risk of being exposed exists include: cassava processing, factory work, electroplating, metal mining processes, metal finishing and plating, metallurgy, metal cleaning, pesticide application, leather tanning, photography and photoengraving, firefighting, gas works operations, dye/pharmaceutical industries (ATSDR, 2006b). NIOSH reports that workers who have been exposed to cyanide over time may experience symptoms ranging from headache, palpitations, loss of appetite, nausea, and irritation of the upper respiratory tract and eyes (2011).

Table 13. Major reported incidents of cyanide spills and leaks

Site/ Operator/ Location[a]	Release Period	Type of Spill / Media	Quantity Spilled	Environmental Consequences	Human Causalities	Source(s)
Summitville gold mine, Summitville Consolidated Mining Co., Inc., Colorado, United States	1986 – 1992	Cyanide, heavy metals and acid leached from the mine site into groundwater below heap leach pad and on several occasions leaked from transfer pipes into surface water	*unknown*	All stocked fish in nearby reservoir and in farm holding ponds died along 17 miles of river. Possible association with cyanide release; probable with acid and metals exposure.	0	(USGS, 2005)
Grouse Creek gold mining plant, Hecla Mining Co., Idaho, United States	1994 – 1999	Several spills of cyanide solution containing sodium cyanide (NaCN)	>18.93 m^3	Unknown. Closed site continues to leak. Fish kills reported.	0	(Cascadia Times, 2000)
Omai gold mine, Cambior Inc., Omai, Guyana	1995	Walls of tailings pond were breached. Waste fluids containing cyanide leaked into surface waters	4,200,000 m^3	At least 20,000 steelhead fish died. Possible effects to nearby wildlife along 50-mile stretch of river.	0 - Human health effects reported	(Beebe, 2001) and references cited therein
Aurul precious metals recovery plant, Esmeralda Exploration (Australian co.) and Romanian government, Baia Mare, Romania	2000	Tailings dam broke, leaked cyanide and metal-rich liquid waste into surface waters	100,000 m^3	Rapid death of aquatic organisms and animals living close to the polluted rivers. Disruption of drinking water supplies in 24 locations and for 2.5 million people.	0	(Soldán et al., 2001, Bacsujlaky, 2004)
Tarkwa gold mine, Gold Fields Limited, Tarkwa, Ghana	2001	Pipe carrying cyanide solution broke, eventually reaching a nearby stream	900-650 m^3	Approximately 50 fish died from exposure. Additional distressed fish caught by residents.	0 – Human health effects reported	(Amegbey and Adimado, 2003)
Granite mine transportation vehicle, Central Australia	2002	Transportation accident spilled cyanide pellets (NaCN)	0.4 m^3	Killed >500 birds and a dingo.	0	(Wakeham and Blair, 2002)
Phu Bia gold mine, Pan Australian Resources, Chai Somboun special zone, Laos	2005	Heavy rainfall caused cyanide to leak from the mine into small nearby river	*unknown*	Killed fish in the nearby rivers, and impacted villagers within at least 3km of the mine site.	0 - Human health effects reported	(Mineral Policy Institute, 2005)
Lucebni Zavody chemicals plant, Kolin, Czech Republic	2006	Cyanide-laced waste water overflowed into nearby river (CN^-)	600kgCN^- per 30 m^3 waste water	Contaminated 85km of the river. 10 tons of fish died.	0	(Balej, 2008, European Rivers Network, 2006)
[a]Not meant to be an exhaustive list.						

3.4 GROUND / SURFACE WATER

Cyanides/nitriles in soil are efficiently biodegraded by microorganisms (Ebbs, 2004) so that their infiltration into the subsurface layers is usually insignificant and aquifers do not become contaminated (ATSDR, 2006b). The exception to that situation is in landfills, tailings, ponds, and spills where high levels of cyanide-containing waste may have been released (Mudder et al., 2001). The concentration of cyanide in landfill leachates can be high enough to kill the microorganisms normally responsible for their degradation (Lagas et al., 1982). Consequently, drinking water wells sunk in the vicinity of these incidents could conceivably become contaminated. Approximately 14% of households in the U.S. rely on private wells for their domestic supplies (U.S. Census Bureau, 2008) – essentially closed systems delivering water directly into homes that potentially could result in the release of HCN gas in enclosed spaces like bathrooms, kitchens, laundries etc. Fortunately, to date, there seem to have been no such occurrences reported.

In the U.S., 0.9 tons of pollutants per year were released into surface waters from registered industrial processes that use hydrogen cyanide. In comparison, 570 tons were released into the air and 779 tons placed into underground injection wells (TRI03, 2005). Free cyanide ($HCN + CN^-$) has been found in Canadian lakes at up to 19 ppb (µg HCN/L water) (Sekerka and Lechner, 1976) and measured in municipal drinking water at up to 11 ppb in Canada and the U.S. (ATSDR, 2006b). At the mean environmental temperature of ~15°C (WMO, 2012), a reasonable estimate for the dimensionless form of Henry's law constant for the partitioning of total cyanide between air and water is $4x10^{-3}$ (Dzombak et al., 2006). Using the reported value of 11 ppb for cyanide ($HCN + CN^-$) in drinking water to calculate the predicted atmospheric concentration of HCN

gives: 11 ppb x $4x10^{-3}$ = 0.044 ppb. The analogous calculation for the Canadian lake data yields: 19 ppb x $4x10^{-3}$ = 0.076 ppb. The background level of atmospheric HCN at sea level is seemingly around 0.1 ppb (Ambrose et al., 2012, Li et al., 2003). Therefore, the level of cyanide that has been found in oligotrophic lakes and processed drinking water is at, or just below, the level predicted by atmospheric exchange according to Henry's law.

In addition, cyanogen chloride, formed as a consequence of water treatment with chlorine, may also be present at up 25 ppb (Zheng et al., 2004). The molecular mass of cyanogen chloride (61.5) is about twice that of HCN (27) and so, there is up to ~22 ppb total cyanide concentration present in drinking water. The LD_{50} for orally administered cyanide in rats is ~3 mg/kg (ATSDR, 2006b). Using this value to estimate the LD_{50} for 70 kg humans, one finds 3 x 70 = 210 mg. Assuming no elimination, achieving this LD_{50} dose by drinking water with 22 ppb (0.022 mg/L) of cyanide would require the consumption of 9,545 L – *i.e.* at the average consumption rate of ~2 L/day, the amount of water that an adult person would normally consume in 13 years. Clearly, in the absence of any tampering, acute cyanide poisoning through drinking a properly managed public water supply should not be a concern. Of course, this statement does not directly apply to water drawn at private wells, where there may be additional sources of cyanide that are likely to persist without further processing.

3.5 EXPOSURE TO CYANOGENS THROUGH DIET

Humans may also be naturally exposed to cyanide through their diet (Dolan et al., 2010). Research indicates that cyanogenic β-glycosides (cyanides bound to sugar molecules containing a nitrile function) in plants help to protect them from being destroyed by pathogens and herbivores

(Poulton, 1993), although the effectiveness of this strategy depends on the organisms that consume the plants (Jones, 1998, Møller and Siegler, 1999). In many animals, cyanide is metabolized into the less toxic thiocyanate (SCN^-), but a variety of foods also contain thiocyanate, including plants, dairy products, and meat. Thiocyanate is efficiently excreted by the body, and presently there is no concern that it may accumulate in humans, even though very little thiocyanate exposure data exist (ATSDR, 2006b).

Approximately 2,650 identified plant species, including fruits, vegetables, and the pits of fruits and nuts, contain cyanogenic glycosides that release HCN upon hydrolysis. For humans, such hydrolysis occurs during digestion (ATSDR, 2006b, Siegler, 1991, World Health Organization, 2007). In plants, cyanogenic glycosides are normally stored separately from the enzyme that converts them to cyanohydrins ($HO\text{-}C(R_2)\text{-}CN$), which are also readily hydrolyzed to produce cyanide (Selmar, 1993). This represents an exposure hazard to humans when the edible part of the plant contains high levels of these cyanogenic compounds and the rate of ingestion is faster than the rate in which the body detoxifies cyanide into thiocyanate (Donato, 2002, Jones, 1998, Westley, 1988). Newly germinated shoots typically contain the most cyanogenic potential (Busk and Møller, 2002, Chand et al., 1992), particularly under drought conditions (Merk Veterinary Manual, 2005). This is why livestock cyanide intoxication due to grazing on the emerging shoots of cyanogenic, heat-tolerant plants after a prolonged drought is a common scenario (Merk Veterinary Manual, 2005) – For example, there were 15 such U.S. cattle deaths recently reported in Texas (CBS News, 2012). Plant-derived foodstuffs may contain high levels of cyanide when the cyanogenic plants have not been properly prepared before consumption (ATSDR, 2006b), and depending on the type of food, as summarized in Table 14:

Table 14. Cyanide concentrations in food products

Plant Type[a]	Releasable HCN (mg/kg or mg/liter)
Cassava – whole tubers (roots)	380 – 445 [b]
Mash (sweet)	81 [c]
Dried roots (bitter)	95 – 2,450 [c]
Leaves (bitter)	347 – 1,000 [b, c]
Dried root cortex (bitter)	2360 [b]
Gari flour (Nigeria)	10.6 – 22.1 [b]
Sorghum – whole immature plant	2400 – 2,500 [b , c]
Leaves (wet weight) (CN^-)	192 – 1,250 [b, d]
Bamboo – immature shoot tip	7,700 – 8,000 [b , c]
Soy protein products (processed)	0.07 – 0.3 [b]
Soybean hulls	1.24 [b]
Lima beans from Puerto Rico (black)	2,900 – 3,000 [b , c]
from Java (colored)	3,000 – 3,120 [b , c]
from Burma (white)	2,000 – 2,100 [b, c]
U.S. lima beans	100 – 170 [b , c]
Commercial cherry juice (processed)	4.6 [b]
Apricot pits (wet weight)	89 – 2,170 [b]
Cereal grains and their products (processed)	0.001 – 0.45 [b]

[a]Unprocessed unless otherwise indicated.
[b]Data obtained from (WHO, 2004) and (ATSDR, 2006b) and references cited therein.
[c]Data obtained from (Eisler, 1991).
[d]Data obtained from (Chand et al., 1992).

For the U.S. population, the number of people exposed to cyanogens naturally in their food is not known (ATSDR, 2006b), although accidental poisoning through the ingestion of cyanogenic food in industrialized countries is uncommon (Baud, 2007). A significant number of cyanide poisonings through ingestion in the U.S. (45%) occur as a result of swallowing a cyanide solution or cyanide salts to commit suicide (Bebarta et al., 2011), as opposed to consuming naturally cyanogenic foods or through accidental occupational exposures (Baskin et al., 2009, Gill et al., 2004).

3.5.1 Dietary Health Hazards

While acute cyanide toxicity is known to be mediated principally through inhibition of mitochondrial cytochrome-*c* oxidase (Ballantyne, 1987, Ballantyne and Salem, 2006), the

molecular mechanism(s) involved in chronic (low-level) cyanide intoxication is (are) presently unknown. Human diets deficient in protein, sulfur, riboflavin (vitamin B_2) and hydroxycobalamine (vitamin B_{12}) show greater risks of health effects from consuming foods high in cyanide, especially cassava and sorghum (ATSDR, 2006b, Oke, 1980, Speijers, 1993). In Africa, chronic cyanide poisoning has been attributed to consumption of cassava and nutritional deficiencies, resulting in spastic paraparesis or "Konzo" (Howlett, 1994, Tylleskar et al., 1992) and implicated in tropical ataxic polyneuropathy and the stunting of children (Oluwole et al., 2003). Exposed individuals often experience significant effects on the central nervous system, including weakness in the fingers and toes, dimness of vision, and deafness. Impacts on the thyroid gland have also been linked to the consumption of highly cyanogenic cassava (ATSDR, 2006b). It should be noted that consumption of cassava or its cyanogen might not be the only potential causes of these health effects. Interestingly, there is some evidence to suggest that low-level cyanide consumption and inhalation (10 ppm for 2 hours) can induce hearing deficiencies and loss through noise promulgation (Fechter et al., 2002). Concern regarding the level of cyanogens in cassava and sorghum is compounded by the sheer number of people whose diet is primarily made up of them – hundreds of millions across the globe (WHO, 2004).

3.5.2 Cassava Consumption

Cassava, in particular, serves as a staple food for developing countries within Africa, South and Central America, Southeast Asia, and India. Other names for cassava include *Manihot esculenta*, tapioca, manioc, or yucca. The cyanogen of concern in cassava is linamarin (Figure 8). With proper processing - which involves drying, fermenting, soaking in water, rinsing and/or baking the cassava - toxic cyanogen levels can be decreased 97-99% (Burns et al., 2012, Ferreira et al., 1995,

Ngudi et al., 2003). Unfortunately, during periods of food shortage, drought, or a rush to get the product to market, cassava may not be thoroughly processed (Nhassico et al., 2008). For example, as recently as 2011 there were reported cases of unsafe levels of cyanide being found in ready-to-eat cassava snacks (Miles et al.).

The amount of cyanide actually consumed through cassava intake is difficult to gauge and varies by region and population. The worldwide average consumption of cassava from 2005-07 was 43 Calories (kcal)/person/day. Daily cassava consumption in some countries such as the Democratic Republic of Congo, Mozambique, and Ghana were as high as 843, 658, and 603 kcals, respectively (FAO, 2010a). There have also been estimations regarding the average concentration of HCN within cassava that disagree with the more commonly accepted ranges reported in Table 14. Table 15 demonstrates the difficulty in estimating the average daily dose per kg body weight of HCN through the consumption of cassava due to this variability, differences in consumption rates per day, and the type of cassava product ingested.

Table 15. Estimating human exposure to HCN through cassava consumption

Daily consumption	**kcal within edible portion/g[b]**	**Estimated HCN intake mg/HCN/person-day[a]**					
		High concentration: 255 mg/HCN/kg[c]		**Medium concentration: 38 mg/HCN/kg[d]**		**Low concentration: 0.1 mg/HCN/kg[e]**	
		43 Cal	*843 Cal*	*43 Cal*	*843 Cal*	*43 Cal*	*843 Cal*
Fresh cassava	1.46	0.1073	2.1034	0.016	0.3134	*n/a*	*n/a*
Meal/flour cassava (heated)	3.38	*n/a* [f]	*n/a*	*n/a*	*n/a*	0.0002	0.0036

[a]70kg body weight assumed per person
[b]Data obtained from (WHO, 1972) and references cited therein.
[c]Assessed fresh cassava (not processed). Data obtained from the following sources: (Yeoh and Sun, 2001, Siritunga and Sayre, 2003, Dufour, 1988). HCN concentration results ranged from 10-500 mg cyanide equivalent/kg dry matter.
[d]Assessed fresh cassava (not processed). Data obtained from (Yeoh and Sun, 2001). HCN concentration results ranged from 15–61 mg HCN/kg.
[e]Data obtained from (Emmanuel et al., 2012). HCN concentration results ranged from 0.08–0.12 mg/HCN/kg dry weight. List of studies and concentrations not meant to be exhaustive.
[f]N/A: Not measured in the referenced study.
Exposure Limits Comparison: Oral LD_{50}: 3 mg HCN-kg (in rats non-fasting) (ATSDR, 2006b). NOAEL: 12.5-28.8 mg HCN/kg-day (mice and rats) (ATSDR, 2006b). Chronic Oral RfD for cyanogen: 0.001 mg HCN/kg-day (daily oral exposure to population and sensitive subgroups without appreciable risk during lifetime) (US EPA, 2010).

In 1996, due to food scarcities in impoverished countries, the World Bank's Consultative Group on International Agricultural Research recommended more cassava cultivation (Babaleye, 1996). Some researchers, however, recommend using caution when promoting cassava cultivation to countries where it was previously never used as this could increase the risk of cyanide poisoning due to improper cassava processing (Nhassico et al., 2008). On the other hand, progress has been made to reduce the risk by creating a cassava strain that contains 60-94% less leaf linamarin and 99% less root linamarin (Siritunga and Sayre, 2003).

As an alternative to cassava, increased sorghum (a hardy cereal grain) production has been recommended to provide food in places where it is difficult to grow most other crops (International Fund for Agricultural Development, 2011). As shown in Table 14, however, sorghum has been found to contain higher levels of HCN compared to cassava according to data compiled by (ATSDR, 2006b) and others. Alternatively, recent data using a chilling method indicate a much lower range of HCN concentrations in sorghum than was originally estimated: 6.65–1.68 mg/100g (Prasad and Dhanya, 2011). In order to properly assess risk and make intelligent policy recommendations these data and measurement discrepancies should be addressed (FAO and WHO, 2011). They challenge the validity of present risk assessments and exposure limits, which were developed primarily from animal studies.

3.6 FIRES AND SMOKE

3.6.1 Fire Smoke

Hydrogen cyanide is also a by-product of the combustion of materials in products used in everyday life (insulation, carpets, clothing, and synthetics), especially manmade plastic and resins containing nitrogen that burn when the fire is hot and in an enclosed space. Common manmade materials that generate cyanide gas during combustion include nylon, polyurethane, melamine, and acrylonitrile. HCN poisoning has even been indicated in injuries and deaths during prison fires when inmates set fire to mattresses (Fortin et al., 2011, Ferrari et al., 2001). Increasingly, research is pointing to HCN as a substance that poses as much of a threat to first responders and victims encountering fire smoke as carbon monoxide (Alarie, 2002, Stamyr et al., 2012). The diverse components of the fire (e.g. heat, CO) can have additive and possibly synergistic effects with the HCN present. Such an environment may induce sub-lethal intoxication and limit the ability to escape the situation or perform rescue operations (Eckstein and Maniscalco, 2006), as may have been the case for several U.S. aircraft incidents involving fires during flight (Chaturvedi and Sanders, 1996). A more detailed discussion of fire smoke can be found in the book chapter by Hall and Borron (2015).

3.6.2 Cigarette Smoke

Although cigarette smoking among American high school students is declining, the proportion of students smoking (19.5%) (National Institute on Drug Abuse, 2011) is in fact the same as the proportion of adults over the 18 that smoke in the U.S. (19.3%) (CDC, 2011). Consequently, the

net level of smoking in the overall population is likely to remain relatively stable for years to come. Worldwide, the proportion of people exposed to secondhand smoke is estimated to be up to 40% of children, 35% of women, and 33% of men (Öberg et al., 2011); in 2006 these relevant percentages represented 126 million Americans. Additionally, it has been suggested that cyanide and thiocyanate can cross the placenta, putting fetuses of smoking mothers at risk of exposure, as well (US EPA, 2010). Although the composition of cigarette smoke and its effects have been studied for many years, new research continues to uncover the various dangers associated with this persistent behavior.

Cigarette smoke is a complex, dynamic aerosol containing approximately 4,000 distinct chemicals (O'Connor and Hurley, 2008). Smoking cigarettes is known to increase levels of HCN in the blood (Chandra et al., 1980). In non-smokers, cyanide levels are reported to be between ~0.2 μM (Tsuge et al., 2000) and ~3 μM (Borowitz et al., 2006). Whereas, in smokers blood cyanide levels are reported to vary between ~0.3 μM (Tsuge et al., 2000) and ~7 μM (Borowitz et al., 2006). While these absolute estimates vary by an order of magnitude, there seems to be a consensus regarding the relative levels of blood cyanide between the two groups: 1.6 – 2.3 times higher in smokers than non-smokers (Borowitz et al., 2006, Tsuge et al., 2000). Due to the complex nature of cigarette smoke and especially the combined effects of its components, disentangling the particular role of cyanide in smoking-related health outcomes continues to be challenging.

Research suggests that the levels of cyanide in mainstream, or inhaled, smoke from cigarettes purchased in the U.S. to range from 10–400 μg per cigarette (ATSDR, 2006b, Guo et al., 2012, Guthery and Taylor, 2011). However, one recent study has reported a higher range of 170-830 μg/cigarette (Bodnar et al., 2012). Cigarettes available outside of the U.S. show similar

ranges of HCN in smoke: 280–550 µg/cigarette (mainstream) and 53–111 µg/cigarette (sidestream), respectfully (ATSDR, 2006b).

Comparatively, marijuana use among youth is now higher than cigarette smoking according to certain parameters (seemingly due to both decreases in cigarette use and increases in marijuana use) (National Institute on Drug Abuse, 2011). While smoking marijuana may be considered a safer alternative to cigarettes by some (Zimmer and Morgan, 1997), marijuana smoke appears to contain roughly five times more cyanide in both mainstream and sidestream smoke compared to tobacco (Moir et al., 2008) (see Table 16).

Table 16. Comparison of the HCN levels found in tobacco vs. marijuana smoke under two smoking conditions

	Mainstream Smoke[a]				Sidestream Smoke			
	ISO[b]		**Extreme[c]**		**ISO**		**Extreme**	
	tobacco	*marijuana*	*tobacco*	*marijuana*	*tobacco*	*marijuana*	*tobacco*	*marijuana*
HCN (µg/cig)	208	526	320	1668	84	685	103	678

[a]All data obtained from Moir et al. (2008).
[b] International Organization for Standardization standard (ISO 3308), Routine Analytical Cigarette-Smoking Machine, Definitions and Standard Conditions
[c] Extreme conditions: >700 °C

3.7 CYANIDES CONCLUSION

The transport and fate of manufactured cyanide compounds entering soil and water has quite recently been reviewed in considerable detail by Dzombak et al. (2006). Within this discourse, Ghosh et al. [Chapter 12] have presented both anthropogenic and natural cycles describing the recycling and transformation of cyanides. At the risk of being too parsimonious with the information content, we present here a minimal global cyanide cycle - delineating the major cyanide fluxes between the biosphere and the environment as they currently appear to be understood.

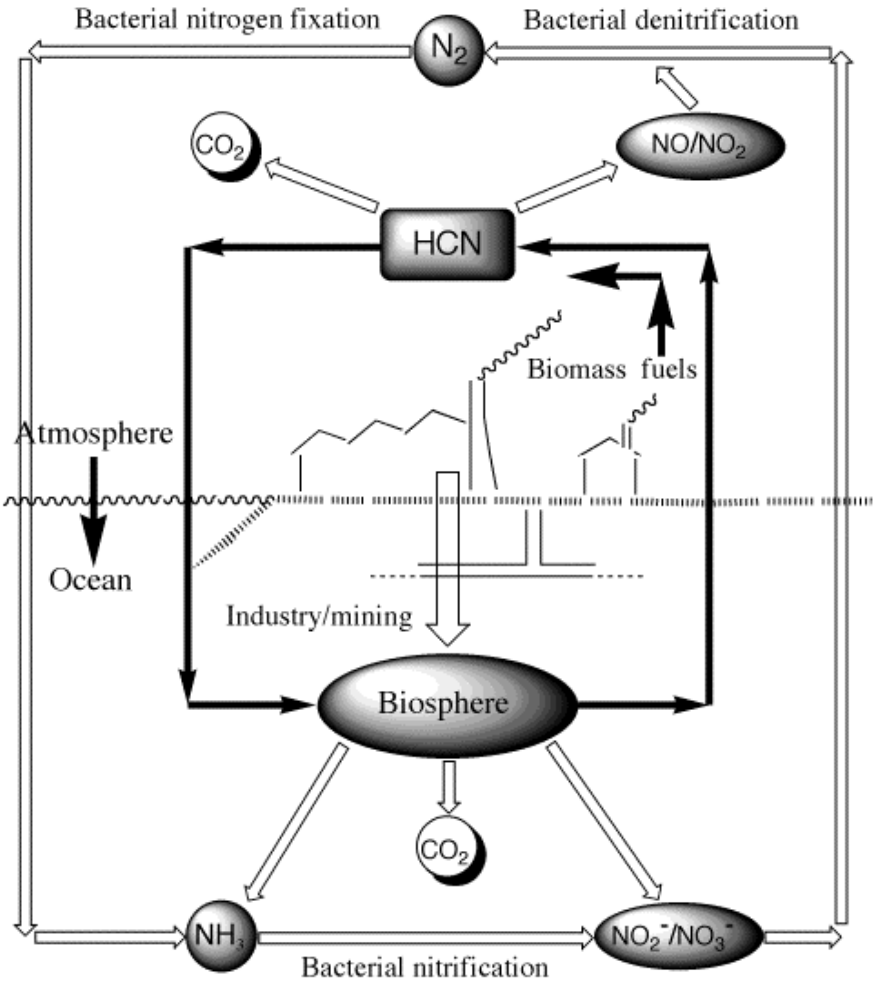


Figure 11. A parsimonious global cyanide cycle

On a global scale, industrial/mining activity is currently responsible for relatively little release of cyanide into the soil and groundwater. Bacteria in landfills process cyanogenic effluent efficiently, preventing any cyanide migration into the wider biosphere/environment. The majority of HCN released into the atmosphere originates in the burning of biomass fuels for both domestic and industrial purposes. Most atmospheric HCN partitions into bodies of water, the oceans being the largest, before it can be transformed in the atmosphere. Bacteria in the hydrosphere initialize the biochemical conversion of HCN to metabolites, some of which will eventually form biomass to be used as fuel, thus beginning the cycle again. The cyanide cycle (Figure 11) is connected to

and subordinate to both the global nitrogen cycle (as shown) and the global carbon cycle (through CO_2).

Provided the carbon and nitrogen cycles remain stable, an enormous increase in the amount of anthropogenic HCN released would be required to significantly disturb the global steady-state levels of the cyanide-cycle components. Consequently, cyanide in the environment is of low concern at this time and, given current trends in the development of cleaner energy sources, can probably remain so in the future despite the increasing demands of Earth's growing population. Never-the-less, due diligence should continue to be observed with regard to the monitoring and management of industrial/mining practices.

4.0 CONCLUSION

The intent of this research was to collect and synthesize available information on the overall toxicity and sources of hydrogen sulfide and cyanide in order to guide the risk management of these two compounds. Endeavors such as this are broad because they reflect the very nature of the environmental health field – from understanding toxicity mechanisms, to preventing releases, to responding to exposures. Hydrogen sulfide and cyanide are agents that offer benefits to society, however they can also significantly risk public health and the environment if poorly managed.

Risk analysis refers to the process by which we research, identify, characterize, communicate, and manage a variety of different risks – from infectious diseases to environmental agents (Renn, 2008). The U.S. Environmental Protection Agency's (EPA) traditional framework for assessing risk (NRC, 1993), and indeed many popular funding models, do not adequately fit the framework needed to understand the risks put forth by cyanide and hydrogen sulfide based on the literature reviewed herein; those models tend to place significant emphasis on epidemiology. The number of people affected by H_2S and cyanide worldwide is relatively small (based on available monitoring data) when compared with infectious diseases or car accidents, for example. Therefore, customary epidemiologic associations in this case would be misleading due to the small sample size. Consequently, in the case of hazards like cyanide and H_2S, where exposures are intermittent and inadvertent, it is reasonable to adopt other approaches to risk characterization. Analysis of national/global release patterns coupled with mechanistic confirmation of cause and effect is one such reasonable approach.

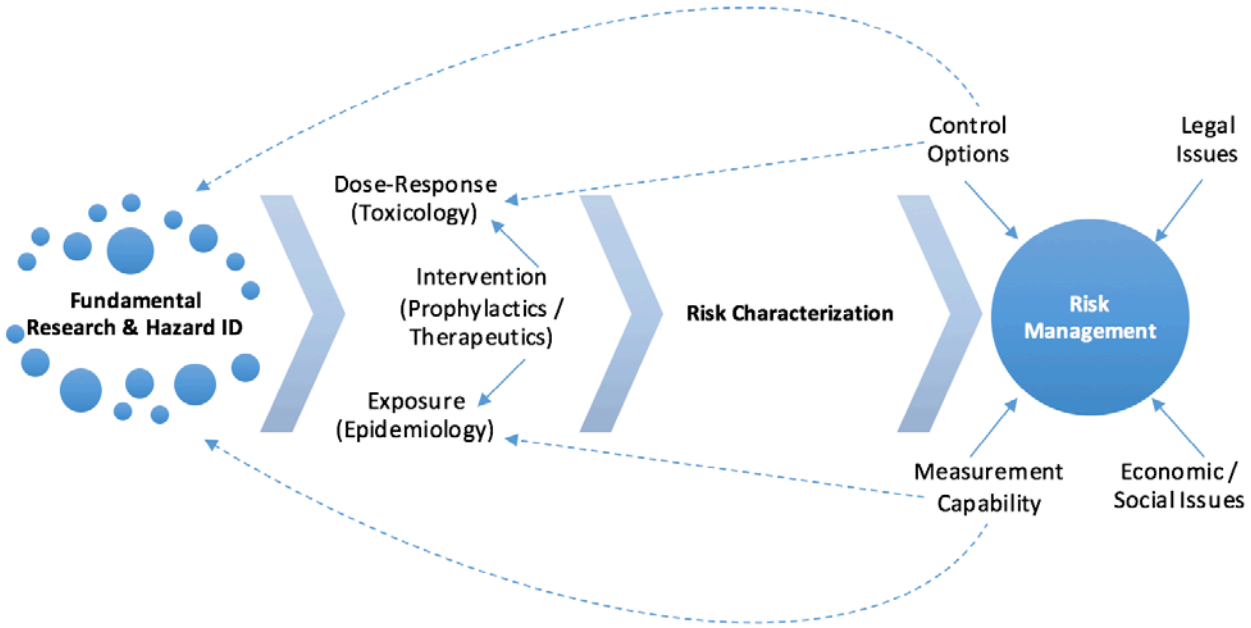


Figure 12. Alternative risk analysis diagram

Figure 12 visualizes such an alternative risk analysis paradigm in order to help situate the current findings within the larger body of environmental health research. Here, *fundamental research* and *hazard identification* play significant roles in characterizing risk, and eventually *risk management*. The initial stage in this process, driven by basic science, must take into consideration the costs associated with controlling such a risk (*control options*) and our ability to measure the reaction of the effects (*measurement capability*). For cyanide and H_2S, many of these precursor pieces of information are still missing. For example, humans are much more adept at discerning the smell of H_2S than any of our current monitoring technologies. Additionally, the fundamental research on antidotes is still being conducted, partially because of historic misunderstanding on toxicity mechanisms, and partially because of gaps in human health effects due to exposures at certain levels. Moving forward, a strategic way of incorporating how these risks compares to other risks that could benefit from further study is referred to as *control options* (e.g. how much effort would need to be put forth to control accidental hydrogen sulfide deaths compared to cyanide in

the U.S.). Both of these facets drive the need to begin such a study, as well as to continue it, into the second stage of risk analysis. Once a need has been identified, *exposure and dose-response studies* (fed by *interventions* such as antidote trials) help determine the number and ways in which people can be affected by the risk in question. The risk can be properly characterized following the compilation of research from the preceding steps. The fourth, and final, stage is *risk management*, whereby the impacts of *control options* and *measurement capability* are seen again. *Risk management* must also consider the broader framework where controlling the risk takes place that could affect how successful the approach is at reducing risk – e.g. the *legal, economic, and social issues*. Gold cyanidation is banned in some countries and regions (Mudder and Botz, 2004), for example, while certain releases of airborne H_2S are permitted but are only monitored on a piece-meal basis (discussed in further detail below), perhaps due to political pressures or economic constraints. And finally, this alternative paradigm assumes a natural feedback loop, wherein new research on hydrogen sulfide and cyanide can continue to feed the process and update how the risks are managed.

Due to the broad scope of this study – from quantifying sources in the environment to identifying gaps in monitoring information to highlighting impacts on the body – the present findings touch upon almost all subdivisions of the risk analysis paradigm. The following sections discuss opportunities for future research and public health efforts for both cyanide and hydrogen sulfide that were identified through this study and should be considered as part of the risk analysis paradigm.

4.1 SYSTEMATIC AIR MONITORING NEEDS

The effects that cyanide and hydrogen sulfide impart at various exposure levels when inhaled are not fully understood, despite extensive knowledge on their sources. One of the root causes of this issue is the lack of systematic monitoring where human exposures can and do occur – located within *Exposure* in the risk analysis paradigm. This issue was highlighted for H_2S in the emissions study detailed in Chapter 2, noting the focus on monitoring animal feeding operation (AFO) emissions over sources that could potentially present higher risks to people such as oil and gas operations, or those that emit H_2S at higher rates such as geothermal activity. Reasons for the focus on AFOs – in addition to funding incentives – could also be related to *Control Options* and *Measurement Capability* in that emissions from manure and animals within AFOs are much more predictable and controllable than intermittent oil and gas drilling or oceanic vent releases, for example.

As discussed in some detail in Chapter 2, H_2S can be emitted into the air at dangerously high rates from sour gas wells (Leo, 2015, Yang et al., 2006), and other more common mining operations such as coal (Chadwick et al., 1987, Simonton and King, 2013). Workers within specific industries in the U.S. are protected by various standards and requirements – such as requiring the use of personal protective equipment. These standards are industry- and exposure-specific, dependent on the likely sources and level of exposure. Monitoring on site is conducted by the company in situations when high H_2S levels may present a risk, but not continually (OSHA, 2016b). There is no national ambient air standard for hydrogen sulfide, however. While some states do have ambient air monitoring standards, most only monitor ambient air for H_2S when the public presents complaints about a particular source in the area (Skrtic, 2006). Reactive monitoring, however, leaves the possibility for the most significant exposure events to go unnoticed. In the

event of a major hydrogen sulfide release from an industrial operation, the lack of monitoring data not only puts nearby residents at risk, it inhibits understanding the human health effects of exposure to H_2S at certain levels.

The Immediately Dangerous to Life or Health Concentration (IDLH) for inhaling H_2S is 100 ppm (NIOSH, 1994b), twice as high as HCN at 50 ppm (NIOSH, 1994a). While inhalation is a route of cyanide exposure, people are primarily exposed to cyanide through ingestion. In comparison to H_2S, the need to conduct continuous, ambient air monitoring for cyanide is not as great. For example, a diluted sodium cyanide solution (NaCN) is used intentionally by workers to separate mined gold and silver from low-grade ore. The application of a cyanide solution via the MacArthur-Forrest process is the most commonly used method to extract these precious metals from the surrounding rock because cyanide easily bonds with them, allowing the metals to be brought into solution (Rubo et al., 2000). Very few human injuries and fatalities have resulted from exposure to cyanide as a result of this process (Mudder and Botz, 2004), and major spills of cyanide have almost never resulted in human fatalities – as detailed in Table 13. Additionally, gaseous HCN is not produced so long as the pH level of the tailings pond is kept alkaline (Rubo et al., 2000). Cyanide is more likely to be released into the air due to combustion of modern day products containing nitrogen, reaching high levels in enclosed spaces (e.g. prison or airplane fires) and under smoldering conditions. Such circumstances do not lend well to systematic air monitoring requirements for cyanide, especially compared to hydrogen sulfide, even though the IDLH is much lower for HCN.

4.2 ANTIDOTES

Another gap identified through this study worth discussing here is how and/or whether certain antidotes function against hydrogen sulfide and cyanide exposures, a discussion that fits into the *Intervention* category of the risk analysis paradigm. Within the body, the active site of the electron transport chain complex IV (cytochrome *c* oxidase) is inhibited by both cyanide and hydrogen sulfide because the compounds bind to ferric heme. In doing so, rapid toxicity and death may result as oxygen cannot be not processed by the affected cells.

Previous literature often mistakenly stated that cyanide antidotes work by generating methemoglobin (metHb), and then scavenging cyanide through the formation of cyanomethemoglobin (metHbCN). Peterson, Pearce, and colleagues have shown that by injecting sodium nitrite, however, NO antagonizes cyanide's inhibition of cytochrome *c* oxidase (Pearce et al., 2003, Pearce et al., 2008). Essentially, then, the NO donor capacity of nitrite is the crucial mechanism for effective cyanide antidotes (Cambal et al., 2011), not metHB formation. Because NO displaces the cyanide anion from cytochrome *c* oxidase, however, NO must be removed by oxygen in order to reinstate enzyme functioning.

There are currently two FDA-approved cyanide antidotes: Nithiodote, which is a combined administration of sodium nitrite and sodium thiosulfate (Hope Pharmaceuticals, 2011), and Cyanokit (e.g. hydroxocobalamin) (Meridian Medical Technologies Inc., 2011). Jiang and colleagues recently provided evidence that administering cobinamide (the penultimate precursor to hydroxocobalamin, or vitamin B12) is a more effective treatment for cyanide than hydroxocobalamin and that it reduces sulfide toxicity efficiently, as well (2016). All of these treatments, however, require intravenous injection. Currently there are no rapidly-acting alternatives, such as one administered through an inhaler. In a follow up to Peterson and Pearce's

studies on cyanide antidotes, Cambal *et al.* demonstrated that inhaled aqueous vapor of sodium nitrite could be an effective and rapid antidote for cyanide, pending innovations in inhaler technologies (the current 0.1 mL inhaler dose would need to be increased to 0.26-0.3 mL, for example) (2013).

Both hydrogen sulfide and cyanide are highly efficient disruptors of mitochondrial electron-transport chain function, with approximately identical inhibition constants (K_i) for cytochrome *c* oxidase (Cambal et al., 2011), and are both capable of producing a knockdown effect to those exposed. These characteristics would suggest that the antidote for acute H_2S exposure would be similar to that of cyanide – by antagonizing hydrogen sulfide's inhibition of cytochrome *c* oxidase (ATSDR, 2006c). While providing immediate cardiac and respiratory support is the primary recommendation within the treatment protocol for H_2S poisoning, ATSDR's own medical management guidelines suggest that nitrite therapy (found in the cyanide antidote kit) can be used immediately following the exposure, but science behind this association is lacking. Some literature even speculates that H_2S is detoxified by the formation of sulfmethemoglobin when nitrites are administered in this fashion (ATSDR, 2014b).

Within the literature, however, there have been a series of doubts and conflicting reports regarding the usefulness of sodium nitrite as a sulfide antidote (ATSDR, 2006c, Beck et al., 1981b, Hall and Rumack, 1997, Huang and Chu, 1987, Smith et al., 1976). Peterson and colleagues found that administering sodium nitrite in mice may only be beneficial prophylactically, but the window of opportunity to administer such an antidote may be longer for human exposures (Cronican et al., 2015). Victims reaching the clinic sometimes succumb hours after the exposure, suggesting slower mechanisms of toxicity in humans secondary to the initial inhibition of cytochrome *c* oxidase (Burnett et al., 1977, Guidotti, 1996). Even the recommended practice of providing cardiac and

respiratory support for H_2S exposure may not be helping matters. Peterson and colleagues recently investigated whether supplemental oxygen ameliorates H_2S intoxication in mice when given both alone and in conjunction with sodium nitrite, and found that supplemental oxygen exhibits no measureable effect (Cronican et al., 2015). As such, while the current recommendation to provide respiratory support to H_2S exposure victims in the field is not harmful, it is likely not abetting survival rates, either.

The absence of an FDA-approved antidote and/or reliable protocol for treating acute hydrogen sulfide (H_2S/HS^-) poisoning raises considerable public health concern; H_2S suicides are on the rise and the gas continues to be problematic occupationally – as discussed previously. Even the understanding of cyanide toxicity mechanisms, although further along, is not complete. The investigations conducted to-date on antidotes are promising, but more research needs to be conducted to properly identify the exact mechanisms of hydrogen sulfide and cyanide toxicity.

4.3 PUBLIC HEALTH PREPAREDNESS

4.3.1 Workforce Education and Training

We cannot expect to be able to prevent all potential exposures to H_2S and cyanide – especially in the case of fires or industrial accidents. We can, however, be prepared for how to respond to them. There are several known deadly incidents where workers and even residents have died due hydrogen sulfide releases – such as the sour well blowout that occurred in Kaixian County, China that killed 243 people in the surrounding area and brought approximately 9,000 to the emergency room (Yang et al., 2006). While the region's topography (large valley) played a key role in the

lethality of this incident, the very chance of its occurrence and the increasing role natural gas may play in future energy generation very clearly demonstrate why workers in the oil and gas industry and similar industries need to be aware of the risks that H_2S poses to health and safety – both on site and in nearby communities. In sharp contrast, major spills and leaks of cyanide have never resulted in human fatalities, often because the utilized solution is incredibly diluted (Table 13).
. In occupational settings, cyanide deaths are also significantly less common than those caused by hydrogen sulfide in the U.S. Between 2003 and 2010, cyanide and cyanide compounds only accounted for three worker deaths. Hydrogen sulfide, even after excluding the category of "sewer and mine gases," was responsible for an order of magnitude more occupational fatalities (n=49) than cyanide (BLS, 2015). Therefore, more attention should be directed to understanding the exposure routes and mitigation strategies for hydrogen sulfide.

It is difficult to discern without extensive further research whether each and every worker who may be exposed to hydrogen sulfide or cyanide on the job is knowledgeable of and prepared for the risks. For a few select examples, in 2012 Esswein and colleagues presented on findings from their work with NIOSH indicating that workers on oil and gas drilling sites in the U.S. were generally well-informed about H_2S risk factors, although less so about other inhalation risks such as silica sand (Esswein et al., 2012). However, Esswein observed drilling operations under normal conditions, i.e. not during or immediately following a sour gas well blowout, for example. Emergency planning and response, in general, is an area that continues to receive criticism in the oil and gas field – especially as oil and gas drilling operations have increased in the last decade in unconventional formations and areas where sour gas may pose a higher risk. For example, it took out-of-state responders more than four days to control a 2014 well fire (exact cause unknown) in Greene County, Pennsylvania that killed one worker and injured another. Additionally, a post-

incident review by PA's Department of Environmental Protection indicated that the drilling company failed to continually provide meaningful updates to regulatory responders and even excluded state regulatory staff from important discussions on scene (Ryder et al., 2014). As drillers attempt to extract fossil fuels from tight shale, oil sands, and other unconventional hydrocarbon resources, the increased presence of H_2S (from both a human exposure standpoint and as an explosion factor) should be a risk for which companies prepare their workforce and community relations personnel.

Contrastingly, almost all mining sites extracting gold or silver utilize cyanide (90%) based on data from 2004. As discussed in Chapter 3, limited observations indicate that workers managing cyanide at mining sites are often highly trained on the risks that cyanide may pose – at least in the U.S. Additionally, in most cases, cyanide releases near mining sites pose more of a physical injury risk (e.g. crushed when a tailings pond fails) than a chemical one (Mudder and Botz, 2004). Monitoring and improving the transportation of cyanide materials to the work site, improving tailings pond engineering practices, and reducing the concentration of cyanide in tailings ponds, are all areas of opportunity for greater cyanide oversight and protection within the mining industry.

An even greater opportunity for workforce education on cyanide and hydrogen sulfide risks may be in the medical sector, however. A 2010 survey of 130 incoming interns after medical school indicated that only a portion (47%) had received any formal disaster preparedness training during medical school. This issue is compounded by the fact that is no national consensus on a disaster preparedness curriculum for medical schools (Jasper et al., 2013). A major sector in the workforce, therefore, may be unprepared for the complex symptoms that an inhalation victim might present, especially in the event of a major industrial release of cyanide or hydrogen sulfide.

Many of the cases involving accidental H_2S deaths and injuries on the job presented in Chapter 2 involved more than one person per incident. This pattern occurs because nearby workers or bystanders attempted to rescue the original victim without proper respiratory protection and were themselves injured. H_2S and cyanide pose a variety of risks to workers, both on the scene and during an emergency response. It is to the benefit of companies who employ these staff to properly train them on the causes of incidents related to these compounds, as well as how best to protect themselves while responding to emergency situations.

4.3.2 Protecting Emergency Responders

Emergency responders may be exposed to cyanide and H_2S in a number of ways, including contact while responding to fires and chemical suicides. As previously discussed, toxic levels of cyanide can accumulate in enclosed spaces when manmade materials containing nitrogen combust. Not only can the levels be lethal by and of themselves, but breathing in low levels can also impair an individual's ability to escape the fire. When responding to a potential chemical suicide (either HCN or H_2S-related), firefighters and EMS are at risk because gas levels can remain high in an enclosed space, continue to off-gas after the initial generation, and/or remain on the victim and/or their personal effects for some time (CHEMM, 2014). Regardless of the cause of the incident, personnel should clear the area and ventilate the space to reduce the risk of bystanders becoming ill, conduct air monitoring including determining wind speed/direction if possible, and then handle rescue operations of the victim(s) and those collaterally affected. Despite these serious risks, emergency responders can easily protect themselves using personal protective equipment (PPE) and a self-contained breathing apparatus (SCBA). However, compliance is not 100%, as it is not always feasible to don a full SCBA, such as when conducting welfare checks.

Departmental medical protocols and operating guidelines for how to handle toxic environments are in place for most if not all emergency response teams. These practices are supplemented by HAZMAT response protocols. Additional training and educational resources are also readily available online for emergency responders, firefighters, and hospital emergency staff (Bohrer, 2015, Adkins, 2010, CHEMM, 2014, DQE, 2011, Firefighters Support Foundation, 2013) but individual awareness of the potential effects from such exposures may not be as widespread. Further study is warranted to determine how often and how successfully best management practices for handling risks associated with gaseous cyanide and hydrogen sulfide are being communicated to and received by emergency responders.

4.3.3 Risks from Localized Terrorist Attacks

H_2S has been a subject of discussion regarding the potential for it to be used as a terrorist agent and as a risk for first responders, especially in confined areas such as trains or buses (Adkins, 2010, DHS, 2008, Kuchikomi, 2008). Risks are heightened for this blood gas because H_2S can be produced by materials commonly available to the public, and because at dangerous levels the characteristic rotten egg odor of H_2S diminishes, as discussed in Chapter 2.

Cyanide, too has been a concern for terrorism response departments because it is readily available from both natural and industrial sources. Attempts have already been made to utilize it as a terrorist weapon, such as in the 1993 truck bombing of the World Trade Center, because of its lethality at low concentrations (DHS, 2009, CIA, 2003). The inhalation of HCN and H_2S likely pose higher occupational risks than they do from a terrorism perspective, however. To be used as an effective terrorist agent, both would have to be employed in enclosed, poorly ventilated spaces since the gases dissipate quickly. Nevertheless, because the approved antidotes for cyanide

exposure do not work on all cases even if administered in time, and because there is no approved antidote for H_2S, these gaseous agents should be seriously considered by emergency planners and personnel. Measures to increase public health preparedness include establishing well-defined plans for ensuring that cyanide antidotes are available to first responders, educating emergency medical personnel on when and how to administer such antidotes (or when to provide cardiac and respiratory support in the case of an H_2S attack), and making sure that the public is aware that such terrorist attacks could take place and how to respond appropriately.

The potential for public exposure to cyanide gas outside of the workplace and a terrorist incident, while not likely, has occurred and should also be part of emergency response plans. For example, a deadly nightclub fire occurred in Brazil in 2013, when the combustion of soundproofing board made of polyurethane contributed to the deaths of 241 people. Due to an insufficiency in their antidote inventory, Brazilian authorities had to request 140 cyanide-treatment kits from the U.S. to administer to the remaining victims (Winter and Simões, 2013). Whether a fire is set deliberately or not, all hospitals and ambulances should be equipped with extensive cyanide antidote supplies given the widespread use of modern-day building materials that could release HCN upon combustion and the large capacity of some buildings. However, due to the high cost of such kits (upwards of $1,000 per kit) adequate supplies may not always be available at a local level. As such, emergency response plans should include a directive to activate the area's supply chain network to obtain additional kits as soon as possible.

4.3.4 Educating the General Public

In addition to the emergency response planning indicated previously, the general public should be made aware of the risks that cyanide and H_2S may pose to their health and why. If properly

educated on these compounds, for example, nearby residents may be able to alert regulatory bodies about violations in H_2S emissions from nearby confined animal feeding operations or HCN gas being released from a metal finishing plant. Educating children and young adults on the high levels of HCN in marijuana smoke may reduce adoption of the behavior. In the event of an attempted H_2S suicide, an informed passerby might save several lives by both recognizing the rotten egg odor of H_2S and that they should alert emergency personnel to respond to the situation with full respiratory gear.[4]

Protection for emergency responders and victims can also occur at the source, by preventing the mixture of chemicals that can produce gaseous HCN and H_2S. The two most common gases produced when attempting a detergent suicides are cyanide and H_2S (CHEMM, 2014). One of the reasons for their "popularity" – so to speak – is because the ingredients are available for purchase over the counter (although the ingredients for producing H_2S are markedly easier than those for HCN). It stands to reason, then, that household products may be accidentally mixed and produce these toxic gases – similar to how chlorine gas can be created by combining ammonia-based cleaning products and bleach. As such, labeling protocols should be reviewed and warnings instituted for cyanogenic and sulfide-containing products.

[4] Acknowledging that the scent of these compounds is not always a reliable indicator of over-exposure. People cannot detect H_2S at the levels requisite to present acute health risks, as they lose their sense of smell after just a few minutes at levels above 100ppm. Additionally, not everyone can even detect the bitter almond scent of cyanide gas.

4.4 GLOBAL CONSIDERATIONS

Burning fossil fuels and introducing gases into the atmosphere primarily since the Industrial Revolution have caused a major shift in the earth's temperatures – since 2000 logging the 10 warmest years since record keeping began in 1880 (NASA GISS, 2014). Such a drastic increase in the overall, average temperature in a relatively short geological timescale will, and already has, produced significant effects worldwide, including but not limited to melting glaciers and sea level rise, shifting seasons, and changes in agriculture (productivity and locations) (Cramer et al., 2014). More specifically, there are two broad situations triggered by global warming and/or climate change whereby people might be exposed to potentially high levels of cyanide or H_2S: 1) in drought-stricken agricultural areas and 2) as ocean temperatures increase.

4.4.1 Drought and Cyanide Ingestion

As was discussed in Chapter 3, cyanogenic glycosides that release HCN are found naturally in approximately 2,650 plant species around the world, and cyanide can be found at higher than average levels in foodstuffs when those foods are not properly processed. This situation is much more likely to occur during periods of drought, food shortage, and/or high demand in the market. Cassava and sorghum, which grow fairly well in drought conditions, have some of the highest natural cyanogenic glycoside potential. Considering that hundreds of millions of people in the world depend on products made from these plants, chronic ingestion of cyanide is of global concern when the rate of ingestion is faster than the rate by which the body detoxifies cyanide into thiocyanate, especially for populations whose diets are already nutritionally deficit.

As global temperatures rise, the rate of evaporation increases, meaning that some areas in the world will see increased precipitation, while others will experience more frequent and/or more intense droughts than usual. Droughts of this nature have already been documented in various parts of the world, such as West Africa, with seasonal variations and human activity contributing to the droughts' severity (Cramer et al., 2014). In light of population increases and drought effects on agricultural viability, recommendations have been made to increase the cultivation of drought-resistant plants such as cassava and sorghum. However, such policy recommendations should be considered with caution. If not properly processed and monitored, these foods could chronically expose large populations of already at-risk individuals to cyanide, since droughts increase cyanogenic glycoside concentrations in plants. While developments to reduce HCN concentrations in food are promising, data and measurement discrepancies reviewed in Chapter 3 suggest that to determine risk at a global level there is still much exposure information to be collected and processed as global warming effects become more pronounced.

4.4.2 Oceanic Hydrogen Sulfide Gas Production

Increased temperatures have also had discernible effects on the amount of dissolved oxygen in some parts of earth's oceans according to 2016 data from The National Center for Atmospheric Research, with expectations that most oceanic regions will see similar effects between 2030 and 2040. The effects are two-fold: Warmer waters absorb less oxygen, and higher surface water temperatures lead to water stratification in the oceans which could lead to anoxia or euxinia (Long et al., 2016). These conditions not only threaten marine life, but they are also ideal breeding conditions for sulfate-reducing bacteria, at times causing H_2S to bubble to the surface. Large and expanding dead zones (high H_2S levels, long periods of hypoxia) due to increased water

stratification and fertilizer runoff (nutrient loading) have been observed in more than 400 systems across the globe (Diaz and Rosenberg, 2008). Expanding dead zones can affect both low- and high-level trophic creatures – from zooplankton to commercial fisheries. On a tangential note, ocean anoxia and H_2S gas production have been implicated in numerous mass extinction events on both land and in the ocean, such as the Permian-Triassic extinction (Kump et al., 2005), so the effects of significant H_2S releases may be even broader than those felt in the ocean.

In 2010 it was estimated that over three billion people worldwide relied on the consumption of fish to supply at least 15% of their average animal protein intake. Fish consumption is even more of a nutritional staple in developing and low-income food-deficit countries (FAO, 2010b). While humans may not be directly or immediately impacted by higher H_2S levels in earth's oceans through direct exposures, dead zone impacts on fish and wildlife could significantly change marine-based food systems and availability. Major shifts in food availability for such a large proportion of the worldwide population would likely produce long-standing and reverberating public health impacts in related sectors (e.g. advanced nutritional deficiencies or increased fertilizer-dependent agriculture cultivation).

4.5 CONCLUDING RECOMMENDATIONS

Scientists and public health officials have known the risks that exposure to cyanide and H_2S can pose to people for quite some time. And yet, based on the results of this research, there are still many gaps within the scientific literature related to their toxicity mechanisms, health effects at various exposure levels, and antidotes. Future research and public health efforts related to cyanide and H_2S should focus on the following recommendations:

1) Identifying precise H_2S and cyanide toxicity mechanisms in humans and developing a tailored antidote for H_2S,
2) Establishing more rigorous environmental monitoring protocols to support Recommendation 1, especially for sulfur compounds in the air and HCN in foodstuffs, and
3) Preparing workers, communities, and emergency responders for the potential release of cyanide and H_2S in both large- and small-scale scenarios.

APPENDIX: TABULATED H_2S EMISSIONS AND CONCENTRATIONS DATA

Table 17. Comprehensive H_2S emissions and concentration data included in the review organized by source category

Source (# monitoring results)	**Trait**[a]	**Concentration** (mg/m3)	**Flux** (mg/m^2)	**Flux Density** ($mg/m^2/hr$)	**Flux Density AU** (mg/AU/hr)	**Reference**
AFO (n=62)	Mean Min	7.05E-01				(Blunden et al., 2008)
	Mean Max	1.01E+00				
	Mean	1.50E+03				(Chénard et al., 2004)
	Mean	1.26E-02				(Donham et al., 2006)
	Max	5.38E+01				(Hoff et al., 2006)
	Mean	3.00E-04				(Hoff et al., 2008)
	Max	4.92E-02				
	Min	1.50E-01				(Jacobson et al., 2005)
	Max	1.50E+00				
	Max	8.55E+00				(Kafle, 2014)
	Max Mean	1.17E+00				(Kalantarifard et al., 2013)
	Max Mean	5.24E-02				(Koziel et al., 2004)
	Mean Max	1.49E+02				(Lemay et al., 2008)
	Mean	7.29E+03				(Moreno, 2009)
	Max	8.66E+03				

Table 17 Continued

	Max Mean	3.96E-02				(Ni et al., 2012)
	Max Mean	6.18E-02				
	Mean	2.91E+01				(Predicala et al., 2007)
	Max	1.43E+02				
	Mean	6.75E-02				(Rahman et al., 2011)
	Mean	9.60E-02				
	Mean Max	3.02E-01				(Sun et al., 2008)
	Max	2.25E-01				(Sun et al., 2010)
	Mean	2.94E-02				(Thorne et al., 2009)
	Mean	2.19E-01				
	Max	2.79E-01				
	Max	1.37E+00				
	Mean			4.80E-03		(Rumsey and Aneja, 2014)
	Mean			2.29E-01		
	Max			3.18E-01		(Blunden and Aneja, 2008)
	Mean			3.55E-01		(Blanes-Vidal et al., 2009)
	Total			3.77E-01		(Wang et al., 2014)
	Max			8.48E+02		
	Mean			1.53E+03		(Hoff et al., 2006)
	Max			1.74E+03		
	Median			2.12E+04		(Grant et al., 2013)
	Total		2.28E+00			(Kaasik and Maasikmets, 2014)
	Total		5.20E+02			
	Total Mean		3.42E+03			(Blunden et al., 2008)
	Total Mean		2.00E+04			
	Max Median		4.32E+05			(Schmidt et al., 2004)

Table 17 Continued

	Max		6.30E+07			
	Median				6.67E+01	(Grant et al., 2013)
	Median				1.46E+00	
	Median				1.70E+00	
	Mean				9.13E-03	(Kaasik and Maasikmets, 2014)
	Mean				4.16E-01	
	Max				3.18E-01 [b]	(Lemay et al., 2008)
	Mean				2.19E+03 [b]	(Li et al., 2008)
	Mean				1.70E-02	
	Mean				2.74E+03	
	Mean				1.83E-01	(Li et al., 2009)
	Mean				7.60E-02	
	Total				3.21E+00	(Li et al., 2011)
	Mean				1.60E+01	(Lin et al., 2012)
	Total				7.91E-03 [b]	(Luo et al., 2004)
	Total				2.54E+00 [b]	(Mukhtar and Mutlu, 2008)
	Mean				3.38E+01	(Pepple et al., 2011)
	Mean				1.35E+02	(Rahman et al., 2011)
	Mean				1.50E+01	
	Mean Max				2.13E+02	(Sun et al., 2008)
	Max				2.96E+02	(Sun et al., 2010)
Decomposition (n=15)	Max Mean	1.50E-03				(Azad et al., 2005)
	Max	3.00E-02				
	Max	2.67E-01				(Colledge, 2008)
	Max	9.36E-01				
	Max	1.29E-02				(Vasarevičius, 2011)

Table 17 Continued

	Max	1.03E+03				(Velusami et al., 2013a)
	Max	3.13E+03				
	Max	3.21E+02				(Velusami et al., 2013b)
	Max	6.81E+02				
	Max	6.41E+05 [b]				(Brüchert et al., 2009)
	Mean			3.40E-04		(Li et al., 2006)
	Max Mean			2.43E-03		(Azad et al., 2005)
	Max			8.97E-03		
	Mean			4.97E-03		(Li et al., 2014)
	Max		1.44E+05			(Bolyard, 2012)
Energy Production (n=10)	Mean	3.30E-04				(Bechtel et al., 2009)
	Mean	3.00E-04				(Burstyn et al., 2007)
	Max	1.25E-02				
	Max	9.24E-02				(Carlsen et al., 2012)
	Max	5.18E+02				
	Min	6.60E-02				(Macey et al., 2014)
	Max	9.10E-02				
	Mean	4.05E-02				(Peralta et al., 2013)
	Mean		4.48E+07			(Baldacci et al., 2005)
	Total		2.57E+09			(Peralta et al., 2014)
Geothermal (n=11)	Max	3.75E+00				(Horwell et al., 2005)
	Mean	1.50E+00				(Watanabe et al., 2013)
	Mean Max	5.55E+01				
	Mean Max	9.45E+01				
	Max	3.79E+06 [b]				(Emeis et al., 2004)
	Max	3.20E+06 [b]				(Weeks et al., 2004)
	Mean			1.75E+00		(Pérez et al., 2012)

Table 17 Continued

	Total			9.95E+03		(Barberi et al., 2008)
	Max		1.36E+02			(Barrancos et al., 2012)
	Max		1.63E+08			(McGee et al., 2010)
	Total		3.78E+08			(Gerlach et al., 2008)
Other (n=3)	Max	4.50E+03 [b]				(Gomez et al., 2011)
	Max	2.25E+00 [b]				
	Max	1.84E+01				(Gladkikh and Korolev, 2014)
Wastewater (n=29)	Total	1.50E+00				(Chen and Szostak, 2013)
	Max	2.70E-03				(Colomer et al., 2012)
	Max	5.30E+02				(Esteban-García et al., 2013)
	Max	4.50E+01				(Latos et al., 2011)
	Max	1.50E-01				(Lehtinen and Veijanen, 2011)
	Mean	4.71E+02				(Martinez et al., 2008)
	Max	7.50E+02				(Matias et al., 2014)
	Mean Max	2.85E+01				(Morton et al., 2006)
	Max	6.44E+01				
	Mean	3.12E+02				(Morton, 2014)
	Max	1.31E+03				
	Max	1.09E-02				(Mudragaddam et al., 2014)
	Max	3.08E+01				(Oviedo, 2010)
	Max	3.95E+01				
	Max	8.00E+03 [b]				
	Max	1.53E+04 [b]				
	Max	3.33E+02				(Pagaling et al., 2014)
	Max	5.85E-01				(Thomas, 2007)

Table 17 Continued

	Max	3.51E+00				
	Max	4.07E+00				
	Mean	3.00E+02				(Zhang et al., 2008)
	Mean	2.84E+02				(Zhang, 2013)
	Max	7.50E+02				
	Max			2.80E+00		(Mudragaddam, 2010)
	Mean Max			1.07E+01		
	Mean		9.08E+02			(Mudragaddam et al., 2014)
	Mean Max		4.17E+06			(Morató et al., 2011)
	Max		6.67E+06			(Colomer et al., 2011)
	Mean Max		8.91E+06			(Colomer et al., 2012)
Maximum		**3.79E+06**	**2.57E+09**	**2.12E+04**	**2.74E+03**	

a. Where possible, the maximum/peak recorded data point was logged in this study. When the maximum measurement was unavailable, alternative traits were recorded – such as mean, median, or total.
b. Reported as sulfur or dissolved sulfide, not H_2S.

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