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Low Level Exposure to Hydrogen Sulfide: A Review of Emissions, Community Exposure, Health Effects, and Exposure Guidelines

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Abstract

Hydrogen sulfide (H_2S) is a toxic gas that is well-known for its acute health risks in occupational settings, but less is known about effects of chronic and low-level exposures. This critical review investigates toxicological and experimental studies, exposure sources, standards, and epidemiological studies pertaining to chronic exposure to H_2S from both natural and anthropogenic sources. H_2S releases, while poorly documented, appear to have increased in recent years from oil and gas and possibly other facilities. Chronic exposures below 10 ppm have long been associated with odor aversion, ocular, nasal, respiratory and neurological effects. However, exposure to much lower levels, below 0.03 ppm (30 ppb), has been associated with increased prevalence of neurological effects, and increments below 0.001 ppm (1 ppb) in H_2S concentrations have been associated with ocular, nasal and respiratory effects. Many of the studies in the epidemiological literature are limited by exposure measurement error, co-pollutant exposures and potential confounding, small sample size, and concerns of representativeness, and studies have yet to consider vulnerable populations. Long-term community-based studies are needed to confirm the low concentration findings and to refine exposure guidelines. Revised guidelines that incorporate both short- and long-term limits are needed to protect communities, especially sensitive populations living near H_2S sources.

Keywords

hydrogen sulfide; chronic; environmental; epidemiology; occupational

1 Introduction

1.1 Background

Hydrogen sulfide (H_2S) is a toxic gas also known as dihydrogen monosulfide, dihydrogen sulfide, hydrosulfuric acid, sewer gas, stink damp, sulfur hydride, and sulfureted hydrogen.

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Declaration of Interest

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Exposure to high concentrations of H_2S has been considered a serious risk in occupational settings for hundreds of years (e.g., Fuller and Suruda 2000; Guidotti 2010, 1996; Lambert et al. 2006; NIOSH 1978), and is the second most common cause of fatal gas inhalation exposure in the workplace, second only to carbon monoxide (Guidotti 2010). A recent and disturbing trend is deliberate H_2S poisoning, which in Japan caused 208 fatalities in 220 suicide attempts over a 100 day period in 2008 using "homemade" H_2S gas and information disseminated by social media (Morii et al. 2010).

The dose-response relationship for mortality from acute, high-level exposure of H_2S is reasonably well understood. Less is known about the health impacts of chronic, low-level exposures and exposure-response relationships for morbidity, the focus of this review. Community exposure to H_2S and other reduced sulfur compounds, which is common around industrial, agricultural and natural sources that emit these gases, mostly occurs concentrations below 0.1 ppm, much lower than in occupational settings. Community exposure has long been considered a nuisance issue. Because people living near H_2S-emitting facilities can experience long-term exposures and frequently have health, racial, socioeconomic, and other disparities that can increase their vulnerability and susceptibility to pollutants, H_2S exposures and health impacts are an environmental justice issue.

1.2 H_2S sources

H_2S is emitted at numerous locations from a variety of sources. These include naturally occurring geothermal and volcanic sources where emissions cannot be altered, and anthropogenic sources such as confined animal feeding operations (CAFOs), oil and gas facilities, paper mills, and wastewater plants where emissions can be controlled using standards, operation practices, and administrative and engineering controls. Geothermal and volcanic sources produce H_2S by hydrolysis of sulfide minerals (Ma et al., 2019). Industrial source such as petroleum refineries release H_2S present in the feedstock (e.g., sour gas) and from the hydrodesulfurization process which generates H_2S prior to removing sulfur from the petroleum product by partial combustion via the Claus process (Guidotti, 1996). In sewers, tanneries, Kraft pulping and paper mills, landfills and waste lagoons (as found at CAFOs) where anaerobic conditions occur, reduced sulfur gases including H_2S but also methyl mercaptan (CH_3SH), dimethyl sulfide $(CH_3)_2S$ and dimethyl disulfide $(CH_3)_2S_2$ are produced by sulfate reducing bacteria that decompose sulfur-containing organic constituents (Guidotti, 1996); Rava et al. 2008).

Trends of airborne and non-air H_2S emissions in the USA are shown in Figure 1, based on industry-provided data reported to the U.S. Environmental Protection Agency (EPA) Toxic Release Inventory (TRI) System since 2012 when reporting was first required (EPA 2020). (Section 1.3 following describes the inclusion of H_2S in the TRI.) Most H_2S releases reported to TRI are emissions to air (9114 tons/year), equal to 65% of reported releases in the U.S. averaged over the last three years. Industrial sectors responsible for most air emissions include the paper industry (5367 tons/year, 54% of total air emissions), chemical industry (1889 tons/year, 21%), and the oil/gas industry including extraction (914 tons/year, 10%). Other economic sectors include the food sector, which has only a small share of H_2S releases (384 tons/year, 4% of airborne emissions), and agriculture. Notably, agricultural

sources like CAFOs, are not required to report to the TRI. Our "high-end" H_2S emission estimates for CAFOs, discussed below, could double emissions to air. Overall, airborne emissions from the industries covered in TRI appear to have slightly decreased in recent years. In contrast, H_2S releases to other media, such as wastewater, increased from 2012 to 2018 due to growth in the oil/gas sector, which is responsible for most non-air releases (EPA 2020). While Figure 1 does not directly represent exposures or health effects, and TRI information itself has uncertainties and omissions (e.g., agricultural and geothermal sources are not included), the emission trends show continuing emissions and increases in some sectors, supporting the need to understand H_2S exposures and health implications.

The existing health literature focuses on a subset of H_2S sources: geothermal or volcanic sources, concentrated animal feeding operations (CAFOs), pulp or paper mills, and wastewater facilities. As detailed later in this review, exposure and health studies examining the top industrial sources (oil and gas extraction, chemical, and petroleum industries) are limited, while the number of studies examining agricultural sources, specifically CAFOs, is growing.

National-level H_2S emission information from agribusiness was not identified. We attempt a rough and preliminary estimate of CAFO H_2S emissions by estimating the surface area of waste lagoons where most releases occur, then multiply this area by the H_2S flux rate (emission per time per surface area of waste lagoon). Because a national total for lagoon surface area was not identified, we considered the number of swine in the U.S. (72.2 million, USDA 2022), the optimal lagoon area (approximately 285 ft^2/AU across a range of animal ages, where AU = animal unit (AU) or 1000 lbs (453.6 kg) live weight; Chastain and Henry 2002), and assume a weight of 55 lb (25.0 kg) per animal; together this gives 1.05×10^8 m^2 of swine waste lagoons. Available measurements of H_2S fluxes from lagoons are limited and highly variable, e.g., Rumsey and Aneja (2014) used a flux chamber to estimate an average winter and summer flux (0.0324 μg/m^2-s) at one CAFO in North Carolina (NC), and Grant et al. (2013) used air monitoring coupled with inverse dispersion modeling to estimate long-term fluxes (0.218, 2.148 and 3.849 μg/m^2-s) at three CAFOs in NC, Indiana and Oklahoma. These flux rates with the estimated lagoon area give a very large range for U.S. emissions: 107 to 12,760 tons/year. The low estimate, based on flux chamber measurements, may incompletely represent mixing processes that might increase emissions; the high estimate, based on inverse modeling, has considerable uncertainty; both may incompletely represent seasonal variation, among other limitations. Overall, the flux rate estimates lack representativeness, a result of the small number of CAFOs tested and strong dependences on the temperature, sulfide content, mixing and pumping activity in the lagoon, wind speed, season, time of day, precipitation, and other factors. In consequence, we cannot provide a reasonably accurate total for CAFO emissions. Because H_2S exposure tends to occur near sources, local conditions are critical. At large waste lagoons (e.g., exceeding 20,000 m^2 in area), annual H_2S emissions may approach 3 tons/year, and short-term emission rates may be considerably higher (Grant et al. 2013).

1.3 Overview of regulations

There is a long and somewhat contorted history of H_2S regulation in the U.S. (e.g., Woodall et al. 2005). In brief, the U.S. Congress removed H_2S as a hazardous air pollutant (HAP) under Title III of the 1990 Clean Air Amendments under pressure from industry (e.g., the American Petroleum Institute; Morris 1997) and the perception that its major impact was nuisance (Kilburn et al. 2010). In its 1993 Report to Congress, the U.S. Environmental Protection Agency (EPA) concluded that there was no evidence that routine releases from the oil and gas industry posed a significant public health or environmental threat and that no legislative action for accidental releases was warranted (EPA, 1993a). EPA's health assessment at that time noted some neurological, respiratory and irritation associated with H_2S exposures below 0.02 ppm, and the lack of long-term and low level epidemiological studies (EPA 1993b). As part of its final rule, EPA added H_2S to the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 toxic chemical release reporting (TRI) requirements on December 1, 1993, on the basis of chronic neurotoxicity in humans and acute aquatic toxicity. On August 22, 1994, EPA issued an Administrative Stay of the EPCRA reporting requirements for H_2S to evaluate issues brought to the Agency's attention after promulgation of the final rule, which concerned the human health effects basis for the listing and the Agency's use of exposure analyses in TRI listing decisions (EPA 2011). This occurred despite recommendations by the Agency for Toxic Substance Diseases and Registry (ATSDR), the federal public health agency established to address chemical exposures, in their draft Toxicological Profile for H_2S to set a reference concentration (RfC) of 0.010 ppm. In 1996, H_2S became subject to the Risk Management Program rule under section 112(r) of the Clean Air Act, a state-administered program that applies to many facilities if a short-term emergency release of H_2S can exceed 10,000 lbs (4536 kg), however, this limit would not apply to most sources since H_2S is not stored or accumulated. In 2003, the EPA derived an inhalation RfC for chronic exposure of 0.0015 ppm (2 μg/m^3), based on a no observed adverse effects level (NOAEL) of 10 ppm and a lowest observed adverse effects level (LOAEL) of 30 ppm for nasal lesions. On February 26, 2010, EPA published a notice in the Federal Register (FR) that provided an opportunity for public comment on its review of the available data on the human health and environmental effects of H_2S and EPA's belief that, based on those data, the administrative stay should be lifted (EPA 2010). The FR notice addressed the concerns raised regarding the exposure analyses in the TRI listing decisions, essentially indicating that exposure analyses need not be considered given the moderate-to-high chronic toxicity of H_2S. EPA (2010) determined that H_2S can reasonably be anticipated to cause serious or irreversible chronic human health effects at relatively low doses and thus is considered to have moderately high to high chronic toxicity, and that it is not appropriate to consider exposure for such chemicals assessment when determining a listing for chronic health effects pursuant to EPCRA Section 313(d)(2)(B) (see 59 FR 61432, 61433, 61440–61442). Although beyond the scope of this review, EPA also determined that H_2S causes ecotoxicity at relatively low concentrations and thus it is not required to consider its exposure when determining listings pursuant to EPCRA Section 313(d)(2)(C) (see 59 FR 61432, 61433, 61440–61442). On October 17, 2011, EPA published a FR notice that it was lifting the Administrative Stay of the TRI reporting requirements, and it summarized and responded to comments received regarding the previous FR notice (EPA 2011). In brief, EPA concluded that H_2S can reasonably be

anticipated to cause chronic health effects in humans and significant adverse effects in aquatic organisms, and reiterated that an exposure assessment was not required to meet TRI listing criteria. Listed chronic human health effects included both upper respiratory tract toxicity (e.g., nasal lesions) and neurotoxicity. The notice references a controlled study of perception and neurological impacts and two dosimetry studies. The effect of lifting the stay was to once again include H_2S on the TRI list of reportable chemicals under EPCRA Section 313 (40 CFR Part 372, Subpart D) beginning with the 2012 reporting year, as illustrated earlier in Figure 1 which trended reported H_2S emissions. Other regulatory levels are described in Section 4. While H_2S remains off the EPA HAP list, which would require source controls and limit ambient exposure, several states have pursued regulatory programs for H_2S or total reduced sulfur (TRS) compounds (Woodall et al. 2005).

1.3.1 Rationale and context—This report builds upon prior reviews, which noted the inconsistent evidence regarding health effects and the need for more robust exposure assessments (Lewis and Copley 2015; Lim et al. 2016; Roth and Goodwin 2003; Skrtic 2006). The most recent review, conducted by Exxon Mobil, found that chronic low-level H_2S was associated with temporary respiratory impairment and possible ocular and neurological effects (Lewis and Copley 2015). A review of neurological and respiratory health in occupational and community settings found inconsistent associations (Lim et al. 2016). An earlier review examining communities near oil and gas facilities found that chronic exposure to low concentrations of H_2S was associated a range of with neurological symptoms, including fatigue, impaired memory, altered moods, headaches and dizziness (Skrtic 2006). However, low-level H_2S exposures in community settings from sources such as oil and gas facilities, CAFOs and landfills are typically experienced as mixtures of contaminants, and unless the mixture components are sufficiently characterized to minimize the likelihood of confounding in health studies, epidemiological findings may be compromised. The potential for this problem is suggested by conflicting results obtained by the few studies using controlled exposures. These and other issues affecting the understanding of low-level exposures are not unique to H_2S, but their importance and implications should be recognized. Having identified the need for more comprehensive analyses of health effects and emission sources, we take an interdisciplinary approach, contextualizing epidemiological studies with toxicology, exposure science, and regulatory perspectives, to better understand the significance of chronic, low-level and community-wide exposures.

1.4 Objective and approach

This report examines the recent literature pertaining to health effects caused by the inhalation of hydrogen sulfide (H_2S) gas, focusing on effects at low exposure levels that are relevant to community exposure. We seek to gather and critically assess evidence of community exposure to H_2S, identify culpable emission sources, and analyze human health effects associated with chronic exposure to H_2S at low concentrations. We specifically focus on literature relevant to low-level community exposure to assess the minimum exposure levels associated with adverse health effects, although we also consider low-level occupational exposures given its relevance to understanding chronic health effects. We define low level exposures as H_2S concentrations below 0.1 ppm, medium level as between

0.1 and 1 ppm, and high level exposures as above 1 ppm. These limits are flexible given the importance of exposure duration and the variation of concentrations that may be measured or estimated in any particular study. An important distinction, however, is that the low and medium-level categories are distinctly lower than current standards or guidelines for workplace settings, which mostly range from 1 to 50 ppm.

The review is designed to reflect our current understanding of the effects of low level H_2S exposure, as based on published papers, reports and other materials prioritized as follows.

- Articles. Recent, published, peer-reviewed studies in the literature were the primary data source.
- Reviews. The health effects of H_2S have been the subject of many previous reviews. Many of these are authored by well-known authorities, such as U.S. Environmental Protection Agency (EPA), U.S. Agency for Toxic Disease and Registry (ATSDR), and the World Health Organization (WHO), while others have been commissioned by governmental authorities and industry. Reviews were primarily used to summarize older literature and to identify key studies (typically older studies), which were then examined. Key assumptions and statements in the reviews were verified by reference to the original articles.
- Abstracts, conference papers, dissertations, industry studies, and presentations. These sources were reviewed, but published peer-reviewed articles were given priority.
- Dates of publications. This review focuses on the recent H_2S literature, beginning in 2004. Previous reviews were examined for literature prior to this year and, as mentioned, original articles were obtained when applicable.
- Exposure routes. While several exposure routes may be relevant, H_2S exposure is dominated by the inhalation pathway in community settings, as well as in the vast majority of workplaces. Exposures via ingestion (e.g., drinking water) and dermal permeation were excluded from the present review.
- Nature of exposure. We focus on low-level and often chronic exposure that is relevant to community (and many workplace) settings. Generally, concentrations in community and most workplace settings fall well below 100 ppm (1,500 μg/m^3).
- Units. H_2S concentrations are converted to units of parts per million (ppm) at 25 C and 1 bar, which for H_2S means that 0.001 ppm = 1 ppb = 1.5 μg/m^3 and 1 μg/m^3 = 0.00067 ppm = 0.67 ppb. If concentrations in the original report were provided other units, these are shown in parentheses.

2 Health effects of exposures to H_2S

Inhalation is the main exposure pathway for the vast majority of exposed communities, although H_2S can be absorbed through the gastrointestinal tract. H_2S and its metabolites (e.g., sulfate, thiosulfate) are distributed throughout the body after exposure (Beauchamp et al., 1984). Considered a broad-spectrum toxicant, H_2S primarily affects tissues with exposed

mucous membranes (eyes, nose) and with high oxygen demand (lungs, brain) (Ammann 1986; Legator et al. 2001). H_2S exposure can cause a wide variety of effects, depending on the concentration, exposure duration, and target tissue, and the literature describes effects on the central nervous, cardiovascular, and gastrointestinal systems. "Primary" toxic effects of H_2S have been characterized as "knockdown" (acute central neurotoxicity), pulmonary edema, conjunctivitis, and odor perception, followed by olfactory paralysis. "Secondary" effects which accompany or are complications of toxicity that include non-specific symptoms such as headaches, memory loss, and acute and chronic respiratory effects (Guidotti 2010). Effects of H_2S exposure can include:

- Asphyxia. At high concentrations, above roughly 200 to 1000 ppm, H_2S acts as an asphyxiant, causing instantaneous loss of consciousness, pulmonary edema, hyperpnoea (rapid breathing), rapid apnea (slowed or temporarily stopped breathing), and death.
- Irritation. At intermediate concentrations (between 100 and 150 ppm), H_2S acts as a tissue irritant, causing keratoconjunctivitis (combined inflammation of the cornea and conjunctiva), respiratory irritation with lacrimation (tears), and coughing (Knight and Presnell 2005). Skin irritation is also common.
- Neurological effects. Neurological effects include dizziness, vertigo, agitation, confusion, headache, somnolence, tremulousness, nausea, vomiting, convulsions, dilated pupils, unconsciousness, anosmia (loss of sense of smell), depression and suicide.
- Cardiovascular and pulmonary effects. Reported effects include cough, chest tightness, dyspnea (shortness of breath), cyanosis (turning blue from lack of oxygen), cardiac arrhythmia and tachycardia, hemoptysis (spitting or coughing up blood), pulmonary edema (fluid in the lungs), apnea with secondary cardiac effects, and impaired lung function in asthmatics.

2.1 Health effects at high exposures

Short duration and high concentration exposures to H_2S are a well-known health hazard, and are among the leading causes of sudden death in the workplace (NIOSH 1978). As mentioned, H_2S is the second most common cause of fatal gas inhalation exposures in the workplace (Guidotti 2010). H_2S exhibits an exceptionally sharp exposure-response curve for lethality (Cantox Environmental 2009; Zelensky 2009), which yields a very small margin of safety, in part due to rapid olfactory paralysis and the loss of consciousness, which reduces the chance of flight. For these reasons, escaping from H_2S exposure can be exceptionally difficult (Guidotti 1996). Deaths from H_2S inhalation have occurred in many different workplace and some non-workplace settings, e.g., sewers, animal processing plants, waste dumps, sludge plants, oil and gas well drilling sites, tanks, cesspools, basements, and bathrooms (ATSDR 2006). Confined spaces, where concentrations can reach high levels, are especially dangerous. Given the significance of the hazard, H_2S awareness training in the workplace has become – or should be – a regular part of health and safety programs where this gas may be encountered. Brief but high exposure of H_2S can cause other impacts,

e.g., reactive airways distress syndrome (RADS), a variant of occupational asthma (Bardana 1999; CDC 1993).

2.2 Mechanisms of toxicity

Mechanisms postulated for the toxicity for H_2S have been reviewed by Knight and Presnell 2005; ATSDR 2006; Guidotti 2010, and others. One mechanism is direct inhibition of cellular enzymes, in particular, cytochrome c oxidase, the terminal enzyme of oxidative phosphorylation, which impairs aerobic metabolism and results in cellular anoxia and tissue hypoxia (Ammann 1986). This has been demonstrated by H_2S concentrations in the range of 5 to 10 ppm, which in humans can cause a shift from aerobic to anaerobic respiration (Bhambhani et al. 1996; Bhambhani and Singh 1991). Several mechanisms have been proposed for neurotoxic effects: changes in the membrane and synaptic properties of dorsal raphe serotonergic cells, potentially due to an interaction with free thiols and disulfide bonds present in the membrane proteins; possible inhibition of monoamine oxidase that disrupts neurotransmission in brain stem nuclei controlling respiration (ATSDR 2006); and hypoxia-induced neuronal cell death attributable to cytochrome oxidase inhibition. Fiedler et al. (2008) notes toxicity due to cellular asphyxiation has been challenged by an animal model of H_2S-induced apnea after “knockdown” caused by an afferent neural signal from the lung via the vagus nerve, which innervates the viscera and provides information about the state of the body’s organs to the central nervous system, rather than a direct effect on the brain stem (Almeida and Guidotti 1999), and that the persistent neurologic effects among those experiencing acute H_2S intoxication resulted from hypoxia secondary to respiratory insufficiency, rather than a direct toxic effect on the brain (Milby and Baselt 1999).

H_2S is present in mammalian tissues at concentrations from the high nmol/L to low μmol/L range (Polhemus and Lefer, 2014), a result of endogenous production where it appears to serve a number of functions, probably acting as a neuromodulator and/or as an intracellular messenger or signaling molecule in the brain (Olson 2011; Qu et al. 2008; Varaksin and Puschina 2011). Although not currently used, a decreased concentration of H_2S in expired air has been suggested as a biomarker of inflammation and asthma (Wang et al. 2011).

The details of the mechanisms and toxicity of H_2S at high concentrations (and case reports and other literature) are beyond our present scope. In brief, however, we note that the most commonly reported nonlethal effect following an acute high concentration exposure is “knockdown”: unconsciousness followed by apparent recovery. While typically unmeasured, rough estimates of concentrations in such events are 500 ppm or more, and the exposure duration is short, typically less than 1 hr (Beauchamp et al. 1984). Following such exposures, common permanent or persistent neurological effects reported include headaches, poor concentration ability and attention span, short-term memory impairment, and impaired motor function. Brief exposure to still higher concentrations can result in respiratory arrest and/or pulmonary edema. Although exact mechanisms are unknown, rapid respiratory failure and possibly pulmonary edema are secondary contributors to the action of H_2S on central nervous system depression or tissue hypoxia. Cardiovascular effects (e.g., cardiac arrhythmia and tachycardia) also have been reported following acute exposures. Extensive discussions of toxicity and effects at high concentrations are provided elsewhere

(e.g., ATSDR 2006; OEHHA 2008; also see review papers cited previously). Interesting and detailed discussions of dose-response and lethality of H_2S have been developed by Alberta's Energy Resource and Conservation Board (Cantox Environmental 2009; Zelensky 2009).

2.3 Health effects at low and chronic exposures

In contrast to short-term (acute) high concentration exposures, it is much more difficult to evaluate effects of long-term (chronic) and low or medium concentration exposures (below 0.1 and 1 ppm, respectively), the focus of Section 3 of this report. Most epidemiological (or observational) studies have deficiencies in terms of exposure characterization, e.g., obtaining little if any information on individual-level exposures, exposure patterns, peak exposures, and co-exposures to other contaminants. The paucity and limitations of controlled chronic animal studies also lead to knowledge gaps of low level chronic exposures (ATSDR 2006). Controlled chronic human studies are neither feasible nor ethical. Thus, it is unsurprising that the earlier studies and reviews have inconsistent findings with respect to the nature and significance of chronic low level exposures, leading several reviews to conclude that there is "insufficient" evidence to link low level H_2S exposures to significant health impacts (Lewis and Copley 2015; Lim et al. 2016; OEHHA 2000; Roth and Goodwin 2003).

A wide range of health effects at H_2S concentrations below 10 ppm have been reported in both occupational and community settings. For example, ATSDR (2006) states: "Exposure to lower concentrations of hydrogen sulfide can result in less severe neurological and respiratory effects. Reported neurological effects include incoordination, poor memory, hallucinations, personality changes, and anosmia (loss of sense of smell); the respiratory effects include nasal symptoms, sore throat, cough, and dyspnea. Impaired lung function has also been observed in asthmatics acutely exposed to 2 ppm H_2S; no alterations in lung function were observed in studies of nonasthmatic workers." In contrast, Guidotti (2010) states: "Exposures on the order of 5 to 10 ppm are sometimes encountered in community settings, although they are more common as background in workplaces such as oil refineries. Levels above 1 ppm are very uncommon in the community, where concentrations above the odor threshold (generally above 0.05 ppm for most people) are normally unacceptable and prosecuted as a nuisance. It has been alleged that health effects may be observed at exposures below 1 ppm, but the evidence is weak." The remainder of this section reviews the recent literature and discusses various health outcomes and symptoms, with the aim of clarifying the dichotomy regarding the occurrence of health effects from low and chronic H_2S exposures.

2.3.1 Odor, nuisance and irritation

2.3.1.1 Odor classification: H_2S is noted for its strong and offensive odor, which resembles rotten eggs. WHO (2006) and many others observe that H_2S is often accompanied by other odorous compounds from the same source: kraft mills emit reduced sulfur compounds such as methyl mercaptan, dimethyl disulfide, dimethyl trisulfide, dimethyl sulfide and dimethyl monosulfide; the viscose industry emits carbon disulfide; and CAFOs emit reduced sulfur compounds, VOCs including phenyls (fresh sludge), ammonia (in the absence of H_2S), dusts and bioaerosols (Blanes-vidal et al. 2009). Co-pollutants can change the odor quality of the mixture (NRC 1979).

It is important to distinguish between odor detection, odor recognition, odor threshold, olfactory fatigue, and olfactory paralysis. In community settings, the literature shows a degree of consistency with respect to odor detection and nuisance thresholds for acute exposures (30 min to 24 hr) at concentrations in the range of 0.0001 to 0.05 ppm.

- Odor detection threshold. Like other odors, inter-individual variation in sensitivity to H_2S is large. A review of 26 studies showed average odor detection thresholds from 0.00007 to 1.4 ppm (0.10 to 2,100 μg/m^3) (Amoore 1985); the geometric mean (GM) of these studies was 0.008 ppm (12 μg/m^3) (OEHHA 2008). Other reviews note an odor detection threshold for H_2S in pure form as low as 0.000013 to 0.0013 ppm (0.2 to 2.0 μg/m^3), depending on purity (van Gemert and Nettenbreijer 1984; Winneke et al. 1979) to 7.3 ppm (11 μg/m^3; Amoore and Hautala 1983). OEHHA (2000) states that at the reference exposure level (REL) of 0.0067 ppm (6.7 ppb = 10 μg/m^3), H_2S would be likely to be detectable by many people under ideal laboratory conditions, but it is "unlikely to be recognized or found annoying by more than a few." ATSDR (2006) gives an odor detection threshold ranging from 0.0005 to 0.3 ppm. Odor responses summarized by Collins and Lewis (2000) and Woodall et al. (2005) list concentrations of 0.5, 2, 4, 8, and 30 ppb being recognized by 2, 14, 30, 50 and 83% of persons, respectively.
- Odor recognition threshold. H_2S is frequently assumed to have an odor recognition threshold that is three to four times higher than the odor detection threshold, as assumed for other compounds. The threshold for perception lies between 0.02 and 0.13 ppm (Costigan 2003).
- Odor nuisance threshold. Odor nuisance occurs when an odor is perceived to be annoying. For H_2S, this can occur due to aesthetic, behavioral or physiological responses, which can include nausea and headache (Amoore 1985; Reynolds and Kamper 1984). The annoyance threshold often is stated to be about five times greater than the odor detection threshold. Using the geometric mean odor detection threshold, the annoyance threshold is about 0.04 ppm (60 μg/m^3) (OEHHA 2008). Slightly lower concentrations (0.03 ppm) have resulted in odor complaints and reports of nausea and headache near geyser emissions (Reynolds and Kamper 1984). These concentrations appear high for a guidance level, i.e., the California Ambient Air Quality Standard (CAAQS) is 0.03 ppm (OEHHA 2008). WHO (2006) states that on the "basis of the scientific literature, it is not possible to state a specific concentration at which odor nuisance starts to appear," however, text supporting the WHO's Air Quality Guidelines indicate that a 30-min average concentration of 0.0047 ppm (7 μg/m^3) is likely to produce substantial complaints (WHO 2006). The WHO guideline is based on two older citations (Lindvall 1970; NRC 1979). A recent and well-controlled clinical test suggests that at 0.05 ppm, the lowest H_2S concentration tested, participants may not fully habituate to the smell, and that continuing exposure may prove to be annoying (Fiedler et al. 2008).

- Olfactory fatigue. At concentrations above approximately 50 ppm (70 mg/m3), olfactory fatigue prevents detection of H_2S odor (OEHHA 2008).
- Olfactory paralysis. Neurotoxicity affecting the olfactory bulb and fibers may be followed by hyposmia or anosmia (permanent loss or reduction of the ability to perceive odor), which has been found in most men who recovered from severe and potentially lethal H_2S exposure (Guidotti 2010).

2.3.1.2 Odor and health: Odorant compounds can affect human health through several mechanisms (e.g., Schiffman et al. 2005; Wing et al. 2008; Woodall et al. 2005). Odor emissions, odor perception, and odor nuisance present quality of life issues that can cause individuals to modify certain physical and social activities (e.g., outdoor physical activity), which can then lead to other health-related issues. Odor perception is often associated with odor nuisance and complaints, and sometimes with psychological responses, e.g., headache, nausea, and loss of sleep. Ocular effects and nasal lesions are discussed in Sections 2.3.2 and 2.3.3, respectively. The WHO (2006) Air Quality Guidelines state that H_2S levels should not exceed 0.005 ppm (7 $\mu g/m^3$) over a 30-min period to avoid substantial complaints about odor annoyance. OEHHA (2008) in California makes the same statement but uses a higher exposure level, 0.03 ppm, developed in 1984 to reduce odors and physiological symptoms (headache and nausea) with a notation that this may need to be revisited. Several other studies have investigated odors and included H_2S measurements around CAFOs and landfills with the following findings:

- Irritation of the eyes, nose, and throat or other toxicological effects through properties of the odorous molecules and stimulation of the trigeminal nerve, typically at concentrations above the nuisance threshold. This is the “Type 1” classification of Woodall et al. (2005), in which symptoms are produced by irritant properties, rather than being odor-induced, often with the odor providing a “warning” of potential adverse health effects.
- Responses to non-odorant components that may be present in the airborne mixture, such as irritants or endotoxins in the case of CAFOs, which can induce inflammation and airflow obstruction. In this “Type 2” classification, a co-pollutant(s) in the mixture, not the odor itself, produces symptoms (Woodall et al. 2005).
- Innate aversion, conditioning, and/or stress responses to the odor, which produces health effects and/or symptoms including nausea, vomiting, headaches, stress, negative mood, and a stinging sensation. This occurs at concentrations above the olfactory nerve threshold, that is, exceeding the odor recognition or nuisance threshold, but below the antrigeminal nerve threshold, which is associated with irritation. This “Type 3” classification (Woodall et al. 2005) can also include odor-related exacerbation of underlying conditions and odor-related stress-induced illness. Odor may also lead to an acute “stress” state among individuals who perceive that the odor source poses a health risk (Shusterman 2001).

Because most facilities releasing H_2S also emit other pollutants, studies based on odor perception alone cannot confirm the role between H_2S exposure and health and psychological effects. Confirmation requires monitoring of H_2S and potentially other components of the pollutant mixture. Still, at least one study suggests that H_2S is often the predominant odor source. Using the threshold (dilution) olfactometry technique with a small human panel and 24 different slurry samples from swine operations, each tested for 35 gases (e.g., reduced sulfur compounds, phenyls, alcohols, ketones, acetic acid, ammonia), H_2S explained 45 to 68% of odor concentration, with most of the remainder attributable to volatile organic compounds (Blanes-vidal et al., 2009). A review of five olfactory studies examining municipal wastewater odors also states the need to complement olfactometric measurements with other tools, e.g., portable H_2S or SO_2 analyzers (Lewkowska et al., 2016). Unfortunately, relevant olfactometry studies identified in the literature are small, and few allow odor intensity to be correlated to the mixture's components. While more studies are examining co-pollutants associated with H_2S sources, the lack of olfactometry studies that characterize co-pollutants remains a gap in the observational studies examining health effects associated with odor.

2.3.1.3 Studies at livestock rearing systems: Livestock rearing systems include CAFOs as well as manure storage and treatment. As noted above, these facilities emit H_2S and other odiferous co-pollutants, e.g., reduced sulfur compounds, phenyls, and ammonia; these facilities can also emit biological contaminants (e.g., endotoxins, fungi and bacteria), aerosols and particulate matter (e.g., entrained dust).

Many surveys have been conducted in communities with or near CAFOs where individuals experience chronic exposure to CAFO-related pollutants (Donham 2010). Occupational studies at CAFOs have documented health complaints, e.g., eye irritation, sinusitis, chronic bronchitis, nasal mucous membrane inflammation, nasal and throat irritation, headaches, and muscle aches and pains, as well as objective health effects, e.g., respiratory inflammation, cross-shift decline in lung function, and chronic respiratory impairment (Schiffman et al. 2005). Acute high level H_2S exposure due to releases from agitated manure can lead to reactive airway distress syndrome (RADS), permanent neurologic damage, and death (Bardana 1999; CDC 1993). A review of health and social issues associated with CAFOs found over 70 papers addressing health issues affecting workers and communities (Donham et al. 2007). In reviewing health effects associated with airborne exposures at CAFOs, Heederik et al. (2007) noted the uncertainty regarding which effects were due to CAFO emissions; uncertainty also applies to attributing the effects to H_2S as compared to other odiferous and irritation-causing CAFO-related pollutants. Below we examine studies since 2004 focusing on odors and nasal irritation from CAFOs. (Later sections address ocular, nasal lesions, respiratory, neurological, and immune effects associated with CAFOs).

The newer studies examining nasal irritation associated with livestock rearing systems follow:

- Bullers (2005) studied residents living near hog farms in North Carolina, U.S. in 1998 and 1999 enrolled using snowball recruitment methods (n = 48), who were compared to a group without this exposure studied in 1999 enrolled using flyers

(n = 34). The exposed group showed increases in 12 of 22 self-reported physical symptoms, including sinus problems. (Additional symptoms are discussed in subsequent sections.) The authors discussed theoretical models regarding effects of environmental stressors. Study limitations include a modest sample size, a non-random sample, lack of control of covariates, differences in interview protocols (interviews in-home, by telephone), payments to participants in the comparison group but not the exposed group, non-simultaneity of interview periods for the two groups, and the lack of objective health and exposure measures.

- Schiffman et al. (2005) used well controlled exposure chamber tests and 48 self-selected human volunteers to evaluate physiologic and psychological responses to 1-hr exposures of dilute swine confinement air, stated to be equivalent to levels that could occur downwind of a swine facility, both within and beyond the property line. Concentrations measured during the exposure were 0.024 ppm (24 ppb) for H_2S, 0.817 ppm (817 ppb) for ammonia, 24 μg/m^3 for particulate matter (PM), 7.4 EU/m^3 for endotoxin, and 56 D/T for odor (factor above the odor threshold). No association between H_2S and nasal inflammation was found. To explain the dichotomy between this and other studies, the authors suggested that either additivity or synergy among the combined components may cause reported effects since no single component was present at sufficiently high concentration to be wholly responsible for symptoms, or that the self-reported “exposure-related avoidance” symptoms are innate or learned warning signals of potential health effects caused at higher concentrations or with prolonged exposure. Study limitations include the short exposure duration, use of healthy volunteers as compared to susceptible individuals (e.g., persons who are sensitized or have asthma) or individuals with involuntary and prolonged exposures, the inability to separate effects of H_2S alone from the CAFO mixture, and differences between experimental tests and occupational or community settings with respect to stress and the resulting neuronal, hormonal and behavioral responses that might affect outcomes.
- A longitudinal study of non-smoking adults (n=101) living within 1.5 miles of industrial hog operations in 16 neighborhoods in eastern North Carolina, U.S. collected survey (twice-daily odor diaries for approximately two weeks) and ambient H_2S and PM_{10} data from 2003 to 2005 (Horton et al. 2009). Typically, nine hog operations were within 2 miles of each community. In nine neighborhoods, odor was reported on ≥50% of study days, and hog odors inside homes were reported on 12.5% of person-days. Odor ratings were strongest in the morning and evening, with higher temperature, humidity and PM_{10} concentration, and both low and high (but not moderate) wind speeds. On 118 occasions, 34 participants reported that they altered activities due to hog odor. The authors concluded that malodor from swine operations was common in the studied communities, reported odors were related to objective environmental measurements, and that malodors interrupted the activities of daily life. Previously, odor was associated with stress levels for a subset of

the same sample population (Horton 2007), while ethnographic interviews for another subset also found that malodor limited many daily physical and social activities that can reduce stress and promote health (Tajik et al. 2008).

- Schinasi et al. (2011) tested associations between pollutants and odors near hog operations and acute physical symptoms using a longitudinal approach to help control the confounding possible in cross-sectional studies. The study used the same sample and monitoring approach described above (Horton et al. 2009). Participants were asked to spend 10 min outdoors twice a day at preselected times, assess odor, complete a symptom survey, and perform (unsupervised) spirometry. Simultaneously, ambient air monitoring was conducted for H_2S, endotoxin and PM_{10}, $PM_{2.5}$, and $PM_{2.5–10}$ in each community. Across the communities, the 1-hr H_2S concentration averaged 0.00030 ±0.00186 ppm (0.30 ±1.86 ppb); 12-hr PM_{10} averaged 19.4 ± 11.8 μg/m^3; and 12-hr $PM_{2.5}$ averaged 10.9 ±5.7 μg/m^3. Nasal irritation increased with general odor perception and ambient H_2S (per 1 ppb increase). Study strengths include the repeated and objective exposure measures and the frequent outcome measurements. The authors note the small sample size and the possibility that emissions during the study were reduced.

These investigations recognize that exposures from livestock related systems involve mixtures of pollutants. Identifying the effect of an individual component like H_2S can be difficult, requiring characterization of the mixture by monitoring its major components at the source or in ambient air, ideally in the community or residence of study participants, and further, H_2S levels must be shown to either dominate the health effect or be sufficiently non-collinear to separate effects of the mixture.

2.3.1.4 Studies at landfills, compost, and wastewater facilities: We identified several newer studies conducted at landfills, compost and wastewater facilities. As noted earlier (Section 1.2), these facilities produce H_2S under anaerobic conditions, and thus emissions will include other reduced sulfur gases. In addition, VOCs and fugitive dust containing odiferous or irritating components may arise from active landfills (i.e., operating faces without grass or other cover) and composting facilities. The dispersal of dusts is likely to be limited to locations very near the source given the rapid settling and dust fall expected for larger particles, e.g., greater than 2.5 μm in diameter.

- A community-based study in Pennsylvania, U.S. measured ambient and indoor levels of H_2S at two elementary schools, one of which was located near a composting plant, in two seasons (spring and fall; Logue et al. 2001). School nurses recorded symptoms and medical history from 749 “exposed” and 518 “unexposed” students. At the control school, concentrations never exceeded 0.01 ppm (1-hr average); at the exposed school, concentrations exceeded 0.01 ppm on 9 days in autumn and 3 days in spring). H_2S was not associated with irritation or olfactory symptoms. (Other outcomes from this study are discussed in later sections.) The negative results may have been due to the minimal exposure contrast between the schools, and other exposures that might have caused exposure misclassification.

- Among studies of wastewater treatment plant (WWTP) workers, only Lee et al. (2007) assessed nasal irritation. In Iowa, 109 workers at WWTPs were compared to 66 workers at water treatment plants (WTP), a group with similar work duties and characteristics but without occupational H_2S exposure. Objective measures of H_2S were used, but odor perceptions were not evaluated. Most (95%) monitored concentrations of H_2S were below 1 ppm, and the overall geometric mean concentration was 0.15 ppm (range from 0 to 42.5 ppm) in the WWTP group. The exposed group had a significantly higher risk of sinus problems. Skin and throat irritation were also found at higher rates in wastewater treatment workers, but these associations were not robust. (Additional outcomes in this study, e.g., neurological and respiratory symptoms are discussed later.) The authors suggested that the symptoms may be promoted due to synergistic or additive effects of the contaminant mixture.
- A panel study of 23 adults in Orange County, North Carolina, U.S., living within 0.75 mile of landfills completed a questionnaire twice daily about odor intensity, alteration of daily activities, mood state, and health symptoms (Heaney et al. 2011). At a site between the landfill and community, monitored H_2S levels averaged 0.00022 ppm (range: 0 to 0.0023 ppm), and were used as an indicator of a complex mixture of odorant chemicals. Conditional fixed effects models were used to associate odor perception to the alteration of daily activities, negative mood states, upper respiratory symptoms, mucous membrane irritation (burning eye, nose and throat), several neurological outcomes (dizziness, lightheadedness, “general ill feeling”), and other physical symptoms. The authors suggested that H_2S concentrations, which were below odor detection thresholds, and were likely correlated with other (unmeasured) landfill pollutants, probably associated with fresh garbage. While odor, health and quality of life impacts were associated with landfills, the study has several limitations, e.g., possible reporting bias since both independent and dependent variables are based on diaries, a small sample size, an inability to separate effects of H_2S from other odorous compounds, a lack of pollutant measurements other than H_2S, and a lack of objective (e.g., clinical) outcome measures.

As discussed in the prior section, identifying the effect of H_2S at these facilities requires adequate characterization and separation of mixture components. This was probably a minor issue in the school study given limited penetration and filtering of particulate matter typical in most buildings; this study had negative results. Both the occupational and landfill panel studies monitored H_2S but no other possible components of the exposure; the issue of co-exposure is particularly likely and limiting in the former study, as acknowledged by the authors.

2.3.1.5 Summary of odor and irritation: Few controlled or occupational epidemiological studies have examined odor and/or irritation related to H_2S. Several community-based studies have evaluated individuals living near H_2S emitting facilities, however, comparisons and synthesis are impeded by the very different exposure assessment methods, which include perception-only studies (i.e., without H_2S measures; Horton 2007), both indoor and

ambient H_2S measurements (Logue et al. 2001), ambient odor and ambient H_2S measures (Schinasi et al. 2011), and indoor odor and ambient H_2S measures (Heaney et al. 2011; Horton et al. 2009). Simultaneous odor and H_2S measures, collected both indoors and outdoors, are lacking, and information on individual-level exposures is also lacking. In studies using objective H_2S measures, odor was associated with ambient H_2S and nasal irritation, as has been shown in toxicological studies examining the irritant properties of H_2S, however, other symptoms did not show robust associations. H_2S odors may induce or exacerbate conditions such as stress or behavior modification. Importantly, studies using only odor as an exposure metric can be problematic for several reasons: they do not account for other pollutants that may be present; outcomes may be affected by response enhancement bias, i.e., an increase in reported symptoms since respondents are both aware of and potentially sensitized to the exposure (Farahat and Kishk 2010); odor thresholds among individuals vary enormously; and finally, odor perception can trigger a range of responses that may be contextual and difficult to assess.

In summary, odors associated with sources that emit H_2S, including agricultural, waste, wastewater, and industrial facilities, are clearly associated with odor-triggered nuisance, complaints and physiological symptoms that can result in health and quality of life impacts. These impacts occur at concentrations above an individual's odor detection threshold, up to the odor nuisance threshold, at short-term H_2S concentrations from roughly 0.001 to 0.050 ppm (Finnbjornsdottir et al. 2016; Heaney et al. 2011; Horton 2007; WHO 2006). Odor sensitivity to H_2S varies greatly among individuals (by over four or more orders of magnitude), and some individuals can detect H_2S at concentrations well below 0.001 ppm. Because the observational and community studies focus on waste management, industrial and agricultural facilities that emit a mixture of odiferous and irritation-causing pollutants, the reported health effects are not necessarily caused by H_2S exposure alone. However, a recent study suggests that H_2S may be the most important odorant at CAFOs, explaining 45 to 68% of the odor, with the remainder attributable to volatile organic compounds (Blanes-vidal et al. 2009). Given these and other study limitations noted above, the relationship between odor detection and harmful health effects has not been consistently found in epidemiological studies.

2.3.2 Ocular effects—Ocular effects of H_2S have been recognized since at least the 18th century. Lambert et al. (2006) provides a lucid review. At moderate concentrations, H_2S is an ocular irritant that affects the eyes in a condition that has been called "sore eye," "gas eye" (EPA 2003), and "spinner's eye" (Glass 1990). In occupational studies, evidence on eye irritation has been called "inconsistent," largely because effects have been reported over a wide concentration range and because several of the viscose-rayon studies likely involved co-exposures to sulfur dioxide, sulfuric acid, and carbon disulfide (Costigan 2003). More recent occupational epidemiology studies show eye irritation attributable to H_2S (e.g., Kilburn 2012; Lee et al. 2007).

The older guidance and recommendations for threshold limit values (TLVs) for occupational exposure listed ocular toxicity at concentrations from 5 to 30 ppm, and ACGIH (2001) noted that a 1-hr 50 ppm exposure results in superficial inflammation and conjunctivitis with ocular pain, lacrimation, and photophobia, which can progress to keratoconjunctivitis

and vesiculation of the corneal epithelium. The AIHA TLV guidance was based on ~10 studies from 1939 to 1969, which examined concentrations that generally are not relevant for community exposures (and thus omitted in this review). As discussed later (Section 4.2.1), the TLV guidance was revised in 2010 and ocular effects are no longer considered a critical effect, i.e., the effect occurring at the lowest concentration that "drives" the TLV.

2.3.2.1 Studies at geothermal sources: Bustaffa et al. (2020) has recently reviewed the health effects associated with populations exposed to emissions from natural geothermal events and geothermal energy plants. Evidence of increased eye damage is based on a few studies that are all ecological in design and limited to a single area of New Zealand. Lambert et al. (2006) reviewed several ocular studies, including community studies in Finland and New Zealand (the latter are discussed in Bustaffa et al. (2020) and reviewed below), and concluded that in community settings, short-term H_2S exposures of ~0.025 ppm appears to be the lowest concentration observed that irritates the eyes, and that chronic exposure is associated with serious ocular effects.

- The New Zealand studies examined communities in Rotorua, the largest naturally H_2S-exposed population in the world, due to geothermal emissions (Bates et al. 1998). About a quarter of its population of 40,000 is routinely exposed to H_2S at concentrations of at least 0.143 ppm (200 $\mu g/m^3$); the highest 30-min concentrations exceed 1 ppm (1,500 $\mu g/m^3$; Fisher 1999); the median concentration is 0.014 ppm (20 $\mu g/m^3$); 35% of measurements exceed 0.05 ppm (70 $\mu g/m^3$) and 10% exceed 0.286 ppm (400 $\mu g/m^3$). Based on hospital discharge data from 1981 to 1990, standardized incidence rates of ocular disorders -- cataracts, diseases of the eye and adnexa (eyebrow, eyelids, and lacrimal apparatus), disorders of the conjunctiva, and disorders of the orbit -- were statistically higher than rates elsewhere in New Zealand (Bates et al. 1998). This ecological analysis did not address the sharp concentration gradients of H_2S observed across the city (Horwell et al. 2005) or the differences between exposed and unexposed populations.
- Bates et al. (2002) updated their earlier study with 1993 to 1996 morbidity data and grouped community exposures into three categories using exposure data based on passive air sampling of H_2S. Again, Rotorua residents experienced significantly higher incidence of adnexa and eye disorders compared to residents elsewhere in the country, and exposure-response trends held across all four ethnicity–gender categories. While improved in the updated study, the exposure assessment remained ecological in nature (individual exposure data were unavailable), and the authors acknowledge the lack of information on possible confounders, e.g., smoking and socio-economic status (SES), and possible selection bias.

2.3.2.2 Studies at sulfate pulp mills and composting facilities: Pulp and paper production is the single largest source of H_2S emissions (Section 1.2). A series of Finnish studies have studied populations living near sulfate pulp mills.

- In Imatra, South Karelia, Finland, Haahtela et al. (1992) examined exposures to H_2S and other reduced sulfides (methyl mercaptan, dimethyl sulfide, dimethyl disulfide). Local mills released an estimated 2,800 tons/year of H_2S in 1989. During a plant upgrade in September 1987, emissions at one mill increased for two days, resulting in a maximum 4-hr concentration of 0.096 ppm (135 $\mu g/m^3$) and 24-hr averages of 0.025 and 0.031 ppm (35 and 43 $\mu g/m^3$) measured 1 km from the source; these levels are 4–20 times higher than those during a reference period believed to be representative. During the 2-day event, sulfur dioxide (SO_2) levels were low, but an intensive "catty" odor due to mesityl oxide was reported. Unfortunately, this unsaturated ketone, as well as reduced sulfur compounds other than H_2S, were not measured; mesityl oxide is also an irritant to eyes and other tissues and has an acute Reference Exposure Level (REL) of 10 ppm (OEHHA 1999) and a US occupational Permissible Exposure Limit (PEL) for the time weighted average (TWA) of 25 ppm (ACGIH 2001). (Occupational limits are discussed later in Section 4.2.) Surveys distributed to persons (n=60) in the affected community shortly after the exposure event and in a subsequent reference period (n=66) showed that a statistically significant number of persons (22% of the sample) experienced direct irritative effect on mucous membranes and eye conjunctivitis, symptoms that corresponded to the physiological effects of acute H_2S exposure.
- A cross-sectional study by Marttila et al. (1994) evaluated ocular (and other symptoms) among children (n=134) under 15 years of age in three communities in South Karelia, Finland. The annual average H_2S levels predicted using air quality dispersion models were 0.00067 and 0.0053 ppm (1 and 8 $\mu g/m^3$) in the moderately and severely polluted communities, respectively, and the 24-hr maxima were 0.01 and 0.067 ppm (15 and 100 $\mu g/m^3$); the available monitoring data indicated lower levels. Parent's reports over the past 4 weeks and 12 months showed increases in the children's eye irritation over time, but changes were not statistically significant; the small sample size and issues in symptom ascertainment may have limited associations. Concentrations of other reduced sulfur compounds were not reported. SO_2 levels were low (averaging 2–3 $\mu g/m^3$) and not indicated as a significant confounder. As in the previous studies, several sulfur compounds were present, including methyl mercaptan (CH_3SH; annual mean from 2 to 5 $\mu g/m^3$ [0.001 – 0.0025 ppb]; maximum 24-h concentration of 150 $\mu g/m^3$ [0.075 ppm]; high exposure area). CH_3SH has a low odor threshold (0.002 ppm), and the acute REL and PEL are 0.5 and 10 ppm, respectively. However, confounding was not expected given that the CH_3SH irritation threshold was estimated to be two orders of magnitude higher than that for H_2S. Still, the potential effects of both acute and chronic exposure CH_3SH, as well as other sulfur compounds, over a long period of time should be considered.
- Marttila et al. (1995) carried out a longitudinal study of adults (n=81) in Lappeenranta, Finland living 1.5 km from a pulp mill. Baseline and six follow-up surveys were administered to the cohort, and pollutants (TRS, SO_2, TSP, NO_x) were monitored continuously in the community over 15 months. Large and

statistically significant differences in symptom intensity were found between the reference, medium and high exposure periods, suggesting a dose-response relationship. The intensity of eye (and nasal and pharyngeal) symptoms was significantly higher during days when TRS levels exceeded 0.0067 ppm (10 $\mu g/m^3$). H_2S was estimated to account for two-thirds of the TRS released in the region; concentrations of other reduced sulfur compounds were not presented; and SO_2 levels were low (5 – 50 $\mu g/m^3$) and not considered to be a significant confounder. The authors concluded that relatively low daily concentrations of malodorous sulfur compounds, i.e., TRS exceeding 0.0067 ppm (10 $\mu g/m^3$), can cause exposure related short-term adverse effects.

- Logue et al. (2001) carried out a community-based study of students at an elementary school near a composting plant located in southeastern Pennsylvania, U.S (described earlier in Section 2.3.1.4). The 749 students from the H_2S exposed school (where measured 1-hr H_2S levels exceeded 0.010 ppm on 9 days) and 491 students from the control school (no such events) participated in the survey of symptoms and medical conditions. Associations between H_2S and ocular symptoms were not statistically significant.

2.3.2.3 Studies of livestock rearing systems

- In well-controlled chamber tests to a CAFO mixture described earlier in Section 2.3.1.3, Schiffman et al. (2005) found increased prevalence of eye irritation. This mixture contained H_2S (0.024 ppm), ammonia (0.817 ppm), total suspended particulates (0.0241 mg/m^3), endotoxin (7.40 endotoxin units/m^3), and odor (57 times above odor threshold).
- Kilburn (2012) compared 25 individuals living from 0.17 to 3 km (most within 0.9 km) of hog manure lagoons with 22 age- and gender-matched individuals living beyond 3 km in Paulding, Ohio (and also to 58 additional controls in Tennessee) for pulmonary performance in a 3-day period in April, 2003. (The main objective of this study was to evaluate neurological endpoints, as described later.) H_2S levels in 12 homes averaged from 0 to 0.03 ppm (but reached 2.1 ppm and varied over 10-fold in one-day's spot check samples), and two outdoor samples exceeded 1.1 ppm; these high levels appear to be outliers. Other airborne constituents, e.g. ammonia, SO_2, NO_2 and particulate matter, were not considered. Questionnaires asked about frequencies of 35 common health complaints, respiratory symptoms, occupational history, exposure history (chemicals, pesticides, tobacco, alcohol, drug use, etc.), and medical history. While outcomes were uncorrelated with distance to the lagoons, frequencies of 18 of 35 symptoms, including eye irritation, differed significantly between exposed and (local) control populations. (Other outcomes in this study are discussed elsewhere in the present report.) Many of the same (and some additional) differences were found between the exposed Ohio population and the Tennessee referent population. While a number of objective outcome measures and some H_2S monitoring were utilized, the sample size was small, co-pollutant exposure was likely, and the exposure assessment was incomplete.

- Schinasi et al. (2011), described earlier, reported increased acute eye irritation following 10 minutes outdoors with perception of odor, as well as correlation with 12-hour mean levels of H_2S, $PM_{2.5}$ and PM_{10}. The log odds of acute eye irritation following 10-min outdoor exposure increased by 0.15 per 1 ppb of H_2S, by 0.84 per 10 μg/m^3 of $PM_{2.5}$, and by 0.36 per 10 μg/m^3 of PM_{10}.

2.3.2.4 Studies at wastewater treatment plants

- Lee et al. (2007), described previously, found that eye irritation was more commonly reported by WWTP workers exposed to mean H_2S concentration of 0.15 ppm (range: 0 – 42.5 ppm) compared to unexposed workers.

2.3.2.5 Summary of ocular effects: The Finnish studies around pulp mills (Haahtela et al. 1992; Marttila et al. 1995, 1994) addressed both acute and chronic exposures and showed statistically significant increases in eye symptoms at (24-hr) concentrations as low as 0.007 ppm. However, these are ecological studies using small populations that likely involve co-exposures to other sulfur gases. In the geothermal area of Rotorua, New Zealand, an ecological approach was also used by classifying the city into high, medium, or low H_2S exposure areas (Bates et al. 2002, 1998). These studies also involve co-exposures, but to different pollutants than the Finnish studies given the different (volcanic) H_2S source. While ocular effects may be experienced at lower concentrations, as concluded by Lambert et al. (2006), the evidence is more consistent that single or repeated short-term H_2S concentrations in the range of 0.007 to 0.025 ppm can produce eye irritation. However, the available observational studies have limitations: they incompletely address the nature of ocular effects other than irritation, their exposure assessments provide limited detail regarding exposures (e.g., short-term but high concentration events are not characterized), and they do not address whether chronic low level H_2S exposure causes irreversible effects on the eye.

In summary, concentrations from about 0.007 to 0.025 ppm correspond with the low end of the range that has been associated with eye irritation in the older cross-sectional studies examining short- and long-term exposures in Rotorua (Bates et al. 2002, 1998) and Finland (Haahtela et al. 1992; Marttila et al. 1995, 1994). Several recent community studies around CAFOs and similar facilities have reported eye irritation (Heaney et al. 2011; Kilburn 2012; Schinasi et al. 2011), as have short-term controlled tests at 0.024 ppm as part of a CAFO mixture containing ammonia and other contaminants described earlier (Schiffman et al. 2005). However, a short-term controlled test of H_2S alone at 0.05, 0.5 and 5 ppm H_2S did not present eye irritation (Fiedler et al. 2008), which suggests the possible role of co-pollutants, rapid fluctuations in H_2S concentrations (that are averaged out in sampling), or longer exposure periods. The available studies have limitations: they do not address the nature of ocular effects other than irritation (Lambert et al. 2006); the exposure assessments provide little spatio-temporal information; the exposure contrasts may be minimal; and the question of whether chronic low level H_2S exposure causes irreversible effects on the eye is not approached.

2.3.3 Nasal lesions—The olfactory epithelium is vulnerable to H_2S induced pathology due to cytochrome oxidase inhibition at lower concentrations than damage to the nasal

respiratory epithelium, and thus this effect has formed the basis for both occupational and environmental exposure standards (Schroeter et al. 2006), including EPA's current RfC and the ATSDR's intermediate duration MRL (Section 4.1.2). These guidelines were informed by Brenneman et al. (2000), who exposed groups of 12 male Sprague-Dawley rats to 0, 10, 30 or 80 ppm H_2S for 6 hr/day for 10 weeks with subsequent examination of nasal epithelium. No adverse changes in olfactory or respiratory epithelia were seen at 10 ppm (13.9 mg/m^3), and thus this concentration became the current NOAEL. At higher concentrations (30 ppm), olfactory lesions and basal cell hyperplasia (a response to the olfactory lesions) occurred throughout the nose; these increased in extent at 80 ppm. As described below, the only updates in the literature pertaining to nasal lesions are dosimetry refinements for an animal study, and a small case-report occupational study (Brenneman et al. 2000; Mousa 2015; Schroeter et al. 2006).

2.3.3.1 Pharmacokinetic modeling: Using interspecies pharmacokinetic computational fluid dynamics (PK-CFD) models, Schroeter et al. (2006) derived a human NOAEL of 5 ppm by extrapolating the nasal lesion and extraction data observed in rats to humans. The modeling used a conservative physiologically-based dosimetric approach for interspecies extrapolation and differences in exposed nasal surface areas, airflows, partitioning, diffusivity and reaction kinetics. Although some data were lacking to support the extrapolation, modeling was consistent with interspecies clearance data, and results showed good correlation with the incidence of olfactory lesions in rats. An investigation of interhuman variability, which simulated H_2S uptake on olfactory epithelium for 5 adults and 2 children using anatomically correct models of the olfactory region generated from magnetic resonance imaging (MRI) or computed tomography (CT) scan data and steady-state inspiratory airflows, showed similar dosimetry (within 20%) over a range in olfactory airflow (Schroeter et al. 2010). While the modeling may incompletely represent population variability, it suggests that differences in nasal anatomy and ventilation do not significantly affect H_2S uptake in the olfactory region. Additional discussion regarding derivation of the NOAEL and modeling contrasting nasal airflows rat and human noses are given by Dorman (2004).

2.3.3.2 Occupational studies: A recent case-report assessed symptom frequencies of oil field workers (n=34) in Iraq exposed to a wide range of H_2S levels (daily ambient average concentrations from 4 – 50 ppm) and an unexposed comparison group (Mousa 2015). No median or interquartile range (IQR) for exposures was reported. 53% of the exposed workers experienced nasal bleeding, and a few experienced additional bleeding.

2.3.3.3 Summary: The effect of the PK-CFD modeling used to extrapolate nasal lesions in rats to humans (Brenneman et al. 2000; Schroeter et al. 2006) would be to halve the current NOAEL of 10 ppm to 5 ppm. This modeling is consistent with observations, and the rat-to-human extrapolation reduces uncertainty compared to simpler dosimetric approaches. However, human data in this concentration range are insufficient for confirmation, and the NOAEL remains at 10 ppm. As discussed later in Section 4, these studies are important as the risk of nasal lesions remains the basis for several H_2S standards and guidelines.

2.3.4 Respiratory and allergic effects—This section first reviews several older controlled studies describing changes in lactate and oxygen levels in blood and muscle measured during H_2S exposure, which remain important in the regulatory context, then proceeds to recent epidemiological studies examining effects of chronic exposure in community settings due to emissions from volcanos, CAFOs, and other sources, and lastly reviews several occupational studies.

2.3.4.1 Controlled experiments: Several controlled experiments examined biochemical markers of respiratory-related function during and after H_2S exposure, most recently in the 1990s. The two studies discussed below (Bhambhani et al. 1996; Bhambhani and Singh 1991) were used to establish Occupational Exposure Limits (OELs) in the United Kingdom (Costigan 2003) and are cited in the REL documentation (OEHHA 2008). More recent studies on lactate or oxygen stress were not identified. The two studies involved short-term exposure to small numbers of healthy individuals, and they may be most relevant to occupational settings. They update an older controlled study by Jappinen et al. (1990), which may be the first controlled study of H_2S effects on respiratory function.

- Jappinen et al. (1990) tested 26 male pulp mill workers with typical exposures from 2 to 7 ppm, and 3 men and 7 women with mild or moderate asthma. (Individuals with severe asthma were excluded.) Among the 10 individuals with asthma, a 30-min exposure to 2 ppm H_2S caused a marginally significant increase in airway resistance R_{aw} (average 26% change), but no change in FEV_1, FVC, $FEF_{25–75}$, or specific airway conductance (SG_{aw}). In 2 of 10 subjects, both R_{aw} and SG_{aw} changed by >30%, a sign of bronchial obstruction.
- Bhambhani and Singh (1991) used 16 healthy young male adults and oral exposures to 0 (control), 0.5, 2 and 5 ppm (7 mg/m3) H_2S under conditions of exercise. Lactate in blood and oxygen uptake showed a graded response, and results at 5 ppm were statistically different from those in controls. The authors suggested that at H_2S doses from 2 to 5 ppm with higher exercise rates, oxygen is being utilized to detoxify H_2S and that the activity of the enzyme cytochrome oxidase is inhibited. Both processes increase dependency on anaerobic metabolism and thus elevate blood lactate levels.
- Bhambhani et al. (1996) compared effects of 0 (control) and 5 ppm exposures on the biochemical properties of skeletal muscle in 25 healthy young subjects (13 men, 12 women), who underwent two 30-min tests a moderate level of exercise, after which biopsies of the vastus lateralis muscle (part of the quadriceps) were obtained and analyzed for markers of anaerobic and aerobic metabolism. In men, levels of citrate synthase decreased significantly with exposure; lactose and lactate dehydrogenase increased although not significantly, and cytochrome oxidase decreased. Although most aerobic enzymes did not have statistically significant changes, short-term H_2S exposure affected aerobic metabolism in a large proportion of men and women tested. Furthermore, exposure at half of the (U.K.) occupational exposure limit (OEL) resulted in a shift from aerobic to anaerobic metabolism. The authors remarked on the need to examine a

larger sample to account for variability, as well as longer duration and higher concentration exposures.

- In a detailed review of the physiological, pharmacological and toxicological effects of H_2S, Olson (2011) noted the classical hormesis relationship between H_2S exposure and O_2 consumption: at low concentrations, H_2S stimulates oxygen consumption (and may even result in net ATP production); while at elevated levels, H_2S inhibits consumption. However, the H_2S concentrations in tissues and blood that cause these effects have not been resolved. The few studies employing controlled H_2S exposures to evaluate respiratory outcomes, which use small sample sizes and only very short exposure periods, are consistent in showing that short (30 min) exposures at or around 2 ppm cause changes in indicators related to respiratory function in both healthy and (mild-to-moderate) asthmatic adults.

2.3.4.2 Community studies near geothermal and volcanic sources: Respiratory impacts of H_2S are not limited to high exposures; low levels also increase the risks of respiratory symptoms, respiratory disease mortality, and anti-asthma drug use (Bustaffa et al. 2020) as shown by studies examining communities near geothermal and volcanic H_2S sources including Reykjavik (Iceland), Rotorua (New Zealand), the Azores (Portugal), and Mt. Amiata (Italy). (Geothermal emissions and hazards have been reviewed by Bustaffa et al. (2020) and Hansell and Oppenheimer (2004).) Portions of these communities experience chronic exposure to H_2S, estimated to be between 0.02 and 1.0 ppm; Nuvolone et al. (2019) found a lower range of 0.0003 to 0.0224 ppm. Both the older and the newer studies have associated chronic exposure with noninfectious respiratory symptoms and disease. For example, in Rotorua, Durand and Wilson (2006) used improved exposure mapping to show greatly elevated risks of a variety of respiratory symptoms and diseases; in Furnas, Amaral and Rodrigues (2007) showed a greatly increased rate of chronic bronchitis with exposure; in Reykjavik, Carlsen et al. (2012) found adverse impacts on individuals with asthma at H_2S concentrations in the range of 0.0067 ppm; and in Tuscany, Nuvolone et al. (2019) found that an increase of 0.0047 ppm (90-day avg) could have both harmful and beneficial respiratory effects, results that may be partly explained by not testing for multiple outcomes. These studies do not demonstrate causal linkages to H_2S exposure given potential confounding with other pollutants and, in some cases, issues regarding the comparability of the populations. The Reykjavik study (Carlsen et al. 2012) appears the strongest given its multiyear time series analysis, large sample, inclusive population, and objective measures of H_2S and other pollutants. Further details on these studies follow.

- Durand and Wilson (2006) investigated respiratory disease among residents in Rotorua, New Zealand, a city of 61,000 where H_2S exposure occurs from geothermal emissions (including sulfur springs, soil gas, and fumaroles). An H_2S mapping survey using passive samplers and several weeks of sampling showed considerable spatial variation in concentrations, which results from varying soil gas emissions and meteorological influences. The analysis used 11 years (1991–2001) of hospital discharge morbidity data, a cross-sectional analysis with groupings that assigned residential census area units (CAUs) to

low, medium or high exposure categories (typical H_2S concentrations of 0.03 – 0.04, 0.5 and 1.0 ppm, respectively), and ecological controls for age, ethnicity, smoking status and socioeconomic status (deprivation). Greatly elevated risks (2 to 5-fold) were seen for all respiratory diseases, chronic obstructive pulmonary disease (COPD), asthma, and respiratory and chest symptoms. Study strengths include the large sample size, control of several potential confounders, and a more detailed exposure mapping than previously available. Study limitations include a lack of individual identifiers, inability to identify repeat hospital visits by an individual, the ecological smoking and deprivation data (linked to the CAU) that is a particular issue for Maori women due to their very high smoking rates, possible exposure misclassification due to short-term temporal fluctuations in H_2S levels, sharp spatial gradients of H_2S levels (Horwell et al. 2005), the likelihood of indoor exposures (Durand and Scott 2005), and (unknown) exposures at work and other non-residential environments.

- Amaral and Rodrigues (2007) investigated the risk of chronic bronchitis using a population-based retrospective cohort design that compared two areas in the Azores, Portugal: one with volcanic activity (Furnas) that emitted H_2S as well as water vapor, carbon dioxide, SO_2, and other gases; and a second area (Santa Maria) without volcanic emissions. H_2S exposures were not quantified, but earlier reports measured SO_2 at average levels between 0.01 and 0.08 ppm in Furnas (Baxter et al. 1999). Age and sex-adjusted incidence rates of chronic bronchitis, based on local medical records and census data from 1991 to 2001, were elevated in the exposed area relative to international norms, and the (all age) relative risk was 4.0 for males and 10.7 for females, based on a comparison of exposed to unexposed areas. High rates of chronic bronchitis in Furnas were partially attributed to chronic H_2S and SO_2 exposure in a very humid atmosphere; co-exposure with SO_2, a known toxicant and bronchoconstrictor, is a potential confounder.
- A population-based time-series study examined the daily number of adults (>18 years of age) in Iceland’s capital Reykjavik and the surrounding municipalities who were dispensed anti-asthma drugs as a function of daily air pollution levels over a nearly 4-year period (Carlsen et al. 2012). Geothermal sites outside the city emit H_2S concentrations producing long term concentrations that averaged 0.0058 ppm (8.7 μg m^{-3}; maximum of 0.062 ppm [93 μg m^{-3}; 24-hr average]), and 1-hr levels that averaged 0.021 ppm (32 μg m^{-3}; maximum of 0.345 ppm [518 μg m^{-3}]). Poisson regression models using 3-day moving H_2S averages, typically lagged several days, along with other pollutants (PM_{10}, NO_2 and O_3) and covariates (e.g., temperature, humidity, pollen count, influenza season, day-of-week, time trend and seasonal trend) showed that a small increase in H_2S levels, 0.0067 ppm (10 μg m^{-3}), was associated with a modest (2%) but statistically significant increases in the number of individuals dispensed anti-asthma drugs, specifically inhalant adrenergics (both long- and short-acting bronchodilators). The authors noted that this was the first study outside of occupational settings to associate short-term changes in H_2S levels

with health-related outcomes. Study strengths include capturing essentially all drug prescriptions and considering multiple pollutants; weaknesses include the ecological design, the use of a single monitoring site, the lack of $PM_{2.5}$ data, a large amount of missing data, the inability to identify individual or group risk factors, and the surrogate indicator used for asthma exacerbation. While other pollutants were monitored, SO_2, a known respiratory irritant, was not mentioned. However, continuous monitoring in Reykjavik shows that SO_2 levels are low relative to 24-hr and annual average limit values (Skúladóttir and Þórðarson 2003).

- Bates et al. (2013) assessed the effect of H_2S on asthma among 1,637 adults in Rotorua City, New Zealand. Recruitment used a 2-stage stratified strategy with mail and phone calls to individuals selected from a centralized patient registry, who then visited the study clinic and completed a questionnaire and clinical tests. Participant age ranged from 18–65 years; most (60%) were female; 50% were former or current smokers; and 24% reported a prior or current asthma diagnosis. A city-wide monitoring network, consisting of 50 passive samplers deployed for 2 weeks in summer and 53 samplers in winter of 2010, was spatially interpolated via kriging to estimate quartiles of ambient H_2S levels at each participant's residence and workplace for the prior 30 years. Ambient levels ranged from 0 to 0.064 ppm (IQR: 0.011 – 0.031 ppm). The H_2S exposure groups were not associated with increased asthma risk or most symptoms, with exceptions of increased coughing in the third exposure quartile (overall not statistically significant) and slightly reduced wheeze in the fourth (highest) exposure quartile. The authors discuss possible issues including selection bias, survivor effect, confounding due particulate matter exposure due to wood smoke (modeled PM_{10} levels were noted to fall below 100 $\mu g/m^3$ and were inversely related to H_2S levels based), NO_2 and traffic pollutant levels (stated to be positively correlated with H_2S). Only minor differences were noted in analyses using exposures at home or work. While participants were required to live in Rotorua for at least 3 years prior to the study, residential and workplace histories were not obtained (only current addresses were used) and participation was limited to city residents.
- Effects of ambient H_2S in Reykjavik also were reported by Finnbjornsdottir et al. (2016). In regions near a geothermal power plant, the risk of an emergency hospital visit (also heart disease and stroke as discussed later) among the 151,095 residents was investigated using a time series model and daily H_2S levels at residences of the 13,383 patients visiting the hospital (32961 visits) over the 7.5 year study period. H_2S levels were estimated using a simple plume-type model, and 24-hr H_2S levels ranged from 0 to 0.047 ppm (69.5 $\mu g/m^3$; IQR: 0 – 0.003 ppm). No association was found between H_2S and respiratory-related emergency visits. An important limitation of this study concerns ascertainment of outcomes, which used only collective categories (heart disease, respiratory disease, stroke).
- Nuvolone et al. (2019) studied 33,804 residents near Mt. Amiata, Tuscany, Italy, home to geothermal power plants. Risks of neoplasms, respiratory diseases, central nervous diseases, and cardiovascular diseases were calculated

using mortality and hospital data (non-respiratory effects are discussed later). Individual H_2S exposures (maximum 90-day moving average estimated using dispersion modeling and geocoded addresses) ranged from 0.00034 to 0.022 ppm (0.5 to 33.5 μg/m^3; mean of 0.005 ppm, SD of 0.005 ppm). A 0.005 ppm (7 μg/m^3) increase in H_2S levels was associated with a 12% increase in respiratory mortality and a 27% increase in pneumonia hospitalizations, and with reduced risk respiratory disease hospitalizations. Lower mortality risks (protective effect) were observed for cardiovascular diseases. Other respiratory effects were found to be less robust. While using medicate records and successfully geocoding most addresses to obtain model-based exposure estimates, the residential cohort design did provide information on individual-level confounders, e.g., smoking, alcohol consumption and diet.

2.3.4.3 Studies regarding livestock rearing systems: Respiratory effects associated with H_2S emissions from livestock rearing systems, including CAFOs, have been investigated in a few controlled and occupational epidemiological studies. However, a number of community-based studies have suggested increased prevalence of respiratory and asthma symptoms and lung function impacts among children and adults experiencing chronic exposure. While designs of these studies vary considerably, as summarized below, all but one identified respiratory-related disease or health symptoms, including breathing difficulty, chest tightness, wheeze (Bullers 2005; Campagna et al. 2004; Mirabelli et al. 2006a, 2006b; Radon et al. 2007; Schinasi et al. 2011), increased asthma prevalence and/or aggravation (Campagna et al. 2004; Merchant et al. 2005; Radon et al. 2007; Sigurdarson and Kline 2006) lung function (PEF and FEV_1) decrements (Radon et al. 2007; weakly in Schinasi et al. 2011), and COPD (Eduard et al. 2009), though the latter association was weak and only present in in farmers with atopy. The single negative study, Villeneuve et al. (2009), had significant limitations: it examined a relatively small farm, had a small sample size, and the “high” exposure group extended 3 km radius from the farm, longer than the distance usually considered for CAFO impacts. Many of these studies used residential proximity to livestock as an exposure surrogate, but several recent studies used objective air quality measurements. Other issues include selection bias, measurement error, and multiple exposures (Section 2.4.3). Of particular note, H_2S exposure due to livestock rearing systems can be accompanied with elevated levels of endotoxins, ammonia, and organic dusts, all of which are strongly implicated in the development of respiratory disease (Woodall et al. 2005). Two studies with objective pollutant measures used time series analyses to show increased rates of unscheduled hospital visits for aggravation of asthma and respiratory disease at 30-min H_2S concentrations above 0.03 ppm in Nebraska (Campagna et al. 2004), and a dose-response relationship for breathing difficulty and wheeze with odor and H_2S at mean levels of 0.0003 ppm in North Carolina (Schinasi et al. 2011).

- Bullers (2005), described previously (Section 2.3.1.3), associated residential proximity to hog farms for 12 of 22 self-reported symptoms investigated, including respiratory problems.
- A time series analysis examined daily unscheduled or emergency hospital visits (N=5009) for respiratory disease among residents of Dakota City and South

Sioux City, Nebraska, U.S. from January 1998 to May 2000 (Campagna et al. 2004). This area contained 13 known reduced sulfur sources; the largest, a beef slaughter and leather tanning facility with a waste treatment complex, emitted an estimated 1,900 pounds/day of H_2S. TRS and H_2S were measured in the community at 3 and 14 sites, respectively, and daily levels were categorized as "high" if any 30-min rolling averages exceeded 0.03 ppm (30 ppb) and as "low" otherwise. Previous sampling identified H_2S as the only sulfur contaminant present in sufficient concentrations to cause concern. High days occurred on ~25% of days in the study. For children less than 18 years of age (N=174 visits), asthma hospital visits were associated with 1-day lagged TRS levels, and hospital visits for all respiratory diseases were associated with 1-day lagged H_2S and TRS levels. Adult asthma hospital visits (N=281 visits) also were associated with 1-day lagged H_2S levels. The study included diagnostic controls (visits for digestive diseases), which was negative. Linkages between TRS and H_2S with exacerbations of asthma and other respiratory diseases appear robust given the community-wide exposure monitoring and the near-complete capture of visits in the local hospitals. Study limitations include issues regarding the quality of exposure data, the lack of individual measures, possible outcome misclassification, and possible omission of residents treated outside the community.

- In Iowa, U.S., children living on farms that raised swine had a very high prevalence rate of asthma-related outcomes (44.1%); children on farms that raise swine adding antibiotics to feed had an even higher rate (55.8%), despite generally lower rates of atopy and personal histories of allergy in farm populations (Merchant et al. 2005). No environmental measurements were conducted, although high occupational exposures to respirable and total dust, endotoxin, H_2S and ammonia have been shown in other Iowa farm studies. Several asthma symptoms were attributable to these co-exposures.
- The controlled study by Schiffman et al. (2005), previously detailed (Section 2.3.1.3), found no association between a CAFO mixture containing H_2S at an average concentration of 0.024 ppm and lung function or vital signs.
- In Saxony, Germany, Radon et al. (2007; 2005) studied 3,131 individuals with farm contact and 2,425 individuals without farm contact living near CAFOs. Among the group without farm contact, odds for all respiratory symptoms and for physician-diagnosed asthma increased with increasing self-reported level of odor annoyance. Odds of self-reported wheeze increased for individuals living within 500 m of 5 or more animal houses, and FEV_1 decreased for those living within 500 m of 12 animal houses. Study strengths include a large sample size, the development of dose-response curves relating health impacts to the number of animal houses, and the exclusion of individuals with professional or private contact with farming environments; author-noted limitations include the surrogate exposure metric, specifically that the number of animal houses is a poor exposure indicator, and the lack of ammonia and endotoxin co-pollutant measurements that be confounders.

- Mirabelli et al. (2006a; 2006b) studied the prevalence of wheezing among children 12 to 14 years of age living in North Carolina, USA. Wheeze prevalence among children with allergies was 5% higher at schools located within 3 miles of swine feeding operation, and 24% higher at schools where livestock odor was noticeable indoors twice or more per month, compared to schools at further distances or without odors.
- Sigurdarson and Kline (2006) conducted a cross-sectional study of children attending two elementary schools in Iowa, USA, one located within 0.5 mile from a CAFO (n=61) and the other distant from large scale agricultural operations (n=248). The former school had a much higher prevalence of physician-diagnosed asthma (19.7%) than the control school (7.3%). Although the two populations differed (e.g., parents in the study school were more likely to work on a farm and to smoke), adjusted models showed that children remained at risk (adjusted odds ratio = 5.71, p = 0.004). No exposure measurements were taken.
- An occupational study by Eduard et al. (2009) examined associations between H_2S and respiratory morbidity and mortality among 4,735 Norwegian farmers on crop-only, livestock-only, and crop-and-livestock farms. Based on personal air sampling, the median annual average exposure was 1.1 ppb (IQR: 0.2 – 36 ppb). If H_2S-related tasks and H_2S odor were absent, levels were assumed to be 0 ppb. Cattle and swine farms had the highest H_2S levels, 0.036 and 0.029 ppm (36 ppb and 29 ppb), respectively; sheep/goats and poultry farms both had levels of 0.0002 ppm (0.20 ppb), and crop-only farms had 0 ppm (0 ppb). A subset of 1,213 farmers with atopy showed a weakly elevated risk of COPD when comparing with high vs. low exposure groups. No dose-response relationship was observed, and H_2S exposure was not associated with chronic bronchitis or lung function. While the study results were negative or inconclusive, the use of personal air sampling is unique among the studies and has the potential to reduce exposure measurement error.
- A cross-sectional study in rural Sarsfield, Ottawa, Canada, found that self-reported respiratory health disease and symptoms (asthma, rhinitis, sinusitis, chronic bronchitis, allergies) of 723 adults and 285 children/adolescents were not associated with distance between residences and hog farm operations (Villeneuve et al. 2009). The authors noted the lack of direct exposure measures and possible biases from using self-reported health measures. (This study did find a higher prevalence of depression and lower health related quality of life measures.)
- Schinasi et al. (2011), described earlier (Section 2.3.1.3), found that wheeze and breathing difficulty increased with general odor perception and ambient H_2S levels in a dose-response fashion (per 1 ppb), and that cough increased with general odor perception. Pulmonary function (PEF and FEV_1) was only weakly associated with odor and pollutant levels (not limited to H_2S). A study limitation acknowledged by the authors is the low quality of lung function data.

- Kilburn (2012), discussed previously (Section 2.3.2.3), found significant differences between exposed and (local) control populations for 18 of 35 symptoms, including chest tightness, palpitations, shortness of breath, dry cough, and several pulmonary function measures (FVC, FEV_1).

2.3.4.4 Studies near other industries: Health effects of H_2S exposures have been examined in industrial settings other than CAFOs.

- Logue et al. (2001), a community-based study detailed above (Section 2.3.1.4), found no association between H_2S and respiratory effects among children attending an elementary school near a composting facility.
- Lewis et al. (2003) examined mortality and morbidity associated with H_2S among 25,292 petroleum workers in Canada in an inception cohort from 1964 onwards. A job-exposure matrix (JEM) estimated cumulative lifetime occupational exposure, which were validated using workplace measures. The median annual H_2S exposure was 0.07 ppm, the IQR was 0.01 – 0.60 ppm, and the 95^{th} percentile is 4.76 ppm. The study included estimates of possible exposure to cigarette smoke, hydrocarbons (solvents, fuels and lubricants), coke and catalysts. No association was found between H_2S exposure and respiratory disease. (Results for additional endpoints (cancer, neurobehavior) are discussed elsewhere (Sections 2.3.6.2 and 2.3.6.3)
- Mirabelli and Wing (2006) found that residential proximity within 10 miles to four pulp and paper mills in North Carolina, U.S. was weakly associated with elevated prevalence of daytime wheezing among students who reported using cigarettes or experiencing second-hand cigarette smoke exposure. The association is based on questionnaires provided by over 64,000 children attending public schools. Although associations attained marginal significance and exposures were not quantified, the study suggests the importance of considering interactions between environmental exposures and personal or household exposures, and possibly that children exposed to cigarette smoke may represent a particularly vulnerable population.
- Lee et al. (2007), discussed previously (Section 2.3.1.4), found that workers exposed to H_2S had higher risks of respiratory symptoms including dry cough, cough with phlegm, wheeze, chest tightness, and breathlessness.
- Al-Batanony and El-Shafie (2011) analyzed effects of sulf-hemoglobin, used as a biomarker of H_2S exposure, in 43 workers at a wastewater treatment plant (exposed) and 43 unexposed workers in Egypt. Respiratory symptoms and cardiovascular functioning were assessed using self-reported data and clinical tests. Sulf-hemoglobin levels were significantly higher among the exposed than unexposed workers (0.41±0.13% vs. 0.08±0.02%, $p<0.001$). No findings linking H_2S exposure and respiratory function were reported. (Results for cardiovascular effects are discussed in the following section.) This is the only study reviewed that used sulf-hemoglobin as an exposure biomarker, however, the characteristics of this biomarker were not well defined.

- Heldal et al. (2019) examined the respiratory function of 148 mostly male wastewater workers (121 exposed; 47 unexposed) using an exposure index derived from personal sampling that reflected the number and duration of H_2S peaks above 0.1, 1, 5 and 10 ppm (Austigard et al. 2018). Airway symptoms were significantly higher in H_2S-exposed workers than unexposed workers, however, H_2S was not associated with FEV_1 or FVC. No interactions were seen between H_2S and endotoxin, a common co-exposure. Nausea and fever were not significantly associated with H_2S.

2.3.4.5 Summary of respiratory and allergic effects: Most of the controlled studies examining acute H_2S exposures are older studies that remain important in the regulatory context. Using 30-min exposures and H_2S concentrations from 2 to 5 ppm, these studies show changes in several indicators of respiratory function in both healthy and (mild-to-moderate) asthmatic adults (Bhambhani et al. 1996; Bhambhani and Singh 1991; Jappinen et al. 1990). The only newer controlled study is Schiffman et al. (2005), who used 1-hr exposures of dilute swine confinement with H_2S at a concentration of 0.024 ppm to show increase prevalence of headache, eye irritation and nausea, but no significant effects on vital signs, lung function, nasal inflammation, salivary IgA, mood, attention or memory were found.

The recent epidemiological studies have examined chronic exposure near volcanic areas, CAFOs, and industrial sources, often extending on older studies. Community studies around geothermal and volcanic emission sources in Iceland, the Azores, Tuscany, and New Zealand tend to show higher prevalence rates of respiratory symptoms and disease. Carlsen et al. (2012), the strongest of these studies, found exacerbation of asthma at H_2S concentrations of 0.0067 ppm; Durand and Wilson (2006) and Amaral and Rodrigues (2007) showed greatly elevated risks of a range of respiratory symptoms and disease; while Nuvolone et al. (2019), Bates et al. (2013) and Finnbjornsdottir et al. (2016) found weak or contradictory associations. A number of new studies examined CAFOs and similar sources, adding to some 70 earlier studies that examined these sources. These show many common impacts, including sore throat, cough, nasal irritation, difficulty of breathing, chest tightness, wheezing, increased asthma prevalence and/or aggravation, lung function decrements, and other impacts. Many of these studies use distance from emission facilities as a proxy for exposure, and the role of H_2S cannot be isolated in most of the studies (Sections 2.4.3.4 and 2.4.3.5). Two studies are notable for their rigor and methodological contributions: Campagna et al. (2004) found statistically significant though small increases in unscheduled hospital visits for asthma aggravation and respiratory disease at 30-min H_2S concentrations above 0.03 ppm; Schinasi et al. (2011) found a dose-response relationship between breathing difficulty and cough with odor and H_2S at mean levels of 0.0003 ppm.

In addition, the recent epidemiology literature has suggested populations that are susceptible to chronic low level H_2S exposure: Campagna et al. (2004) identified that individuals with asthma are more susceptible to respiratory disease aggravation; Eduard et al. (2009) found that farmers with atopy are more susceptible to increased prevalence of COPD; and Mirabelli et al. (2006a) remarks that children using cigarettes or experiencing second hand tobacco smoke are susceptible to increased prevalence of wheeze with H_2S exposure. Such

results are unsurprising given the increased sensitivity of individuals with asthma and/or allergies to odors and respiratory irritants (EPA 2017).

The community and occupational studies hint that industrial emission sources such as wastewater facilities may affect respiratory health (Lee et al. 2007), although evidence is severely lacking and scattered across many industries.

2.3.5 Cardiovascular and metabolic effects—Over the past several years, many studies have investigated the effects of H_2S on the cardiovascular system using animal models. In large part, this is motivated by the therapeutic potential of H_2S, which has been considered a "hot" new signaling molecule that seemingly affects all organ systems and biological processes, as discussed in several recent reviews (Olson 2011; Qu et al. 2008; Varaksin and Puschina 2011). On systemic blood vessels and other organ systems, H_2S can have a vasodilatory effects via signaling and other mechanisms, although mechanisms remain unclear and may involve interactions between H_2S, NO and CO. The cited reviews discuss multiple metabolic mechanisms and effects. For example, male mice exposed to H_2S at 80 ppm for 6 hr showed marked but reversible cardiovascular abnormalities, including bradycardia (50% reduction in heart rate and irregular heart rate), lower cardiac output, lower core body temperature, lower respiratory rate, and reduced spontaneous physical activity, possibly due to inhibitory effects of H_2S on metabolism, among other reasons (Volpato et al. 2008). ACGIH (2001) discusses metabolic changes in people exposed to H_2S at 20 ppm and above (Blackstone et al. 2005), and similar studies and potential applications are discussed by Aslami et al. (2009). Because studies are animal-based, typically use high concentrations, and are not intended to address concerns related to community exposures and public health, they are not further discussed in this report. The following summarizes epidemiological studies that have investigated cardiovascular effects of H_2S at low concentrations in community and occupational settings.

- An occupational study by Al-Batanony and El-Shafie (2011), detailed previously (Section 2.3.4.4), assessed the relationship between sulf-hemoglobin, which they used as a biomarker for H_2S exposure, and cardiovascular functioning. Overall, workers with higher exposure (higher percent sulf-hemoglobin) were more likely to have heart problems but the sample size was very small (n = 12) and no additional statistical tests were conducted.
- A previously-described study (Section 2.3.4.2) by (Finnbjornsdottir et al. 2016) assessed the relationship between ambient H_2S and risk of emergency hospital visits due to heart disease and stroke. H_2S concentrations exceeding 0.005 ppm (7 $\mu g/m^3$) were associated with a slight increase in same-day emergency hospital visits with heart disease as the primary diagnosis. This association with heart disease was higher among males and among those 73 years and older. Associations were weaker when analyzing H_2S measurements from days prior to hospital admittance. H_2S was not associated with stroke.
- A community-based study by Nuvolone et al. (2019), described previously (Section 2.3.4.2), concluded that a 0.005 ppm (7 $\mu g/m^3$) increase in H_2S was associated with an increased risk of hospitalizations for heart failure and vein/

lymphatic disease, but also a lower risk of ischemic heart disease mortality. Other effects were suggested with weaker associations.

2.3.5.1 Studies regarding livestock rearing systems.: Livestock rearing systems have been studied in relation to various health effects, as discussed earlier. Only one study by Kilburn (2012) has evaluated possible cardiovascular effects associated with proximity to CAFO facilities. Kilburn (2012), described in Section 2.3.2.3, found significant differences between exposed and control populations for 18 of 35 symptoms, including chest tightness and palpitations.

2.3.5.2 Summary of cardiovascular and metabolic effects.: Epidemiological studies of cardiovascular effects are inconclusive, suggesting both weak positive and negative associations with outcomes such as ischemic heart disease mortality, acute myocardial infarction mortality, and vein or lymphatic disease hospitalization among others. The studies assessing additional cardiovascular outcomes generally found no significant effects.

2.3.6 Neurological and neurobehavioral effects—In animals, chronic medium level H_2S exposure (6.7 ppm) has been shown to adversely affect myelination of the central nervous system (Solnyshkova 2003; Solnyshkova and Shakhlamov 2002). Earlier human studies of low-to-medium level exposures suggested many neurological/neurobehavioral symptoms, e.g., memory defects, lack of concentration, depression, and other cognitive and sensory defects. These studies have highlighted a lack of understanding regarding H_2S toxicity and the pathophysiological mechanisms affecting brain function, and they reinforce the need for larger and better controlled studies (ATSDR 2006; Fiedler et al. 2008; Hirsch 2002). Many of these studies can be criticized given the general lack of objective measures of cognitive performance, imprecise and highly variable exposure estimates, and the mixture of pollutants involved in most cases. Exceptions are the controlled study by Fiedler et al. (2008), a community study by Inserra et al. (2004), and the newer studies by Kilburn (1999, 2012); Kilburn and Warshaw (1995).

2.3.6.1 Controlled studies: Two recent controlled studies examined neurological and neurobehavioral effects:

- Schiffman et al. (2005), previously described (Section 2.3.1.3), positively associated H_2S exposure with the prevalence of headache and nausea; associations were not found with mood, memory, or attention.
- Fiedler et al. (2008) exposed 74 adults to concentrations of 0.05, 0.5 and 5 ppm H_2S in 2-hour periods over three consecutive weeks; the subjects completed ratings and tests before and during the final hour. The subjects were relatively young (mean of 24.7 ± 4.2 years of age), highly educated (16.5 ± 2.4 years), and healthy. A broad set of symptoms were investigated, and included physical (headache, fatigue, lightheaded, drowsy, nausea), cognitive (difficulty concentrating, disoriented/confused, dizzy), eye irritation (burning, dryness, itching, runny/watery eyes), anxiety (feel jittery in body, feel nervous, heart palpitations, feel tense, worried), upper respiratory (sneeze, nasal congestion, choking, throat irritation, nose irritation), lower respiratory (shortness of breath,

wheezy, chest tightening, chest pain, coughing, somatic control (skin irritation or dryness, stomach ache, numbness, ear ringing, leg cramps, back pain, sweating, body aches), environmental quality (light intensity, ventilation, air movement, air quality, noise level, room temperature, humidity, odor level), and odor ratings (irritation, intensity, pleasantness). Dose–response relationships were observed for odor intensity, irritation and unpleasantness, but not for sensory or cognitive measures. While the total symptom severity was not significantly elevated for any exposure condition, anxiety symptoms significantly increased at 5 ppm compared to 0.05-ppm; verbal learning was also affected. The authors concluded that while exposure increased several symptoms, the magnitude of the changes was relatively minor, and that increased anxiety was due to irritation associated with odor. They also noted the need for further investigation to confirm effects on verbal learning, which could represent a threshold effect of H_2S, fatigue, or some other factor, and issues in generalizing results to communities or workers who are chronically exposed with a range of health conditions and ages.

2.3.6.2 Occupational studies: A number of occupational studies have investigated neurological endpoints associated with mostly acute H_2S exposures above 10 ppm. Headaches have been associated with acute (30 – 60 min) and high (240 – 500 ppm) H_2S exposures, followed by neuropsychiatric clinical disorders, unconsciousness, and respiratory failure (Hirsch 2002; Kilburn 1993; Sjaastad and Bakketeig 2006). In a survey of residents of Vågå, Norway, Sjaastad and Bakketeig (2006) found 2 cases of “hydrogen sulphide headaches” among 1,838 WWTP workers exposed to at least 100 ppm, but no individuals in the (mostly soapstone) mining industry reported such headaches. Kangas et al. (1984) reported headaches at 20 ppm. More commonly, headaches are reported following acute exposures at concentrations of 300 – 500 ppm (Sjaastad and Bakketeig 2006). In addition to headaches, earlier studies have investigated neurobehavioral function among acutely exposed workers (n = 16) in several industries in Texas, Louisiana, and elsewhere, among residents living downwind of oil fields in Kentucky and Texas (Kilburn 1997), and among highly exposed individuals (n = 19) in several states and Canada (Kilburn 2003).

The following studies have examined chronic, low-level exposure in occupational settings.

- Kilburn and Warshaw (1995) found that H_2S-exposed workers (n = 13) at and residents (n = 22) living near an oil refinery in California, U.S. had different neurophysiological outcomes (e.g., reaction time, balance, color discrimination, digit symbol, immediate recall) and mood state scores than controls, which consisted of residents drawn randomly from towns free of known contamination (N=359). H_2S exposures averaged 0.01 ppm (1-week average) and peaks reached 0.1 ppm at neighboring homes and 8.8 ppm (24-hr average) at the refinery. Other pollutants measured included carbonyl sulfide (2.6 – 52.1 ppm) and mercaptans (1 – 21.1 ppm; 24-hr averages). Workers and exposed residents were combined into one “exposed” group, which increased power but reduced the exposure contrast and precluded the opportunity to observe a potential dose-response relationship. The petroleum refinery, which included coking units and a desulfurization plant, likely emitted a number of pollutants in addition to H_2S,

e.g., mercaptans, carbonyl sulfide, combustion-related gases, particulate matter, and VOCs, that were not characterized in this early study.

- Lewis et al. (2003), described earlier (Section 2.3.4.4), examined the relationship between H_2S exposure and potentially neurological-related outcomes, including accidental falls and transportation accidents. For workers exposed to a (median) lifetime H_2S concentration of 0.07 ppm (IQR: 0.01 – 0.60 ppm), males showed no association between H_2S and neurological-related mortality or death due to accidental falls, but a slight positive association was shown for mortality due to transportation accidents when comparing upper and lower exposure tertiles (≥1.5 versus <0.1 ppm-years). The median cumulative concentration was 0.17 ppm after adjustments for employment duration (average 8.8 years). This study has a small sample size (n = 15) and lacks a dose-response relationship. More recent assessments note that individuals with underlying neurological conditions or temporary impairment to motor functioning, cognition, or vision may be at greater risk to adverse neurological outcomes from H_2S exposure (Lococo et al. 2018; WHO 2018).
- In the study of 175 WWTP and WTP workers in Iowa, U.S. discussed earlier (Section 2.3.1.4), workers with H_2S exposure had higher prevalence of neurological symptoms (headache, dizziness, memory or concentration difficulties, tiredness), and higher rates of depression (Lee et al. 2007).
- In Egypt, H_2S exposure was associated with cognitive impairment among sewer maintenance workers (n = 33) compared to an unexposed group (n = 30) matched for age, education and socio-economic status (Farahat and Kishk 2010). H_2S levels measured in and around manhole openings ranged from 9 to 11 ppm (12 – 15 mg/m^3) and 5 to 7 ppm (7 – 9 mg/m^3), respectively. The exposed group had higher rates of non-specific neurological symptoms (headache, memory defects, lack of concentration), prolonged reaction time, delayed P300 latency, and poorer performance on most neuropsychological tests. As noted earlier, a H_2S biomarker of exposure, urinary thiosulfate, was elevated among exposed workers, although no quantitative relationship was found between this marker, H_2S exposure, and neurological outcomes. Possibly the most significant outcome was delayed P300 latency, suggesting slowing of cognitive function, in contrast to the non-specific symptoms (Guidotti 2010). The authors noted that sewer workers are exposed to multiple chemical and biological hazards, as well as occasionally high levels of H_2S, although levels are normally low during routine work, and that their results are generally supported by other studies of sewer workers, e.g., in Sweden (Thorn et al. 2002).

2.3.6.3 Community studies: Neurological symptoms and outcomes in community settings were examined in a number of older studies, mostly using self-reported questionnaires. For example, Partti-Pellinen et al. (1996) used a cross-sectional design and a self-administered questionnaire to examine central nervous system symptoms (as well as eye irritation and respiratory-tract symptoms) in adults (n=336) living near a pulp mill and an unpolluted reference community (n = 380) in South Karelia, Finland. In the exposed community, TRS

levels averaged approximately 0.001 – 0.002 ppm (2 – 3 μg/m^3) and 24-hr levels ranged from 0 to 0.038 ppm (0 – 56 μg/m^3) and SO_2 averaged 1 μg/m^3 and 24-hr levels ranged from 0 – 24 μg/m^3; TRS levels were below 0.0007 ppm (1 μg/m^3) in the reference community. An elevated risk of headache was found in the exposed community for the prior 4 week and 12 month periods. (Risk of cough also increased for the preceding 12-month period.)

The newer studies examining neurological outcomes in community settings are diverse.

- Portions of Khozestan Province, Iran experience leakage of natural "sour gas" that contains up to 40% H_2S. Saadat et al. (2006) evaluated exposed (n = 64) and unexposed adults (n = 64) matched by sex, age, and educational levels for depression and hopelessness using Beck's depression inventory (BDI) and Beck's hopelessness (BHS) questionnaires. Airborne reactive sulfur compounds in the exposed areas are reported as 0.023 ± 0.002 ppm of SO_2 equivalents; unfortunately this metric is difficult to interpret. Exposed individuals had elevated risk of depression and hopelessness, supporting earlier findings of increased rates of suicide attempts and suicide in the same area (Saadat et al. 2004).
- Kilburn et al. (2010) contrasted neurotoxic effects among 49 adults in three towns located in sour gas/oil areas in New Mexico and 42 unexposed adults in Arizona, U.S. H_2S exposures occurred resulted due to emissions from several oil refineries, a gas desulphurization facility, and a WWTP. Short-term (grab) samples showed 2 – 74 ppm at the WWTP and H_2S odors were detected at the other sites; few other measurements were available. An earlier study in this area showed daily H_2S levels from 0 to 0.014 ppm (0 – 14 ppb) (Dubyk and Mustafa 2002). H_2S exposure was associated with higher rates of neurological and cognitive dysfunction (e.g., vocabulary, short- but not long-term recall memory, attention/coordination), neurophysiological indicators (e.g., reaction time, balance, hearing, grip strength), and mood state (e.g., tension, vigor, anger, confusion, fatigue). Findings for the three exposure groups were consistent for impairment of neurobehavioral function, mood disturbance, and increased frequencies of irritative, indigestion, respiratory, mood, sleep, balance, memory and limbic system symptoms. Study limitations include a small sample, the likelihood of both acute and chronic exposures in each town (due to episodic releases associated with malfunctions at the WWTP), and the lack of exposure data.
- Reed et al. (2014) examined cognitive function among adults in Rotorua City, New Zealand exposed to H_2S, using the same study population and design as Bates et al. (2013). No effect was seen for visual and verbal episodic memory, attention, fine motor skills, psychomotor speed, or mood.
- Finnbjornsdottir et al. (2016), described earlier, found no association between ambient H_2S at concentrations up to 0.047 ppm (69.5 μg/m^3; IQR: 0 – 0.003 ppm) in the Reykjavik capital area and the risk of emergency hospital visits due to stroke.

- In Rotorua City, New Zealand, Pope et al. (2017) examined peripheral nerve function using the same study design and almost-identical study population (n = 1,635) as Reed et al. (2014) and Bates et al. (2013). H_2S concentrations ranged from 0 to 57.9 ppb (IQR: 5.6 – 18.4 ppb). Peripheral nerve function was not associated with H_2S.
- In the community-based study by Nuvolone et al. (2019), discussed earlier, a 0.005 ppm (7 μg/m^3) increase in H_2S was associated with an increased risk of hospitalizations for peripheral nervous system, as well of suggestions of additional effects. They did not account for the problem of multiple testing, which may have led to spurious findings.

2.3.6.4 Community studies of livestock rearing systems: Recent studies examining neurological and neurobehavioral effects potentially associated with exposures due to livestock rearing systems are discussed below.

- Bullers (2005), described previously (Section 2.3.1.3), found an association between residential proximity to hog farms and 12 of 22 self-reported symptoms including nausea.
- In Dakota City, Nebraska, U.S., Inserra et al. (2004) used computer-assisted standardized neurobehavioral tests to investigate differences among residents (n = 171; ≥16 years of age) living in an area with repeated H_2S exposure due to emissions from a beef slaughter/leather tanning facility and wastewater lagoon and a reference population (n = 164) with comparable demographic characteristics and health conditions. An exposure map was generated using the monthly highest 1-hr H_2S concentration measured at 14 residential locations, which was then classified into exposed (≥0.09 ppm) and comparison (<0.05 ppm) areas (Inserra et al. 2002); these classifications were consistent with odor complaints. A battery of 14 tests was administered to study participants that addressed sensory (vision, vibration, grip strength, fatigue), affect (health and physical functioning), cognitive (complex function, memory, attention), and motor (response speed, coordination) domains. H_2S exposure was associated with sensory function (increased vibration sensitivity), motor skills (lower hand grip strength), cognitive (memory) function (match to sample score, and 8-s delay test of match to sample). Of the 28 neurobehavioral tests, 21 showed no adverse relationship with residence area (the H_2S exposure surrogate), after adjustment for potential confounders. Overall, the authors concluded the two groups showed similar or only marginal differences. This study's strengths include the use of standardized tests (potentially reducing measurement error), standardized protocols (reducing interviewer bias), random sampling of participants (reducing selection bias), and standardized protocols including "blinded" examiners (reducing interviewer bias); its limitations include the possibility of exposure misclassification, uncontrolled occupational exposures, and modest participation rate (<75%).

- Horton et al. (2009), described earlier (Section 2.3.1.3), associated CAFO emissions (malodor, H_2S concentrations, and semi-volatile PM_{10} concentrations) with stress and negative mood states, e.g., being stressed or annoyed, nervous or anxious, gloomy and angry). In this study, participants spent 10 min outdoors before returning indoors to complete surveys; these assessments were made repeatedly. The study obtained objective measurements of pollutants including H_2S, which averaged from 0.00001 to 0.0015 ppm (0.01 to 1.5 ppb) and ranged to 0.09 ppm (90 ppb) (averaging time not specified). The contemporaneous and subjective assessment of both exposure and outcome is susceptible to response enhancement bias that can increase reports of symptoms since respondents are aware of and potentially sensitized to their exposure (Farahat and Kishk 2010), however, this potential bias should not affect associations with H_2S.
- A cross-sectional Canadian study, discussed previously (Section 2.3.4.3), found a higher prevalence of depression (18.2%) among people who lived within 3 km of farms relative to those who lived more than 9 km distant (8.0%; Villeneuve et al. 2009). Individuals living near farms were more likely to worry about environmental issues (water quality, outdoor and indoor smells, air pollution) and had lower health-related quality of life scores. No associations were observed with migraines. This study's strengths included a relatively large sample and the use of a standardized instrument; limitations were modest participation rates, differences in socioeconomic characteristics among the groups, and the lack of direct exposure measures.
- Kilburn (2012), detailed previously (Section 2.3.2.3), found significant differences between exposed and control populations for 18 of 35 symptoms, including headaches, dizziness, and lightheadedness.

2.3.6.5 Summary of neurological and neurobehavioral effects: Memory and learning impairment lead complaints that are associated with H_2S exposure (Partlo et al. 2001), although a broader set of persistent neurological effects (e.g., headaches, poor concentration ability and attention span, impaired short-term memory, and impaired motor function) have been reported in persons recovering from H_2S-induced unconsciousness resulting from very high concentration exposure (ATSDR 2006). Animal studies have demonstrated effects on brain function, e.g., rats exposed to 125 ppm for 4 hours/day, 5 days/week for 5 consecutive weeks showed impaired performance and learning of spatial tasks (Partlo et al. 2001), findings stated to have relevance for humans (Woodall et al. 2005). Other animal studies with H_2S inhalation exposure suggest decreased motor activity and task response rates from which a LOAEL of 80 ppm for 3 hr/day for 5 days has been derived (ATSDR 2006). Biochemical changes include decreased brain stem total lipids and phospholipids shown in guinea pigs exposed to 20 ppm H_2S for 1 hr/day for 11 days (Haider et al. 1980), and harmful CNS myelination after chronic exposure to 6.7 ppm (Solnyshkova 2003; Solnyshkova and Shakhlamov 2002). Still, the NOAEL for impaired performance in rats remains 100 ppm for 2 hr (Elovaara et al. 1978). No new animal studies on learning relevant to this review were identified.

We identified two recent controlled studies of humans. Schiffman et al. (2005) used 1-hr exposures of dilute swine confinement with H_2S at 0.024 ppm and showed increased prevalence of headaches, eye irritation, and nausea. Fiedler et al. (2008) used 2-hr exposures of H_2S alone at 0.05, 0.5 and 5 ppm and found dose–response relationships for odor intensity, irritation and unpleasantness; compromised verbal learning was shown without a dose-response relationship. A small and older controlled study reported headaches among 3 of 10 asthmatics exposed to 2 ppm H_2S for 30 min (Jappinen et al. 1990). Additional neurobehavioral effects in humans and animals include alterations in balance, reaction time, visual field, and verbal recall, with effect severity depending on exposure duration and concentration (ATSDR 2006). While the few controlled human studies have shown odor, irritation and nuisance symptoms, e.g., irritation and headache, neurological or neurobehavioral affects have not been observed. However, many of the studies examined a single acute exposure event with a small number of healthy individuals, and the ability to capture subtle neurological impairments may be limited (EPA 2011). Additionally, these studies may not be generalizable to other populations, e.g., communities and workers experiencing chronic exposure, or individuals that have greater susceptibility due to their health conditions and age (Fiedler et al. 2008).

The observational studies, both occupational and environmental, complement the controlled studies, but can be challenging to evaluate and synthesize. In comparison to community conditions, both the controlled and occupational epidemiological studies tend to reflect higher concentrations, as do the case reports. Further, all of the observational studies have significant limitations in their exposure assessments that preclude an understanding of potential dose-response relationships pertinent to neurological and neurobehavioral outcomes. As has been noted (and see Sections 2.4.3.4 and 2.4.3.5), other pollutants often accompany H_2S in community and occupational settings, and isolating effects of H_2S in a mixture can be challenging. In addition, objective evaluation of many neurological and neurobehavioral outcomes can be difficult for due to their linkage to educational attainment and other factors, the potential of measurement bias, the likely wide range of sensitivity among individuals, the influence of psychological responses to odor, irritation and nuisance perceptions accompanying H_2S exposure (e.g., headache and nausea), and the flight response, though such biases in outcome ascertainments can be controlled using blinded assessments, objective tests, and other means. Additional issues in cross-sectional studies include generally modest sample sizes, the comparability of groups, and adequate control of potential covariates and confounders. Several of the newer epidemiological studies, which tend to better address these issues, highlight behavioral and neurological effects at low but chronic exposure, and often report similar outcomes as earlier studies. The older studies show, for example: persistent cognitive impairment (reaction time delay, neurological and neurobehavioral deficits) in individuals acutely exposed to high but unknown concentrations of H_2S, but unremarkable neurological and physical examinations (Wasch et al. 1989); reduced perceptual motor speed, impaired verbal recall and remote memory, visual field performance decrements, and abnormal mood status was found in subjects (n = 16) referred for evaluation of effects of reduced sulfur gas exposure compared to referents (n = 353; Kilburn 1997); differences in neurophysiological outcomes (reaction time; balance, color discrimination, digit symbol, immediate recall) and mood state scores

(Kilburn and Warshaw 1995); and some memory impairment (Kilburn 1999). Among the newer studies, Nuvolone et al. (2019) assessed a variety of neurological-related mortality and hospitalization diagnoses, but a dose-response effect was seen only for peripheral nervous system hospitalizations (per 0.0047 ppm increase in ambient H_2S); and Legator et al. (2001) reported elevated risks of self-reported central nervous symptoms (e.g., fatigue, headache, and difficulty sleeping) in Odessa, Texas (n = 126) and Puna, Hawaii (n = 97), two communities with H_2S levels averaging from 0.007 to 0.027 ppm, compared to reference communities (n = 170); short-term H_2S levels (1–8 hr averages) were reported to reach 0.5 ppm. The effects observed in these and the other newer studies examining workplace and community populations are not well understood mechanistically, and some of the past literature has been criticized (Guidotti 2010).

Sixteen new observational studies evaluated a range of neurological and neurobehavioral effects among workers and communities in geothermally active regions or around CAFOs, sewer, oil and gas facilities. Three of these studies had negative findings for visual and verbal episodic memory, attention, fine motor skills, psychomotor speed, mood, peripheral nerve function, or stroke (Finnbjornsdottir et al. 2016; Pope et al. 2017; Reed et al. 2014); each of these studies employed spatially modeled estimates of ambient H_2S exposure. A study using universal kriging to estimate residential exposure positively associated H_2S and some neurological outcomes (Inserra et al. 2004). The dozen other studies with positive associations used a variety of designs and instruments, and showed a degree of agreement with respect to non-specific neurological symptoms (headache, memory defects, memory or concentration difficulties (Farahat and Kishk 2010; Inserra et al. 2004; Kilburn 2012; Kilburn et al. 2010; Lee et al. 2007; Partti-Pellinen et al. 1996), more objective neurophysiologic outcomes (e.g., peripheral sensation and discrimination; Inserra et al. 2004; Kilburn 2012; Kilburn and Warshaw 1995; Nuvolone et al. 2019), affect (Fiedler et al. 2008; Kilburn et al. 2010), and mood states or feelings of stress, hopelessness or depression (Bullers 2005; Horton et al. 2009; Kilburn et al. 2010; Kilburn and Warshaw 1995; Lee et al. 2007; Saadat et al. 2006; Villeneuve et al. 2009). The relatively few studies with robust H_2S measures more commonly associated non-specific neurological symptoms and mood states than objective neurophysiologic outcomes (Farahat and Kishk 2010; Inserra et al. 2004; Kilburn et al. 2010; Kilburn and Warshaw 1995; Nuvolone et al. 2019; Partti-Pellinen et al. 1996). Finally, several community studies indicated health-related quality of life impacts on populations living within ~3.6 km (2 miles) of large-scale farming operations (e.g., Horton et al. 2009; Villeneuve et al. 2009), a finding which diverges from (short-term) controlled studies that show only irritation and anxiety (e.g., Fiedler et al. 2008). Full explanations for the dichotomy between controlled and observational studies, the identification of specific and plausible neurological and neurobehavioral mechanisms at play, and the dose-response relationships involved, all remain unresolved.

2.3.7 Reproductive and developmental effects—No new reproductive or developmental studies were identified. The existing literature is summarized here.

- Several animal studies found harmful neurodevelopmental effects from chronic H_2S exposure at the following concentrations: 75 ppm (Hayden et al. 1990); 20 and 50 ppm (Roth et al. 1997; Skrajny et al. 1992); 25 and 75 ppm (Skrajny et

al. 1992). All of these concentrations exceed 10 ppm, our cutoff for low-level exposure.

- ATSDR's (2006) review notes that only limited human data links maternal or paternal exposure to H_2S to an increased risk of spontaneous abortion among rayon textile, paper mill, or petrochemical workers (or spouses), although other hazardous chemicals present in these occupations may have contributed to the increased risk. The reproductive performance of rats exposed to between 10 and 80 ppm H_2S for an intermediate duration was unaffected, and the available animal data suggest that H_2S is not a developmental toxicant at concentrations below 80 ppm. ATSDR (2006) concludes that no structural anomalies, developmental delays, performance in developmental neurobehavioral tests, or impacts in brain histology were observed in a well-conducted rat study, and that while alterations in Purkinje cell (large neurons in the brain) growth was noted in offspring of rats exposed to 20 or 50 ppm H_2S during gestation and lactation periods, the significance of this finding given unaltered neurobehavioral performance is unknown (ATSDR 2006).
- California's OEHHA (2008) review highlights Xu et al. (1998), a retrospective study examining spontaneous abortion among never-smoking married women (n = 2,853), 20 to 44 years of age who reported at least one pregnancy during employment at a large petrochemical complex in Beijing, China. Based on employment records, most (57%) workers had occupational exposure to petrochemicals during their first trimester. Comparisons within and across plants showed that frequent exposure to petrochemicals greatly increased the risk of spontaneous abortion. Similarly, increased risk of spontaneous abortion was found for the 106 women exposed to only H_2S; unfortunately, this study did not report concentrations. Exposures at refineries can involve many pollutants, and this study is atypical given the stated exposure conditions.
- Finally, a review of occupational, environmental and lifestyle factors associated with spontaneous abortion (Kumar 2011) discusses several additional studies, including an older Russian study examining effects of H_2S exposure on menstrual function and the estrous cycle (Vasiljeva 1973).

2.3.7.1 Summary of reproductive and developmental effects.: Animal studies examining exposures above 10 ppm have not shown reproductive or developmental toxicity. Of the few human studies, several suggest that maternal or paternal exposure to H_2S is associated with an increased risk of spontaneous abortion (ATSDR 2006; Xu et al. 1998), however, these studies likely are confounded by simultaneous exposures to multiple pollutants.

2.3.8 Carcinogenic effects—Inhalational exposure of H_2S has not been consistently shown to cause cancer in humans, and its ability to cause cancer in animals has not been studied. For these reasons, H_2S has not been classified in relation to cancer (ATSDR 2006). While clinical studies have linked sulfate-reducing bacteria or H_2S in the colon with chronic disorders, e.g., ulcerative colitis and colorectal cancer, evidence remains circumstantial

and underlying mechanisms undefined (Attene-Ramos et al. 2007). Several recent studies have evaluated potential carcinogenic effects of low-dose H_2S exposure in community and occupational settings, including those reviewed by Bustaffa et al. (2020):

- Lewis et al. (2003), described earlier in Section 2.3.4.4, found no evidence of increased risk of cancer with occupational exposure.
- Kristbjornsdottir and Rafnsson (2012) examined cancer incidence among 74,806 Icelandic children and adults, contrasting rates among individuals living in geothermal and non-geothermal areas. Residing in a high temperature geothermal location was positively associated with increased risk of cancers (both individual cancer types and overall cancer risk); the greatest risks were found for pancreatic cancer followed by non-Hodgkin's lymphoma. The analysis stratified by age groups to control for possible biases, however full results were not reported and H_2S was not measured, and thus the use of residence location may have resulted in exposure measurement error and confounding, particularly with radon.
- A community-based study in Italy by Nuvolone et al. (2019), described earlier in Section 2.3.4.2, found that a 0.005 ppm (7 μg/m^3) increase in H_2S was associated with slightly reduced risk of malignant neoplasm mortality. The protective dose-response relationship was minimally significant and the analysis did not account for multiple testing.

2.3.8.1 Summary of carcinogenic effects.: Two of the three recent studies that examined cancer found some effect on the incidence of some cancers with H_2S exposure, but each study had methodological weaknesses, including a lack of direct exposure measurements. The finding by Nuvolone et al. (2019) of a protective association between H_2S and neoplasm(s) is likely spurious. The strong positive associations with risks of pancreatic cancer, breast cancer, basal cell carcinoma, and non-Hodgkin's lymphoma found by Kristbjornsdottir and Rafnsson (2012) might be explained by factors other than H_2S. Overall, the literature on carcinogenic effects of H_2S is inconclusive.

2.3.9 Immunological effects

- A review by Heederik et al. (2007) notes the limited evidence regarding changes in immunoglobulin A responses in individuals that have been associated with odor, which might result from psychophysiological changes related to stress and sensitization.
- Heldal et al. (2019), described earlier, investigated effects of H_2S (and other wastewater workplace-related exposures) on inflammatory reactive markers (C-reactive protein; CRP), surfactant protein D (SpD), club cell protein 16 (CC16), interleukin 8 (IL-8), intercellular adhesion molecule 1 (ICAM-1), and macrophage inflammatory protein (MIP)-1alpha. The H_2S exposure index was negatively associated with the level of ICAM-1, but not with CPR, SpD, CC16, IL-8, or MIP-1alpha.

2.3.9.1 Studies regarding livestock rearing systems.: Earlier sections of this review have discussed a variety of health endpoints associated with livestock rearing systems; here we focus on immune effects.

- Avery et al. (2004) investigated CAFO exposures and immune function suppression using secretory immunoglobulin A (sIgA) measurements obtained twice daily for 14 days from 15 adults living within 2.4 km of hog farming operations in North Carolina, USA, along with odor intensity perceptions. The longitudinal analysis suggested that odor intensity was associated with a decline in sIgA, although the association was not statistically significant and sIgA levels stayed within the normal range. The authors noted that salivary glands are largely under autonomic central nervous system control, are part of "stress" circuits and centers for homeostatic regulation, and that sIgA forms a response to invading microorganisms at mucosal surfaces. Like most of the CAFO studies, exposure to co-pollutants (especially endotoxin) can confound results. Additionally, H_2S levels were not measured.
- Schiffman et al. (2005), described previously (Section 2.3.1.3), found no association between H_2S and salivary IgA.

3.3.9.2 Summary of immunological effects.: Very few studies have examined immune effects of low-level H_2S exposure. At higher exposure levels, an occupational study has associated H_2S exposure with lower ICAM-1 levels although CPR, SpD, CC16, IL-8, and MIP-1 alpha levels were unchanged (Heldal et al. 2019). Other studies have not found significant results, and are limited by a lack of H_2S measures, often using proximity or odor as an exposure proxy. Overall, the literature on the immunological impact of H_2S is inconclusive.

2.3.10 Effects on livestock—While an analysis of the literature pertaining to environmental exposures of H_2S on beef cows and other animals is beyond the scope of this report, we note several papers examining beef cattle in Alberta, Canada, a major oil and (sour) gas producing area, due to the study size (27,000 cattle in 207 herds), chronic low-level exposures, and data completeness (including exposure monitoring). The study methodology is presented by Waldner (2008a; 2008b; 2008c) and commented on by the study's Science Advisory Board co-chair (Guidotti 2009). H_2S concentrations ranged from 0.00009 to 0.00033 ppm (0.09 to 0.33 ppb) (5th to 95th percentile). Results are summarized below.

- Waldner (2008d) found that SO_2, H_2S and VOC exposures during gestation were not associated with the odds of calf treatment in the first 3 months of life, however, exposure in the first month after calving was associated with a small increase in these odds after the first month of life (typically for diarrhea, pneumonia and umbilical infections), and that the H_2S linkages were consistent with possible mechanisms.
- Bechtel et al. (2009) found that VOC exposure was associated with an increase in CD4 T lymphocytopenia in cattle, showing modulation of the immune system,

although the significance of the change is unclear. In addition, H_2S exposure was associated with an increase in rabies antibody titer; the authors noted several discrepancies and stated that it was unlikely that this exposure would increase antibody production.

- Waldner (2009) found no evidence that SO_2, H_2S and VOCs exposures affected abortions or still births in the beef herds.
- Waldner and Clark (2009) found associations between VOCs (measured as benzene) and respiratory lesions for calves older than 3 weeks, and between SO_2 and lesions during gestation.

2.4 Synthesis of the studies

2.4.1 Weight of the evidence—We start with a general "weight of the evidence" discussion to provide context and a conceptual framework for evaluating study strengths and weaknesses. Discussions pertaining to weight of the evidence are presented elsewhere (e.g., EPA 2005; OEHHA 1999), and typically involve both qualitative and qualitative assessments, a summary narrative encompassing the individual lines of evidence, and a critique often using (Austin Bradford) "Hill's Criteria." These nine well-known "criteria for causation" date from a 1965 article on smoking and include consistency of association, strength of association, dose-response, temporality, experimentation, specificity, biologic plausibility, coherence, and analogy. Key issues in the weight of evidence discussions include the following:

1. The strength of associated adverse health effect with a chemical exposure can be measured in terms of high observed effect incidence or high relative risk, statistical significance of differences between control and exposed groups, and a positive dose-response relationship.
2. The consistency of associated adverse health effect with a chemical exposure is noted by the similarity of effects found in different studies and among different populations and/or species.
3. The specificity of associated adverse health effect to an exposure strengthens the case for causality; however, it is well-recognized that such highly specific associations are rare.
4. The temporal association between the adverse health effect should occur at a time following exposure that is consistent with the nature of the effect, e.g., respiratory irritation immediately following H_2S exposure is temporally consistent, as would be tumor development that involve a latency period of months or years.
5. The coherence of the adverse health effect with the exposure reflects the scientific plausibility of the association, which is based on an understanding of the pharmacokinetics and mechanism of action.
6. Results utilizing human data are most relevant to assessing human health effects. Sources of human data, i.e., epidemiological studies, controlled exposure

experiments, and case reports, can each provide important information, but each has strengths and weaknesses.

As an example of the application of weight-of-evidence considerations, OEHHA's (1999) evaluation of acute RELs emphasized dose-response relationship, reproducibility of findings, mechanism of action, and consistency with other studies. More recent thinking for causality consolidate and refine the necessary criteria to four factors: the strength of association (including analysis of plausible confounding); temporality; plausibility (addressing articulate mediation and interaction); and experimental support (including implications of study design on exchangeability) (Shimonovich et al., 2021).

As noted earlier, while hazards and risks from high concentrations of H_2S are well known, information pertaining to low level human exposure remains relatively scarce and more difficult to interpret. In the following, we discuss key weight-of-the-evidence issues that pertain to many or most of the studies.

2.4.2 Definition and scope of adverse effects—Definitions of adverse effects vary. OEHHA (1999) cited EPA (1989) in defining adverse effects: "A biochemical change, functional impairment, or pathological lesion that either singularly or in combination adversely affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge." Thus, the perception of even an objectionable odor was not necessarily considered as an adverse health effect unless accompanied by other symptoms or signs, e.g., nausea and vomiting, or by actions or behaviors that affected quality of life. Similarly, odor complaints to city or state departments do not constitute a permit violation, although they may trigger an inspection of a facility. Because self-reports of symptoms (and exposure) can be influenced by many factors, including odor, socioeconomic status and interviewer bias (e.g., Radon et al. 2007), the general preference is to control for such factors using objective outcome measures and not to rely on symptoms, although odors may affect quality-of-life issues. Temporary and reversible impacts, including odor, also are sometimes excluded, especially in occupational settings. WHO's (1948) well-known definition of health, "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity," encompasses a broader view of adverse effects that would include odors and symptoms that might affect mental and social well-being. Inclusion of odor impacts as an adverse effect is further supported given that objectionable H_2S odors can inhibit outdoor activity of individuals, including exercise that can contribute to their well-being, as noted in several studies (Brancher et al. 2017; Heaney et al. 2011; Ulutaş et al. 2021).

Adverse effects investigated in the H_2S literature are predominantly morbidity outcomes, mostly ocular, respiratory, and neurological/neurobehavioral symptoms and disease. Only one study has examined mortality due to chronic, low-level H_2S exposure (Bates et al. 1997), and only few older studies were identified that examined immunological, reproductive or pregnancy outcomes in humans.

2.4.3 Nature and characterization of exposure—Many of the observational studies of H_2S are limited with respect to the exposure assessments, and addressing and minimizing

adverse effects of *exposure measurement error* is important to obtain credible results. These errors can result from multiple factors, e.g., the difficulty of differentiating acute from chronic exposure, estimating exposure using distance proxies or spatial models, and multi-pollutant mixtures, among other challenges. *Reporting or awareness bias*, noted earlier, also can affect self-reported exposures. Such concerns are particularly pertinent to community-based studies of livestock rearing operations and geothermal sources that use non-objective or proxy measures of H_2S exposure, often due to difficulties of collecting samples at or near emission sources, or due to a focus on generating hypotheses that might explain observations in a region known for a particular industry, e.g., hog farms in North Carolina, U.S., or geothermal plants in Tuscany, Italy. The following discusses challenges in characterizing exposure, addressing biological monitoring, duration of exposure, spatial variation, pollutant mixtures, and cumulative effects.

Measurements (or validated estimates) of H_2S concentrations are needed to develop dose-response information relevant for establishing air quality guidelines and standards, comparing results among studies, confirming exposure estimates, and other purposes. A growing number of community-based and occupational epidemiology studies have included concentration measurements. Organized by health effect investigated, objective measures of H_2S were used in studies investigating odor and sinus irritation (Heaney et al. 2011; Horton et al. 2009; Lee et al. 2007; Logue et al. 2001; Schiffman et al. 2005; Schinasi et al. 2011); ocular effects (Bates et al. 2002, 1998; Fisher 1999; Haahtela et al. 1992; Kilburn, 2012; Lee et al., 2007; Logue et al., 2001; Marttila et al., 1995, 1994; Schiffman et al., 2005; Schinasi et al. 2011); nasal lesions (Mousa 2015); respiratory health (Bates et al. 2013; Campagna et al. 2004; Carlsen et al. 2012; Durand and Wilson 2006; Eduard et al. 2009; Farahat and Kishk 2010; Finnbjornsdottir et al. 2016; Heldal et al. 2019; Kilburn 2012; Lee et al. 2007; Logue et al. 2001; Nuvolone et al. 2019; Schinasi et al. 2011); cardiovascular health (Finnbjornsdottir et al. 2016; Kilburn 2012; Nuvolone et al. 2019); neurological and neurobehavioral health (Bates et al. 2013; Dubyk and Mustafa 2002; Farahat and Kishk 2010; Horton et al. 2009; Inserra et al. 2002, 2004; Kilburn 2012; Kilburn et al. 2010; Kilburn and Warshaw 1995; Lee et al. 2007; Nuvolone et al. 2019; Partti-Pellinen et al. 1996; Pope et al. 2017; Reed et al. 2014); immune (Heldal et al. 2019; Schiffman et al. 2005); reproductive and developmental health (Vasiljeva 1973); and cancer (Nuvolone et al. 2019). Given that H_2S is found as a component of a mixture of pollutants emitted from most sources of concern, other components in the mixture that might be associated with the health effect of interest must also be characterized to avoid confounding, as described below in Section 2.4.3.4.

Studies without H_2S measurements can serve several purposes. These include: helping to confirm and extend results of other studies, e.g., showing the prevalence of health issues; evaluating the effectiveness of interventions and emission controls, e.g., documenting reduced numbers of complaints or symptoms; generating hypotheses; and providing preliminary investigations.

2.4.3.1 Biological monitoring: In an attempt to better understand the relationship between external and internal exposure, H_2S measures may be combined with biological monitoring of sulfhemoglobin or urinary thiosulfate. Several studies, noted above, lack H_2S

measurements and instead utilize biological monitoring. Depending on the circumstance, biomarkers in blood and urine may be more difficult to obtain than ambient or indoor air samples. However, if a biomarker is not specific to the compound of interest and data for potential confounding factors are not collected, the biomarker may not be useful in assessing true exposure.

Urinary thiosulfate is the most common biomarker of H_2S exposure (ATSDR 2016). Thiosulfate is produced through oxidative metabolism of H_2S. The process occurs in two steps, which may explain the delayed buildup of thiosulfate in the body following H_2S exposure (WHO 2003). Urinary thiosulfate can be used to confirm low-level exposures, although the responsiveness of this biomarker to low-level exposures may vary significantly between individuals (Durand and Weinstein 2007). H_2S can promote red blood cells (RBCs) to form sulfhemoglobin, a sulfheme protein complex (Kurzban et al. 1999; Ríos-González et al. 2014). H_2S is produced endogenously (see Section 3.10) but at levels too low to form sulfhemoglobin, while exogenous H_2S may occur at levels high enough to warrant the use of sulfhemoglobin to assess its presence in tissues and cells (Ríos-González et al. 2014). However, blood sulfhemoglobin is not specific to H_2S, and can be formed following exposure to drugs (e.g., phenacetin, dapsone, and sulfonamides) as well as other sulfur-containing agents (Gharahbaghian et al. 2009; Bhagavan 2002). If sulfhemoglobin accumulates, it can cause sulfhemoglobinemia and cyanosis, although these are rare conditions.

Biological monitoring of H_2S in epidemiological studies is rare; exceptions are a few studies that measure urine thiosulfate (Farahat and Kishk 2010) or blood sulfhemoglobin (Al-Batanony and El-Shafie 2011). Other studies have measured these biomarkers to assess exposure in humans (Ensabella et al. 2004; Saeedi et al. 2015) and animals (Drewnoski et al. 2012). In Italy, Ensabella et al. (2004) used ambient workplace H_2S measures to verify blood sulfhemoglobin as a reliable measure of individual worker exposure to environmental H_2S. In contrast, Saeedi et al. (2015) found that workers exposed to higher levels of H_2S had lower mean sulfhemoglobin levels, yet these results are largely inconclusive due to the study's minimal exposure contrast and the limited statistical analysis. Drewnoski et al. (2012) investigated cattle exposed to environmental sulfate, which is converted to H_2S in the rumen of cattle, by measuring both urine thiosulfate and blood sulfhemoglobin. To date, use of H_2S biomarkers is uncommon, and all of the human biological monitoring studies discussed occurred in occupational settings. Validation of H_2S biomarkers for low level exposures in community settings must consider sources of H_2S – endogenous or exogenous, clearance rates, sensitivity, and other factors to avoid exposure measurement error. Thus, at present, it would be prudent to collect ambient or personal H_2S air samples in addition to urine thiosulfate or blood sulfhemoglobin. Further, the invasiveness and inconvenience of conventional blood draws may limit the use of biomonitoring in community studies to clinical settings, however, this may change as techniques evolve that allow convenient and minimally invasive (e.g., finger prick) sampling and analytical techniques.

2.4.3.2 Duration of exposure: acute, intermediate, and chronic: Exposure to H_2S (and other chemicals) in community and occupational settings will involve both acute and chronic exposures. In practice, these terms are not well defined. Acute exposure events,

vary in concentration, length of exposure period, and their periodicity. For many pollutants including H_2S, acute exposures are characterized as the maximum 15-min, 1-hr, or 24-hr average concentration. (Section 4 discusses the form of standards and guidelines that utilize different averaging periods.) Additionally, acute exposures can be a once-in-a-lifetime event, e.g., a result of a rare natural disaster or major industrial failure. In contrast, chronic exposures result from repeated exposure events over multiple years, and sometimes from a continuous or an ongoing release. Chronic exposures also vary in concentration, and are usually represented as an annual average concentration. For some pollutants (e.g., lead), intermediate durations are also sometimes used, e.g., a 3-month average.

Real-world H_2S exposures can include both acute events, e.g., one or few events in a lifetime, intermediate or intermittent exposures, e.g., multiple events in a week or month, and chronic exposures, e.g., occurring on nearly a daily basis due to occupational exposures or proximity to emission sources.

Exposures in community settings near H_2S emission sources (e.g., volcanoes, CAFOs, oil and gas facilities) will likely include intermediate duration and chronic exposures, although acute exposures also may occur. For example, upsets due to malfunctions at an industrial source may greatly increase levels over the chronic exposure normally expected, as documented by Haahtela et al. (1992). More generally, for pollutants like H_2S that are primarily emitted by localized outdoor sources, community exposures will be time varying due to the combined effects of: (1) the emission rate, which changes depending on activity, temperature, and other factors; (2) meteorological influences on dispersion, which is determined by winds, insolation, atmospheric stability, boundary layer height, precipitation, landscape features, and other factors; (3) sheltering or attenuation of H_2S concentrations in buildings and other “microcompartments”, which are affected by air change rates, mixing, filtration, etc.; and (4) an individual’s activity patterns (movement between microcompartments), breathing rate, and other individual-level factors. A key point in community settings is that time-averaged concentrations of H_2S are likely to be low, but occasional concentration spikes at much higher levels for periods of minutes to hours may occur. High pollutant events lasting several days can occur if sufficient H_2S emissions are released and if certain meteorological conditions that inhibit dispersion are persistent, e.g., prolonged subsidence inversion. These factors produce considerable spatial and temporal variation in H_2S concentrations, including daily and seasonal patterns, that affect both occupational or environmental exposures, discussed further the following section.

The time-varying (dynamic) behavior of pollutant concentrations can be captured with fast-response real-time instruments, which are available for H_2S and some other pollutants (e.g., SO_2, CO, $PM_{2.5}$, O_3), but not for other pollutants (e.g., endotoxin). Several studies have used continuous monitors for H_2S at locations designed to reflect population exposure, and several studies have used (short-term) indoor measurements in residences. Unlike the low-cost $PM_{2.5}$ sensors now being widely deployed across the world, low-cost (less than say $200) H_2S sensors that operate reliably at low concentrations (0.001 – 0.1 ppm) are unavailable.

The use of biomarkers or personal exposure monitoring, the “gold standard” in exposure assessment, has not been attempted in community studies of H_2S. As described earlier (Section 2.4.3.1), H_2S biomarkers have limitations, and personal monitoring can involve substantial cost, logistical and participant burden impacts. As noted, only a subset of studies reviewed employed monitoring for H_2S and other pollutants. In the studies that did use monitoring, there was little discussion of the temporal nature of exposures. Because different averaging times were used, it can be difficult to compare studies examining acute impacts. Generally, temporal fluctuations of H_2S levels in a community would be expected to be similar to that of other pollutants arising from localized outdoor sources. *A recommendation is to collect and analyze long-term (ideally ≥1 year) continuous monitoring records of H_2S at sites representative of population exposure around various types of sources*. Such data for several other pollutants exist in both public and industry-operated ambient air quality monitoring networks in the U.S., Canada and elsewhere. Occasionally, citizen complaints or permit violations may initiate such monitoring for a limited period, in the U.S. most typically conducted by the U.S. ATSDR, states or industry as part of a exposure and health assessment, e.g., MDHHS (2023). While primarily used to compare community exposure to reference levels (discussed in Section 4.1), such initiatives rarely yield peer-reviewed publications that advance epidemiology, possibly a missed opportunity.

Ideally, data with 5-min or higher time resolution would be obtained and used to analyze concentration distributions at 5-min, 10-min, 30-min, 1-hr, and 24-hr averaging periods. In recent years, new technology has enabled the measurement of H_2S with ppb precision e.g., cavity ring-down technology with high performance.

2.4.3.3 Spatial variation of community exposure: For mostly the same reasons just discussed, ambient H_2S concentrations in a community will vary from place to place. Spatial variation will always occur from localized outdoor sources and can lead to measurement error. Issues of cost and logistics generally preclude the use of a sufficient number of monitors to fully understand spatial variation across a community, although reasonable estimates can be made with a small set of monitors. Several (Finnish) epidemiological studies have used dispersion models to attempt to “fill-in” the inevitable data gaps from monitoring data (Häkkinen et al. 1985; Marttila et al. 1994; WHO 2006), an approach which is reasonable if data exist to confirm (“ground-truth”) model predictions. Using measured or modeled concentrations, researchers may divide a region or city into zones based on concentration levels (i.e., high, medium, and low). The definition of cut-off points for exposure categories should consider climate factors such as wind direction and good characterization of background levels. For example, in the geothermally active city of Rotorua, New Zealand, the main emission sources of H_2S are spatially clustered and thus not all residents are equally exposed; three zones were defined as high (~1 ppm), medium (0.5 ppm), and low/background levels (0 – 0.04 ppm) (Bates et al. 2002). Considering the lack of standardized exposure category definitions, it is vital to consider each study’s definition of exposure and exposure groups. The use of spatially-defined groups or zones (defined by monitoring, modeling, proximity, or other data) in an cross-section epidemiological study design requires careful consideration and control of covariates to avoid potential bias and confounding..

The majority of community studies around geothermal sources or livestock rearing operations used indirect proxy exposure measures, most often residential or school proximity to a facility or the number of facilities in the community (Bustaffa et al. 2020). Such indirect measures do not capture differences among sources and emissions, effects of meteorology and terrain on contaminant dispersion, impacts from other emission sources, and other factors that affect exposure (Huang and Batterman 2000). Thus, it is not expected that concentrations will be proportional to inverse distance from the source, or radially symmetric around the source, assumptions that have been used in the literature. Urban/rural differences are additional spatial challenges in studying the health effects of environmental exposures around geothermal plants or CAFOs. Urban and rural populations may differ with respect to sensitization and acclimatization to CAFO pollutants, e.g., a potential bias may result due to the lower prevalence of respiratory allergies sometimes seen among populations with early farm-animal contact (Radon et al. 2007).

Exposure assessments for H_2S are just beginning to use the hybrid approaches that have become common in air pollution epidemiology for pollutants like $PM_{2.5}$ and NO_2. These approaches synthesize a variety of data sources (satellite and remote sensing, *in situ* or ambient monitoring, land use features, emission inventories, chemical transport modeling, and sometimes housing features) to improve accuracy in comparison to any single approach. These techniques are particularly applicable to obtaining intermediate to long-term (e.g., weekly to annual) concentration estimates over large areas with high spatial resolution. A recent pilot study couples *in situ* and satellite data to estimate concentrations and emissions of several pollutants (CO_2, CH_4, H_2S, and NH_3) from a California dairy (Leifer et al., 2020), an approach that may have considerable value when linked to health data.

2.4.3.4 Pollutant mixtures: Air pollution exposures experienced in communities and often workplaces involve mixtures of many chemicals. Measurement error can occur in trying to characterize exposure to an individual pollutant without considering potential co-pollutants. Both the components in the mixture, and the relative concentrations of components in the mixture depend on emission sources that are present. Thus, the “typical” exposure can vary considerably between individuals and between studies. As examples, H_2S exposures from oil and gas facilities will likely include other reduced sulfur compounds and combustion-related compounds like SO_2 and CO; H_2S exposures associated with CAFOs and manure management will likely be accompanied with other gases such as ammonia, mercaptans, sulfides, and ketones, and may also include particulate matter containing organic dusts containing bioactive substances (endotoxins, glucans, fungi and molds) (Donham 2010; NRC 2003). In addition, the composition and rate (strength or intensity) of emissions from most sources (e.g., oil and gas facilities, geothermal plants, or CAFOs) will differ among facilities and during different operations. For example, emissions may increase during hot weather and during manure spraying, an intermittent activity. Thus, the composition and concentration of exposures in community settings will vary in time and space, and the correlation among mixture components will also vary.

Ideally, each individual pollutant would be separately and objectively measured, otherwise effects of individual pollutants will be difficult to disentangle. Of the newer community-based livestock rearing studies identified, only five measured H_2S (Campagna et al. 2004;

Eduard et al. 2009; Inserra et al. 2004; Kilburn 2012; Schinasi et al. 2011). Even fewer measured additional co-pollutants likely to confound observed health effects (Campagna et al. 2004; Eduard et al. 2009; Schinasi et al. 2011); these may provide the best dose-response information for setting air quality standards. In their controlled exposure study, Schiffman et al. (2005) opines that while individual components of the mixture at low concentrations were not expected to produce health effects, the observed health effects may represent a combined and potentially synergistic effect. To date, no attempt has yet been made to evaluate health effects of components isolated from real CAFO mixtures, although this is technically possible. For example, subjects could be exposed only to CAFO-related gases by using filters to remove particulate matter and microorganisms. However, for practical reasons, controlled chamber studies are limited to short-term exposures and small sample sizes. Although exposure to the entire mixture may be more relevant to community exposure, such tests could be useful in demonstrating the effectiveness of occupational interventions e.g., N95 masks for workers and mechanical ventilation with particulate filtration for facilities. The results of both controlled and observational studies suggest the need for or desirability of a multipollutant approach to control emissions from livestock-related and potentially other types of facilities. Thus, controls should include both regulation of individual pollutants and broader technology or performance requirements. This approach would be more responsive to health impacts resulting from additive or synergistic effect of multiple pollutants from H_2S sources.

The presence of pollutant mixtures is a real-world condition. In observational studies it may be difficult to discern effects of an individual pollutant when present in a mixture, however, effects may still be discerned despite spatial, temporal, and compositional variability if a study involves a sufficiently large sample of subjects, large geographic domain, sufficient duration, and appropriate pollutant measurements. Moreover, observational studies usually are the only practical approach to examine chronic and low-level exposures, to investigate potential synergies between mixture components and host factors like susceptibility, and to study large populations. The nascent but evolving hybrid models noted in the prior section may be valuable to provide exposure estimates for these studies.

If multiple pollutants are present and reasonably likely to influence a particular health outcome due to their concentration and toxicity, then ideally each pollutant should be objectively measured. It may be sufficient to screen for co-pollutants, or use the threshold olfactory technique (Section 2.3.1.2) in certain studies, to target the exposure assessment. Otherwise, effects of an individual pollutant in the mixture may be difficult or impossible to disentangle. Given information regarding the major components of the mixture, then controlled, occupational and community studies can utilize a variety of experimental and statistical techniques to understand effects of individual components, including potential interactions (e.g., synergies) with other mixture components, as discussed in the next section.

2.4.3.5 Cumulative effects of multiple chemical exposures: The term “cumulative effects” refers to the overall impact of concomitant exposures to multiple chemicals and other stressors in a particular condition or scenario. For exposure to chemical mixtures, this can include effects that are equal to (additive), less than (antagonistic), or greater

than (synergistic) predictions based on the effects observed with exposures to individual chemicals.

As discussed above, H_2S exposures often occur with exposures to other pollutants. Of the current literature, few studies provided information that can shed light on cumulative effects. Schiffman et al. (2005) addressed CAFO emissions, which involve a mixture of H_2S, other reduced sulfur compounds, endotoxin and dust that may act on the same target tissues. One of few controlled human studies, it offers some evidence that the mixture may increase the hazard of H_2S at low concentrations (documented as headaches, eye irritation, and nausea), since no single component was present at sufficiently high concentration to be wholly responsible for these symptoms (H_2S levels were only 0.024 ppm) (Schiffman et al. 2005). Lee et al. (2007) also opined that symptoms observed may result from synergistic or additive effects of the mixture components; they found WWTP workers to have higher risks of respiratory symptoms (dry cough, cough with phlegm, wheeze, chest tightness, breathlessness), although H_2S concentrations averaged 0.15 ppm and 95% of measurements were below 1 ppm (although the maximum value was high, 42.5 ppm). Finally, Mirabelli et al. (2006a) suggested that children using cigarettes or experiencing secondhand tobacco smoke were susceptible to increased prevalence of wheeze, suggesting co-exposure to environmental exposure as an additional risk factor.

Although more complex than investigating a single component, multipollutant studies are needed to provide the most meaningful approach to deal with actual exposures and health effects from pollutant mixtures (Dominici et al. 2010; Greenbaum and Shaikh 2010; Mauderly et al. 2010). Multipollutant approaches may lead to better management strategies because real world H_2S exposures often occur with other toxic pollutants.

2.4.4 At-risk populations and susceptibility—Three definitions are intended to provide some consistency in the discussion, although these terms are often comingled in the literature.

- The term “susceptibility” or “susceptible population” has been used to recognize groups that are at greater risk than the general population for health risk(s) from a specific pollutant, generally due to biological or intrinsic factors (e.g., life stage, gender, health and preexisting disease/conditions, nutritional status, and effects of exposure to other toxic substances such as cigarette smoke). A susceptible population would exhibit a different or enhanced response to a pollutant (like H_2S) than most persons with the same exposure, and detoxification or excretion of the pollutant, organ function or other processes may be reduced or compromised (ATSDR 2006).
- The term “vulnerability” or “vulnerable population” typically refers to nonbiological or extrinsic factors (e.g., socioeconomic factors, limited access to health care, lower quality housing located near emission sources). Vulnerability may affect susceptibility, and thus these terms are often comingled.
- Finally, the term “at-risk” or “at-risk population” refers to groups more that are likely to have higher risk of health effects than the general population, potentially

a result of separate or combined influences from susceptibility, vulnerability, and higher exposure. (Populations with unusually high exposure to H_2S are discussed in Section 3.)

Generally, the scope of the H_2S studies available permits limited insight with respect to susceptibility, and only to some health outcomes. Few studies examined potential effect modifiers that might identify more susceptible or vulnerable populations. Given the malodor of H_2S, it is reasonable to anticipate that individuals with asthma, who show increased sensitivity to odors, would have a worsening of their condition upon exposure (ATSDR 2006). Strong supporting evidence of asthmatic vulnerability is provided by Carlsen et al. (2012) who studied a population exposed to volcanic emissions with daily H_2S averages of 0.006 ppm and daily peaks of 0.062 ppm (1-hr averages of 0.021 ppm and 1-hr peaks of 0.345 ppm), and by Campagna et al. (2004) who studied a population around CAFOs with 30-min concentrations above 0.030 ppm. Earlier, controlled 30-min tests with 2 ppm H_2S of a small group of subjects with mild-to-moderate asthma noted some sensitivity by increased airway resistance and decreased specific airway conductance, implying bronchial obstruction; however, this study excluded individuals who may be most susceptible, specifically, severe asthmatics and children (Jappinen et al. 1990). Finnbjornsdottir et al. (2016) found a weak association between H_2S and heart disease in adults that increased slightly among those 73 years and older. Besides underlying conditions such as asthma, environmental and social factors have been evaluated as potential effect modifiers. Being raised on a farm may increase a child's risk of asthma, even after accounting for atopy and allergy (Merchant et al. 2005). Children may be more susceptible to a broader range of respiratory diseases than adults (Campagna et al. 2004). Children who smoke cigarettes or experience secondhand smoke have higher risk of wheezing than children who do not (Mirabelli and Wing 2006). However, not all studies that stratified health risk by susceptibility factors have found significant effects. Villeneuve et al. (2009) found no difference in health effects between children/adolescents and adults. Sigurdarson and Kline (2006) noted that children with parents who farmed and smoked were not more likely to have asthma than children of parents who did not.

The broader literature points to several groups that are at-risk for morbidity and mortality effects from air pollutants. Examples for two pollutants are given. For particulate matter ($PM_{2.5}$), susceptible and at risk groups include children and older adults, individuals with pre-existing heart and lung disease, and persons with lower socioeconomic status and with genetic differences. Emerging though still limited evidence exists for additional potentially at-risk populations, including individuals with diabetes, people who are obese, pregnant women, and the developing fetus (EPA 2012). For sulfur dioxide (SO_2), at-risk groups include those with pre-existing respiratory disease, children and older adults (but possibly not adolescents), and people who spend extended periods of time outdoors and/or at elevated ventilation rates (EPA 2017). EPA concluded that large portions of the US population are likely to be at increased risk from these pollutants, and health-protective standards were set based on the at-risk groups. Clearly, a very large number of individuals are exposed and affected by air pollutants $PM_{2.5}$ and ozone. Over the past four decades, SO_2 emissions, concentrations, and the numbers of individuals affected have likely dropped considerably e.g., in 2021, nonattainment areas for SO_2 included 26 areas with a population

of 2.13 million persons (EPA 2010b). In this report, the number of individuals affected by high concentrations of H_2S is not estimated, however considering the many facilities that routinely or intermittently release H_2S across the nation (e.g., refineries, CAFOs, wastewater facilities, etc.), the population exposed or potentially exposed may be substantial.

2.4.5 Potential biases in observational studies—While observational studies provide opportunities to examine chronic low-level exposures, results of these and other epidemiological studies can be limited by several types of biases. *Reporting or awareness bias* can affect self-reported symptom assessments, potentially important for H_2S considering its odor that may make subjects more aware and likely to report effects and symptoms. Reporting bias also occurs for other reasons, e.g., economic interests associated with industry and study participants. *Recall bias* is a second potential issue in symptom studies, particularly for longer recall periods. A third bias is the *sensitization* – or conversely *tolerance bias* – to exposures and odors; this bias also may affect results of experimental (chamber) investigations. Schiffman et al. (2005), for example, discusses possible differences in responses obtained from volunteers in chamber studies compared to those who are chronically and involuntarily exposed, however, the literature is equivocal on this topic, showing that repeated exposure can increase sensitivity to an odor (especially among women), but that some workers appear tolerant of swine confinement air.

Other types of biases in observational studies, particularly in community-based studies, include *selection bias* (e.g., the need for a randomly selected case population and, in case-control studies, an appropriately selected comparison population), the possibility of *confounders* (including co-pollutants), and *effect modifiers* (e.g., due to urban/rural differences) (Donham 2010; Heederik et al. 2007; Radon et al. 2007).

Section 2.4.3 earlier discussed issues and weaknesses in exposure estimates used in the observational studies. Exposure measurement error or misclassification is a topic that has received considerable attention in the epidemiological literature (Carroll et al. 2006). *Exposure measurement error,* that is, differences between the measured (or predicted) exposure used in the analysis compared to the underlying or true exposure, or *exposure misclassification,* the analogous term for a categorical exposure variable, can lead to incorrect inference, specifically, biased and/or imprecisely estimated effect coefficients that may be serious enough to invalidate the inference regarding the effect of H_2S on health (Sheppard et al. 2012). The framework for exposure measurement or misclassification error refers to standard categories: *classical measurement error* due to random errors resulting when the true exposure is measured but with noise, which causes biased effect estimates as well as higher or lower standard errors; *Berkson measurement error* when only part of the true exposure or aggregated exposure is measured, which causes unbiased but more variable exposure-response (effect) estimates; *Berkson-like measurement error* due to smoothing the exposure surface; and *classical-like measurement error* when noise is not independent (Szpiro and Paciorek 2013). Related classifications of errors due to spatial issues include: the *modifiable areal unit problem* (MAUP), which can bias outcomes when a point-based measure (e.g., H_2S level measured at a site) is assumed to apply to a district (e.g., census tracts) and lead to the so-called ecological fallacy (Ganguly et al. 2015; Shafran-Nathan et al. 2017); *location-based covariate measurement error*, e.g., when proximity to a H_2S source

like a CAFO is used to define exposure; and differences between *ambient and personal exposures* (Kioumourtzoglou et al. 2014). Finally, studies investigating chronic disease can be susceptible to *exposure timing bias*, e.g., the use of current exposure conditions that may have limited relevance for a disease that developed years or decades earlier (Lipfert and Wyzga 2008).

2.4.6 Summary of the studies—Table 1 summarizes many of the health effects associated with H_2S. Only a subset of studies that measured or estimated H_2S levels are included. Estimates listed of H_2S exposure levels, durations, and co-pollutants are approximate. The case reports and the available epidemiologic and toxicological literature clearly indicate that the high H_2S concentrations that sometimes occur in occupational settings such as viscose rayon and pulp manufacture, and oil, gas and geothermal energy production have the potential to produce morbidity and death. The dose-response relationship for mortality is well understood. However, the literature does not include any large occupational epidemiological studies that address morbidity or mortality due to chronic occupational exposures. Such studies are recommended and could shed light on the low-level exposures that are the focus of this report. There is also a paucity of large studies addressing chronic low level H_2S exposures occurring in community settings. Such studies are needed to evaluate the potential of H_2S to cause health effects on susceptible and vulnerable individuals. In addition, although there are numerous reports of adverse effects, many involve concurrent exposures and the data and/or analyses do not quantitatively link effects with H_2S exposure for this and other reasons (ACGIH 2001).

The newer literature includes several medium-sized studies using (daily) time-series analyses and objective measures of both pollutants and respiratory-related symptoms and disease. Unscheduled hospital visits for aggravation of asthma and respiratory disease increased at H_2S concentrations above 0.03 ppm in Nebraska (Campagna et al. 2004); irritation (nose and eye), odor, difficulty of breathing and cough was associated with higher H_2S concentrations or odor in North Carolina (Schinasi et al. 2011); and exacerbation of existing asthma at H_2S concentrations of 0.0067 ppm was indicated by (increased) dispersal of anti-asthma drugs in Reykjavik (Carlsen et al. 2012). The latter study has the strength that multiple pollutants were considered, which due to differences in pollutant emissions may have had greater influence on the CAFO-oriented studies (i.e., Campagna et al. 2004; Schinasi et al. 2011). These studies strongly suggest that short-term (30 min to 24-hr) H_2S concentrations in the range of 0.007 to 0.03 ppm, roughly around the odor detection/nuisance threshold, can significantly exacerbate asthma. Individuals with asthma are highly susceptible to air pollutants, and thus this finding is consistent with the literature for other pollutants. Although findings in these studies appear robust, ecological designs (and typically a single monitoring site) were used, which limits the ability to identify and control for individual or group risk factors (effect modifiers and covariates).

Many of the other studies discussed in this review show elevated risks for other symptoms and diseases, including ocular symptoms, sore throat, cough, nasal irritation, nasal lesions, difficulty of breathing, chest tightness, wheezing, increased asthma prevalence and/or aggravation, lung function decrements, depression, neurological and neurobehavioral changes among individuals in communities and workplaces where H_2S concentrations are

elevated or likely to be elevated. In particular, eye irritation may result at concentrations starting in the range of 0.007 to 0.025 ppm. The modeling by Schroeter et al. (2010; 2006) had the effect of changing the NOAEL for nasal lesions. In community settings, odor-triggered nuisance, complaints and physiological symptoms are expected with short-term concentrations in the range of 0.001 to 0.050 ppm, and odor nuisance thresholds are in the range from 0.03 to 0.05 ppm or lower. The newer observational studies document neurological and neurobehavioral abnormalities in community settings around H_2S sources, but the identification of the causal mechanisms and the dose-response relationships remains unresolved.

Exposure assessment limitations in these studies just mentioned, including a lack of objective monitoring, preclude establishments of dose-response relationships. Exposure assessments continue to represent a significant weakness of H_2S studies (OEHHA 1999); this is a common problem in air pollution epidemiology. Additionally, results of some studies may have been affected by co-pollutants, biases in participant recruitment/selection, symptom ascertainment (especially when self-reported), occupation and exposure history, and other factors. Many studies used cross-sectional designs that have a high likelihood of bias due to the difficulty of accounting for covariates and confounding variables. Good discussions of methodological limitations are provided by Radon et al. (2007) and (OEHHA 2000) for the H_2S studies, and by Götschi et al. (2008) for air pollutants in general.

There is a large divergence between experimental animal and human studies with respect to the concentrations that are associated with adverse effects. These types of studies typically employ different types of health effect measures (OEHHA 2000). Moreover, animal and controlled human exposures are typically very short-term in nature, likely to miss health effects with long latency periods, rarely evaluate effects relevant to susceptible individuals (including children, the elderly, and persons with preexisting medical conditions), and may not reflect other factors important to actual exposures and real-world conditions. However, experimental studies represent an essential criterion in causality determinations (Section 2.4.1)

As in most of the epidemiological literature, it is difficult to assess publication bias in the H_2S literature. Few studies with exclusively null findings were identified, although Inserra et al. (2004) and Villeneuve et al. (2009) reported largely negative findings. The lack of negative studies and the preponderance of smaller studies suggest that publication bias is likely (Götschi et al. 2008).

3 Exposure to H_2S

A short discussion is provided of populations exposed to H_2S. Elevated levels and exposures of H_2S occur near several types of air pollution sources.

- Industry. H_2S is emitted more or less continuously in certain industries. These include natural gas production, shale oil industry, petroleum refining, petrochemical synthesis, municipal sewage pumping and treatment plants, landfills, swine containment and manure handling (including confined animal confinement facilities or CAFOs), pulp and paper production, construction in

wetlands, asphalt roofing, pelt processing, animal slaughter facilities, tanneries, coke production plants, viscose rayon manufacture, sulfur production, iron smelting, ocean fishing, and food and meat processing, pulp and paper mills, oil refineries, hot springs and geothermal energy installations, Superfund and other waste sites, and chemical (and other) waste lagoons (ATSDR 2006, 2002; Glass 1990).

- Accidental releases. H_2S can be emitted in large amounts resulting in acute exposures due to industrial accidents, pipeline failures, and geothermal sources. Based on a multistate surveillance program, 637 H_2S events occurred from 1993 to 2001, resulting in 63 public evacuations and 185 people injured (ATSDR 2002). In Alberta, Canada, 357 sour gas incidents occurred from 1990 to 2005 along pipelines, including hits, leaks, releases and ruptures (Section 3.8).
- Natural sources include volcanoes, sulfur springs, undersea vents, swamps and stagnant bodies of water and in crude petroleum and natural gas. Additionally, bacteria, fungi, and actinomycetes release H_2S during the decomposition of sulfur-containing proteins and by the direct reduction of sulfate (SO_4^{2-}; ATSDR 2006).

Typically, background levels (away from industrial or strong natural sources) are low, falling below 0.001 ppm (1 ppb), while proximity to strong natural sources or industries emitting H_2S can produce much higher concentrations that often exceed 0.09 ppm (90 ppb) (ATSDR 2006).

This section emphasizes exposures of H_2S reported in the scientific literature relevant to community exposure. It does not include the “gray literature,” which potentially includes a large number of exposure assessments that sometimes result from citizen complaints, regulatory requirements, or permit violations that are conducted by the U.S. ATSDR, states, and industry (e.g., MDHHS 2023).

3.1 General urban levels

In one report, the average ambient H_2S level was estimated at 0.0002 ppm (0.3 μg/m^3). In north-west London, over a period of 2.5 years, air levels of H_2S were generally <0.0001 ppm (0.1 ppb; 0.15 μg/m^3) under clear conditions (WHO 2006, 1981). ATSDR (2006) reports that ambient air concentrations from natural sources range between 0.00011 and 0.00033 ppm (0.11 and 0.33 ppb), and that levels in urban areas are generally below 0.001 ppm (1 ppb).

3.2 Geothermal sources

H_2S has been continuously monitored in the city of Rotorua, New Zealand, where geothermal activity is sufficient to cause odors and where studies of mortality (Bates et al. 1997), cancer (Bates et al. 1998), morbidity (Bates et al. 2002), respiratory disease (Durand and Wilson 2006) and cognitive function (Reed et al. 2014) have been performed. H_2S concentrations exceeded 0.05 ppm (80 μg/m^3) over 55% of the time in the mid-winter months (WHO 2006, 1981). Horwell et al. (2005) mapped levels in the city using passive samplers and indicated that maximum 8-hr levels in the center city may reach 1 ppm regularly, while 10-min peaks may be order of magnitude higher. Other studies in Rotorua

have detected similarly low levels: a range of 0.03 to 1.0 ppm (Durand and Wilson 2006); IQR of 0.0056 to 0.184 ppm (Pope et al. 2017); IQR of 0.011 to 0.031 ppm (Bates et al. 2013); median of 0.014 ppm (Bates et al. 2002, 1998). Different sampling techniques and spatial variation in concentrations due to soil gas emission fluxes and meteorological influences could explain the differences in measured ambient levels (Durand and Wilson 2006). Durand and Scott (2005) reported on levels inside nine buildings in Rotorua and discussed the lack of effectiveness of preventative measures, such as under-laying of concrete floors with a gas-proof butanol seal, under-floor ventilation systems, and positive-pressure air conditioning.

Reykajavik, Iceland is also known for high geothermal activity with ambient H_2S at concentrations averaging 0.0058 (Carlsen et al. 2012). According to Finnbjornsdottir et al. (2016), the interquartile range (IQR) of H_2S levels is 0 to 0.003 ppm. In another geothermal "hotspot," Mt. Amiata, Tuscany, ambient H_2S concentrations averaged 0.0003 to 0.022 ppm (Nuvolone et al. 2019).

3.3 Oil and gas production facilities, including sour gas wells and pipelines

H_2S is both routinely and episodically released at sour gas wells, gas and crude oil batteries, gas and oil processing plants, oil refineries, and tar sands mining operations. Possibly the most extensive H_2S monitoring has been performed in Alberta, Canada. Alberta Environment (2004) provides statistics from about 80 monitoring stations in Alberta over a three-year period at sites potentially affected by oil and gas exploration and production facilities. The three highest (1 hr) concentrations ranged to 3 ppm; excluding these values, the average concentration was 0.006 ppm (6 ppb or 8.5 $\mu g/m^3$). Alberta Environment also summarized pipeline incidents, including hits, leaks, releases and ruptures, reports 10 to 41 sour gas incidents per year (total 357 from 1990 to 2005), most of which were attributed to corrosion (AEUB 2007). The overall rate of sour gas pipeline incidents ranges from 1.2 to 3.2 incidents per year per 1000 km, and a declining trend is noted across the Province of Alberta. Pipeline accident rates are typically expressed in terms of number of incidents per year per km of pipeline, and rates can vary significantly in different regions. A health study of Canadian petroleum workers did not directly measure H_2S but used a job-exposure matrix to back-estimate lifetime occupational median exposures of 0.07 ppm (Lewis et al. 2003).

The US EPA conducted some monitoring around the Gulf Coast in the aftermath of the BP oil spill (AER 2022). Based on website notes, most sites had levels below detection limits (0.1 ppm); some levels exceeded 0.5 ppm in Venice, Alabama, and typical values at Chalmette, Louisiana (some 50 miles from Venice) were 0.002 to 0.004 ppm (EPA 2016). Lusk and Kraft (2010) reported on H_2S monitoring (and an avian risk assessment) in oil and gas production facilities in New Mexico and found that most peak levels were below 6 ppm; the maximum peak level was 33 ppm. Another occupational study of oil/sour gas facilities in New Mexico found levels ranging from 0 to 0.014 ppm (Dubyk and Mustafa 2002).

Natural gas venting during well testing and development, as well as testing and maintenance of other energy infrastructure, can be a short-term source of H_2S emissions and exposure. This appears to have become more common in the past decade due to the expansion of hydraulic fracturing and natural gas fields in North America, e.g., sour gas fields in Alberta,

Canada. Typically, venting during well tests and other non-routine activities has been limited to a maximum duration of three days, and monitoring and modeling may be required to ensure that ambient H_2S concentrations (and SO_2 concentrations if flaring is used) do not cause odors (1-hour level H_2S level below 0.01 ppm) or exceed standards (AER 2022; AH 2020). Venting typically would not be utilized subsequently, e.g., during well operation.

3.4 Pulp and paper mills

Emissions from pulp and paper mills can include a mixture of particles, sulfur dioxide and several malodorous compounds including H_2S, methyl mercaptan, and methyl sulfides, which are often measured and reported as total reduced sulfur (TRS). H_2S can constitute a variable form of TRS, e.g., Jaakkola et al. (1990) indicate 70%. Some of the studies reporting concentrations around these facilities are listed below.

- Peak concentrations up to 0.13 ppm (200 μg/m^3) were measured near a pulp and paper-mill in California (WHO 2006, 1981).
- In an occupational survey of H_2S and other sulfides at six kraft mills in Finland, concentrations ranged from below 0.05 ppm (75 μg/m^3) to 20 ppm (30,000 μg/m^3), the highest concentrations being found near vacuum pumps (Kangas et al. 1984; WHO 2006).
- In a Finnish town with two sulfate pulp mills (annual emissions of 1993 and 794 T/year of H_2S, respectively), dispersion models estimated average annual concentrations up to 0.037 ppm (55 μg/m^3), monthly average concentrations up to 0.067 ppm (100 μg/m^3), 24-hr concentrations up to 0.36 ppm (540 μg/m^3), and 1-hr concentrations up to 1.07 ppm (1600 μg/m^3) (Häkkinen et al. 1985; WHO 2006).
- Observational health studies of communities near sulfate pulp mills in South Karelia, Finland reported average concentrations of 0.00067 to 0.0053 ppm (Marttila et al. 1994) and 0.001 to 0.002 ppm (Partti-Pellinen et al. 1996).
- Monitoring data near five kraft mills in Alberta, Canada is reported by Alberta Environment (2004).
- Korhonen et al. (2004) summarized occupational exposures in the paper industry across 12 countries; however, relative few measurements of H_2S are reported.
- Mirabelli and Wing (2006) reported odors near four pulp and paper mills in North Carolina, but exposures are not quantified.
- H_2S monitoring in seven localities near around Ružomberok, Slovakia, a polluted area containing a kraft pulp mill, showed long-term average concentrations (2002 through 2004) up to 0.004 ppm (5.8 μg/m^3) and maximum levels of 0.014 ppm (21 μg/m^3) (Drimal et al. 2010). Using the 95th percentile 24-hr samples as a worst-case, a RfC of 0.001 ppm (2 μg/m^3) (EPA 2003), the authors report hazard quotients up to 7. This represents the first air monitoring of H_2S in Slovakia.

3.5 Viscose rayon mills

Near a viscose rayon mill in Finland, H_2S concentrations were measured and predicted using a dispersion model (FNBH 1982; WHO 2006). For a 55 m high smokestack, average annual concentrations exceeded 0.007 ppm (10 μg/m^3), 24-hr concentrations were approximately 0.134 ppm (200 μg/m^3), and hourly concentrations reached 0.302 ppm (450 μg/m^3). A higher smokestack reduced maximum annual, 24-hr and hourly concentrations to 0.003, 0.023, and 0.054 ppm, respectively (4, 35 and 80 μg/m^3). A Japanese survey of 18 viscose rayon plants showed very high occupational exposures of H_2S, which ranged from 0.3 to 7.8 ppm (450 to 11,700 μg/m^3), with a mean of 3 ppm (4,500 μg/m^3) (Higashi et al. 1983; WHO 2006).

3.6 Livestock rearing systems

Livestock rearing systems include confined animal feeding systems (CAFOs) and manure storage and treatment. H_2S is the main toxic emission from livestock rearing systems with liquid manure storage; other emissions can include ammonia, mercaptans, sulfides, ketones and particulate matter, which can include organic dusts with endotoxins, glucans, fungi, molds and other microbes. A very complete review of emissions, with recommendations, is provided by NRC (2003). Acute exposures have been reviewed by Donham et al. (1982), and updated reviews of community and occupational concerns are given by the same team (Donham 2010; Donham et al. 2007). An increasing number of studies are examining odors and contaminants in communities near CAFOs.

- H_2S and TRS measurements at multiple indoor and outdoor locations in Dakota City and South Sioux City, Nebraska, an area affected by a large animal waste treatment facility and other sources, exceeded 0.030 ppm (30 ppb) about a quarter of the time (ATSDR 1997; Campagna et al. 2004; Inserra et al. 2002; White et al. 1999).
- Donham et al. (2006) measured H_2S outside 35 homes located near swine farms in three regions -- those with CAFO facilities, hoop structure facilities, or crop-only production (control) -- in the Upper Midwest, U.S. The time weighted average concentrations of H_2S (8.42 ppb) was higher ($p = 0.047$) in the CAFO area than the control area (3.48 ppb). The concentration of H_2S exceeded the ATSDR limit (30 ppb) for chronic exposure at two of the 12 homes in the CAFO area (17%). Average H_2S levels exceeded the EPA recommended community standards (0.7 ppb) in all three regions.
- Wing et al. (2008) measured odors, H_2S and PM_{10} at 16 neighborhoods in eastern North Carolina, US that had between one and 16 CAFOs within a radius of 2 miles. Monitoring periods in each neighborhood were at least 2 wks. Average H_2S concentrations ranged from 0.00 to 0.00148 ppm (0.00 to 1.48 ppb), and 15-min levels reached 0.090 ppm (90 ppb). Odor ratings made by 101 participants during 10-min periods of sitting outside twice a day were associated with weather conditions and concentrations of H_2S and PM_{10} (Horton et al. 2009; Wing et al. 2008).

- Eduard et al. (2009) used personal air monitors to measure individual-level H_2S exposure among 4,735 Norwegian livestock farmers. The authors reported levels ranging from 0.0002 ppm (sheep, goat, poultry farms) to 0.036 ppm (cattle farms).
- Thorne et al. (2009) collected measurements of toxicants upwind, downwind and in barns of swine facilities in central Iowa, U.S., including $PM_{2.5}$, endotoxin, odor threshold, H_2S, bacteria, fungi and airborne microbes. H_2S measurements averaged 0.0024 to 0.0032 ppm at a distance of 160 m from the barn; indoor measurements averaged between 0.020 and 0.146 ppm, depending on the type of confinement building. H_2S levels were low compared to earlier literature, in part as the facilities studied were relatively small, and site activities (e.g., manure pumping) and meteorological conditions were noted to affect the downwind concentrations.
- Across 16 communities in eastern North Carolina, U.S., 12-hr H_2S concentration averaged 0.00030 ±0.00186 ppm, 12-hr PM_{10} averaged 19.4 ± 11.8 μg/m^3, and 12-hr $PM_{2.5}$ averaged 10.9 ±5.7 μg/m^3 (Schinasi et al. 2011).
- Kilburn (2012) reports some measurements in and outside of homes within 3 km of hog manure lagoons in Paulding, Ohio, U.S. Average H_2S levels in 12 homes ranged from 0 to 0.03 ppm (but reached 2.1 ppm in one home and varied over 10-fold in one-day's spot check samples). Two outdoor samples exceeded 1.1 ppm.
- In Iowa, U.S., Pavilonis et al. (2013) measured ambient H_2S near (<40 m) a single, medium sized swine CAFO over 7 months to determine the temporal and spatial variability of H_2S, near two schools over a 2 weeks period, and near 13 CAFOs also over a 2-week period. Near the single CAFO, concentrations ranged from 0.0002 to 0.0486 ppm, depending on the sampling period and proximity to a lagoon on the property. 2-week concentrations near the schools were below 0.001 ppm, and 2-week concentrations near the 13 CAFOs were 0.001 to 0.043 ppm, although several measurements exceeded the state's ambient limit of 30 ppb (24-hr average).
- Additional community-based health studies have assessed odor but not H_2S (Avery et al. 2004; Radon et al. 2005).

It is significant to note that the NRC (2003) expert panel made management recommendations for H_2S: "For air emissions important on a local scale (hydrogen sulfide [H_2S], particulate matter [PM], and odor), the aim is to control ambient concentrations at the farm boundary and/or nearest occupied dwelling. Standards applicable to the farm boundary and/or nearest occupied dwelling must be developed."

3.7 Sewage and waste treatment facilities

H_2S exposure is a well know hazard for WWTP workers. Ho et al. (2008) reviewed a number of H_2S sources associated with wastewater facilities. A study of WWTPs in Iowa, U.S. found the average H_2S level typically below 1 ppm (95% of samples were below this

value), an overall geometric mean of 0.15 ppm, and a range from 0 to 42.5 ppm (Lee et al. 2007). A study of wastewater pump stations in Tianjin, China, measured 15 volatile organic compounds (VOCs) including H_2S and found that it occurred at levels higher than other VOCs, with a geometric mean of 0.020 ppm (29.42 μg/m^3) and range of non-detect to 0.059 ppm (87.50 μg/m^3); researchers then used modeling to predict that at these levels, H_2S would confer non-carcinogenic health risks, most likely olfactory mucosa damage, with a hazard quotients of 1.14 and 1.13 for the mean and median exposures, respectively (Niu et al. 2014). Additional occupational studies of wastewater workers have found concentrations ranging from 0.4 to 13.1 ppm (Austigard et al. 2018); from 5 to 11 ppm (Farahat and Kishk 2010); and from 2 to 74 ppm (Kilburn et al. 2010). Exposure to H_2S from wastewater plants may extend beyond the industrial setting into nearby communities.

Attention has been increasing with respect to H_2S levels from municipal and other solid waste management facilities, possibly due to the development of nearby or adjoining residential development. A study of residential exposure nearby a landfill found average ambient levels of 0.00022 ppm with a range from 0 to 0.0023 ppm (Heaney et al. 2011). Ko et al. (2015) measured levels of H_2S at and near landfills and evaluated technologies to control H_2S emissions at landfills; Colón et al. (2017) focused levels within waste processing plants in Spain using mechanical-biological waste treatment designed to reduce the biodegradable fraction and stabilize municipal wastes. The highest H_2S concentrations (1.85 ppm) were found in a mechanical-biological treatment facility for municipal solid waste in Portugal, followed by a biofiltration unit (0.546 ppm), over the landfill (0.022 ppm) and then a composting treatment hall (0.019 ppm); this paper also summarizes H_2S levels found at eight other landfills or waste processing facilities (Nunes et al. 2021).

3.8 Accidental exposures

During accidental exposures, concentrations from 100 ppm (150 mg/m^3) to 12,000 ppm (18,000 mg/m^3) have been reported (WHO 1981). Accidental releases can have severe effects. For example, the malfunction of an oil field flare in the small community of Poza Rica, Mexico resulted in a H_2S release that caused 320 people to be hospitalized and 22 deaths; H_2S levels were not measured (WHO 1981). Haahtela et al. (1992) presents an epidemiological study of short-term upset at a paper mill that greatly increased exposures for several days. Leaks in sour gas pipelines, discussed earlier (Section 3.3), are another potential source of accidental exposure, although the number of individuals affected appears small in most cases.

Failures of flares, a rudimentary emission control system, and other controls used at industrial sources of H_2S and other pollutants can produce periods of high emissions and high exposures. Emergency, process and production flaring at refineries, sour gas processing facilities, and gas extraction well development normally convert H_2S, if present in the waste stream, to SO_2, which is considerably less toxic and odiferous. (In developed countries, process flaring would not normally be utilized to control H_2S given concerns over SO_2 emissions and exposures.) There are no known statistics on flare failure rates that have led to sizable H_2S emissions and such events are rarely documented in the scientific literature, although such incidents have led to community exposure in multiple settings.

3.9 Other exposures

H_2S exposure can result from other environmental and industrial sources, including production of pesticides and intermediates, in particular, sodium tetrathiocarbonate (STTC), and a need for more studies on co-exposure to CS_2 (another by-product) and H_2S has been expressed (Silva 2013).

H_2S exposure can result from mining activities, including underground and surface mining, as well as the injection of waste slurry into abandoned underground mines. These activities can generate large quantities of sulfate, which under anaerobic conditions in the presence of carbon, can be reduced to sulfide by naturally occurring bacteria; some of the sulfide will remain dissolved in groundwater (Simonton and King 2013). In mining regions in West Virginia, U.S., Simonton and King (2013) found sulfate in all 73 residential drinking water wells tested and observed rotten-egg odor in all homes, however, H_2S concentrations were not measured. Further studies of mining related H_2S exposure are needed to quantify levels and temporal and spatial variability.

3.10 Endogenous production

Exposure to H_2S occurs endogenously, that is, from the production of H_2S in the body, in addition to the external sources discussed previously. In brief, most endogenous production results from the metabolism of sulfhydryl-containing amino acids by bacteria in the intestinal tract and the mouth, and some is produced in the brain and several smooth muscles by enzymes in these tissues (ATSDR 2006). In the mouth, H_2S is a component of halitosis, and concentrations between 0.001 and 0.1 ppm (1–100 ppb) have been measured in mouth air. In the large intestine, H_2S can be generated by bacterial reduction of inorganic sulfate and sulfite, and by fermentation of sulfur-containing amino acids. H_2S can compose up to 10% of intestinal gases, and mean concentrations range in flatus are between 1 and 4 ppm, although levels reaching 18 ppm have been recorded among individuals on a normal diet. In the brain, H_2S produced from reactions catalyzed by the cystathionine β-synthase enzyme from the desulfhydration of cysteine acts as a neuromodulator, enhancing the N-methyl-D-asparate (NMDA) receptor-mediated response, facilitating the induction of hippocampal long-term potentiation, and serving as a widely distributing signaling or messenger molecule (Section 2.2).

3.11 Summary of exposure sources

This section has focused on airborne emissions of H_2S from various types of sources that produce on-site (occupational) and off-site (downwind community) exposures. In communities near pulp and paper mills, the largest source of airborne emissions, H_2S concentrations can vary widely, e.g., a Slovakian study (Drimal et al. 2010) reported a long-term average of 0.004 ppm and maximum concentrations up to 0.014 ppm, while a Finnish study (Häkkinen et al. 1985; WHO 2006) showed annual average concentrations up to 0.037 ppm (annual average) and 1-hr peaks up to 1.07 ppm). Typically, much higher levels are found in occupational settings, e.g., up to 20 ppm in kraft mills in Finland (Häkkinen et al. 1985; WHO 2006), and 42.5 ppm at sewage and waste treatment facilities in Iowa, U.S. (Lee et al. 2007). Yet greater differences between community and occupational exposures have been found at viscose rayon mills (FNBH 1982; Higashi et al. 1983; WHO

2006). Oil and gas production facilities, the next largest H_2S emission category, include a diverse set of sources, e.g., sour gas wells, pipelines, gas and crude oil batteries, processing plants, and refineries. These facilities may routinely (e.g., continuously) release H_2S that produce generally modest concentrations and exposures in community settings, but more widespread and sometimes much higher exposures may result from facility startup or testing activities, e.g., well-development, and sometimes from upsets and accidents, e.g., spills and pipeline leaks. As examples: across 80 monitoring sites in communities with sour gas facilities in Alberta, Canada, H_2S concentrations averaged 0.006 ppm and 1-hr peaks reached 3 ppm (Alberta Environment 2004); and concentrations in coastal communities following the large BP oil spill Louisiana, US were mostly below 0.1 ppm (EPA 2016). The third largest emission category, livestock rearing systems including CAFOs, has had the largest number of studies. These have reported some of the higher H_2S concentrations in community settings, e.g., short-term measurements exceeding 1 ppm in and outside of near swine facilities in Iowa, U.S. (Kilburn 2012). However, these levels appear atypical and long-term average concentrations generally average well below 0.1 ppm and often much lower, below 0.01 ppm (Schinasi et al. 2011; Thorne et al. 2009). Other potentially important H_2S sources can include water and waste processing facilities. Finally, community exposures to volcanic and geothermal sources of H_2S, have received attention in Portugal, Iceland, New Zealand and Italy; community monitoring shows great variability with long term averages typically below 0.1 ppm but occasional short term peaks that may reach one to two orders of magnitude higher (Section 3.2).

Emissions of H_2S from industrial and agricultural sources can be controlled or further controlled to protect workers and community members, unlike the volcanic or geothermal sources. It is notable that H_2S emissions – in comparison to on-site or environmental concentrations – are rarely measured, and the reliability of the existing emission data is unknown.

4 Exposure recommendations and regulatory levels

H_2S exposure limits recommended for workers and the general population range over several orders of magnitude, differing for a number of reasons including the literature that was available and selected as relevant and meaningful, the type of endpoint or critical effect considered, the duration of exposure, the populations considered, the degree of protection desired, and the adjustment, safety and uncertainty factors applied. Guidelines and limits may differ among agencies even though the same study may be used to define the critical effect, reflecting the agency's assessment of the evidence, attitudes towards risk averseness, and agency practices and policies. This concern is particularly relevant for community standards and guidelines developed from occupational, controlled human or animal studies given the need to protect susceptible and vulnerable populations. Adjustment and uncertainty factors (sometimes called safety factors) reflect animal-to-human (or other) dosimetry issues, as well as the recognition that community exposure can occur to susceptible and vulnerable populations who are not adequately represented in the underlying studies. To date, guidelines and limits for H_2S have not utilized approaches or adjustment factors that consider H_2S as a surrogate for the toxicity of a mixture of co-pollutants emitted from the same source.

4.1 Community standards and guidelines

Existing community guidelines in the U.S. are summarized in Table 2 and discussed below. Several European guidelines are discussed later in the text.

4.1.1 U.S. Reference concentration (RfC)—The EPA defines the inhalation RfC as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It is based on the assumption that a concentration or exposure *threshold* exist for certain toxic effects such that no adverse effect will occur below a given exposure. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extra-respiratory effects). The current RfC for H_2S (EPA 2003) is derived from a no-adverse-effect level (NOAEL) of 10 ppm based on a controlled exposure of rats by Brenneman et al. (2000) described in Section 3.3.3. The RfC was derived following EPA guidance, which adjustments for a continuous exposure concentration (factor of 4), dosimetric and physiological adjustments for differences between rats and humans (factor of 5), and standard uncertainty factors for interspecies extrapolation, sensitive populations and subchronic exposure (factors of 3, 10 and 10, respectively), resulting in a RfC of 0.0013 ppm (2 $\mu g/m^3$). The product of the uncertainty factors is 300, the highest among agency standards and guidelines reviewed. As noted in Section 3.3.3, Schroeter et al. (2006) derived a NOAEL of 5 ppm for this effect using data from Brenneman et al. (2000), which would have the effect of changing the dosimetric and physiological adjustment (formerly 5) to a factor of 2, thus increasing the RfC to 0.0033 ppm.

4.1.2 Minimal risk level (MRL)—The MRL is an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure (ATSDR 2006). MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. They do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Although methods have been established to derive these levels, uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, MRLs will be revised.

Several estimates of MRLs have been made for H_2S (derivation shown detailed in ATSDR 2006). The following summarizes ATSDR's discussion.

- Acute MRL: ATSDR (2006) has set an inhalation MRL of 0.067 ppm (100 $\mu g/m^3$) for acute exposure duration (≤ 14 days) based on suggestive evidence of bronchial obstruction among asthmatics exposed to 2 ppm H_2S for 30 min (Jappinen et al. 1990). This concentration was considered a minimally

adverse effect level because changes in airway resistance and specific airway conductance were observed in only 2 of 10 subjects. The MRL was calculated by dividing the unadjusted LOAEL by an uncertainty factor of 27 (3 for use of a minimal LOAEL, 3 for human variability, and 3 for database deficiencies). The LOAEL from Jappinen et al. (1990) is supported by the LOAEL of 5 ppm for increased blood lactate levels observed in exercising subjects (Bhambhani et al. 1996). As noted, the Jäppinen study excluded individuals with severe asthma.

- Intermediate duration MRL. An MRL of 0.02 ppm has been derived for intermediate-duration inhalation exposure to H_2S (15 – 364 days). ATSDR noted the limited data on the toxicity of H_2S in humans following intermediate-duration exposure. Acute- and chronic-duration studies suggest that the respiratory tract and nervous system are sensitive targets of H_2S. Like the EPA (2003), the Brenneman et al. (2000) study was selected as the basis of the intermediate-duration inhalation MRL, and the critical effect was nasal lesions. The MRL was derived using the NOAEL/LOAEL approach, utilizing an uncertainty factor of 30 (3 for extrapolation from animals using dosimetric adjustments and 10 for human variability), adjusting for duration, and adjusting for regional gas dose ratio for the extra thoracic region. The same limitations, noted above, would apply to the MRL.
- Chronic MRL. ATSDR cites several human studies that have examined the chronic toxicity of inhaled hydrogen sulfide dating from 1951 to 1990, including Jaakkola et al. (1990), Jappinen et al. (1990) and Kangas et al. (1984) in the present review, plus several others. Most of these studies reported increases in the occurrence of subjective symptoms of respiratory irritation in workers or residents living near paper mills. However, due to limitations including poor exposure characterization (including the lack of information on peak exposure levels), co-exposures to other chemicals, and the lack of animal studies examining chronic toxicity, a chronic-duration inhalation MRL was not derived.

4.1.3 California reference exposure level (REL)—Similar to the EPA RfC, OEHHA (1999) defines the REL as the concentration level at or below which no adverse health effects are anticipated for a specified exposure duration. RELs are based on the most sensitive, relevant, adverse health effect reported in the medical and toxicological literature and are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety. Since margins of safety are incorporated to address data gaps and uncertainties, exceeding the REL does not automatically indicate an adverse health impact. A chronic inhalation REL of 0.0067 ppm (10 μg/m^3) was established by OEHHA (2000) on the basis of histopathological inflammatory changes in the nasal mucosa of mice study (CIIT 1983). Adjustments to human exposures included a subchronic uncertainty factor of 3, interspecies uncertainty factor of 3, intraspecies uncertainty factor of 10, and cumulative uncertainty factor of 100. It was noted that 50% of the population would be able to detect the odor of H_2S under controlled conditions, but only 5% would find it annoying at this level. An acute REL of 0.028 ppm (42 μg/m^3) for 1 hr was established by OEHHA (2008) on the basis of headache, nausea, and other physiological responses to odor.

4.1.4 WHO Air Quality Guidelines—WHO (2006) Air Quality Guidelines provide a value of 0.1 ppm (0.15 mg/m^3) with an averaging time of 24 hr based on ocular damage. WHO also states that to avoid substantial complaints about odor annoyance. H_2S concentrations should not be allowed to exceed 0.0046 ppm (7 μg/m^3) with a 30-min averaging period.

4.2 Occupational standards and guidelines

There are several widely used occupational standards and guidelines. As pointed out specifically for H_2S by Milby and Baselt (1999), acceptable air levels in workplace environments are based on very different considerations than acceptable levels in community air. In brief, persons in the workplace are assumed to be in reasonably good health, generally remain in the workplace environment for no more than 8 hr/day and 40 hr/wk, and generally are exposed to a limited number of agents. In contrast, community residents comprise all ages and all states of health and may be physically present in the community for most or all of any 24-hr period or longer. Residents also tend to have a reasonable expectation that their community air will be generally free of noxious substances that create health or nuisance problems. Thus, while H_2S levels possibly as high as 10 ppm have been considered acceptable for workplace settings (but see the new TLVs below), much lower concentrations (well below 0.1 ppm) can create unacceptable health and nuisance conditions in community settings (Table 1). For example, community health assessments performed by state agencies have used the US EPA RfC (Section 4.1.1) of 0.0015 ppb as a long-term level that might result in an increased risk of nasal irritation (MDHHS 2023).

4.2.1 U.S. threshold limit values (TLV)—The TLV-TWA is defined as “the time-weighted average concentration for a conventional 8-hr workday and a 40-hr work week, to which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effect” (ACGIH 2001). The TLV recommendations are widely used in occupational settings throughout the world. Since 1966, ACGIH (2001) has recommended a TLV-TWA (time weighted average) of 10 ppm and a TLV-STEL (short-term exposure limit) of 15 ppm for H_2S to protection against significant health risks of sudden death, eye irritation, neurasthenic symptoms such as fatigue, headache, dizziness, and irritability, or permanent central nervous system effects that may result from acute, subchronic, or chronic exposure. In part, the basis was a number of studies indicating that 10 ppm exposure will not cause eye irritation, the most commonly reported adverse physical effect of exposure to H_2S at concentrations of 50 to 100 ppm.

In 2010, ACGIH revised the exposure limits to 1 ppm (TWA) and 5 ppm (STEL) (ACGIH 2001). The basis and rationale for the changes is to be protective of upper respiratory tract irritation and central nervous system impairment. The TLV documentation cites that 1 ppm should be sufficient to protect against all the unwanted effects of H_2S and that peak exposures of 5 ppm may produce minor irritation and a brief change in oxygen uptake but would not be expected to produce more serious effects on the respiratory, central nervous or cardiovascular system. Cited studies supporting this conclusion included Bhambhani et al. (1996), Bhambhani and Singh (1991), Blackstone et al. (2005), Brenneman et al. (2000),

Dorman et al. (2004), and Fiedler et al. (2008), among others. ACGIH (2001) also notes that it may be necessary to control exposures below the TLV to prevent complaints of odor.

4.2.2 U.S. Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs) and National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits (RELs)—

OSHA has a Ceiling Limit of 20 ppm, Short-Term Exposure Limit (STEL) of 50 ppm (maximum 10-min peak per 8-hr shift), and a TWA of 10 ppm (vacated in 1989). These levels date back to 1978 (NIOSH 1978). The NIOSH REL is a ceiling of 10 ppm and an Immediately Dangerous to Life and Health (IDLH) limit of 100 ppm.

4.2.3 U.K. Occupational Exposure Standards (OES)—

In the U.K., OES were set in 2002 at 5 ppm for the 8-hr TWA and 10 ppm for the STEL. The basis for these levels are studies on young, fit, and healthy adult human volunteers undergoing maximal and submaximal exercise which demonstrated that brief periods (15 – 30 min) of exposure to 5 and 10 ppm, respectively, caused a shift towards anaerobic respiration (Bhambhani et al. 1996; Bhambhani and Singh 1991; Costigan 2003).

4.2.4 Scientific Committee on Occupational Exposure Limits (SCOEL)—

Following the UK OES, in 2007 the European SCOEL recommended setting the 8-hr TWA and the STEL to 5 and 10 ppm, respectively, based on experimental studies of nasal lesions in rats (SCOEL 2007). Their report discussed studies examining eye irritation and lung function impairment, but concluded that workers in the occupational studies examined were also exposed to CS_2 gas, and that effects could not be attributed to H_2S alone at levels below 20 ppm.

4.2.5 Dutch Expert Committee on Occupational Standards (DECOS)—

The Dutch set standards in 2006 (DECOS 2006) and 2010 (DECOS 2010) at 1.6 ppm for long-term exposure to H_2S, substantially below the UK OES and European SCOEL. No recommendations were made for a short-term standard. Again, nasal lesions in rats served as the critical effect with a NOAEL of 10 ppm. The DECOS added an additional safety factor after considering the potential for differences among people, specifically pregnant women and asthmatics who may be more sensitive to exposure.

4.2.6 German maximum workplace concentration (MAK)—

In 2006, the German review committee recommended a Maximum Workplace Concertation (MAK) of 5 ppm, stipulated as the highest concentration assessed that will not interfere with occupational activity or cause adverse effects. This recommendation was based on a review of toxicity data (including ATSDR 2006; DECOS 2006), and included studies on skin irritation, lung function impairment, and cardiovascular effects.

4.3 U.S. Emergency response guidelines

Like the occupational limits, emergency response guidelines are not intended as general community standards. Several sets of guidelines are listed here for completeness and reference.

4.3.1 Emergency Response Planning Guidelines—Existing short-term exposure guidelines include the American Industrial Hygiene Association (AIHA 1991) Emergency Response Planning Guidelines (ERPGs), which are defined as concentration ranges where adverse health effects could be observed. Three ERPGs are available for many substances, with the definitions are provided below (Cavender et al. 2008).

- The ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for 1 hr without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odor, which is set to 0.1 ppm for H_2S (60 min peak).
- The ERPG-2 is the maximum airborne concentration below which nearly all individuals could be exposed for 1 hr without experiencing or developing irreversible or other severe health effects which could impair an individual's ability to take protective action, which is 30 ppm (60 min peak).
- The ERPG-3 is the maximum airborne concentration below which nearly all individuals could be exposed for 1 hr without experiencing or developing life-threatening health effects, which is 100 ppm (60 min peak).

4.3.2 U.S. Acute Exposure Guideline Levels (AEGLs).—AEGLs are a second set of emergency response guidelines developed through a collaborative and worldwide effort involving the public and private sectors. AEGLs describe risks to humans resulting from once-in-a-lifetime, or rare, exposure to airborne chemicals. The National Advisory Committee for the Development of Acute Exposure Guideline Levels for Hazardous Substances (AEGL Committee) is involved in developing these guidelines to help both national and local authorities, as well as private companies, deal with emergencies involving spills, or other catastrophic exposures (NRC 2001). AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 min to 8 hrs.

AEGLs are used for emergency planning and response, often in combination with computer-assisted air dispersion models to estimate "vulnerability zones" associated with releases of chemical substances, e.g., as stipulated under the U.S. EPA Risk Management Program (section 112(r) of the Clean Air Act Amendments for eligible sources (Section 1.3). Then, human health risks associated with a chemical release can be estimated by comparing the projected airborne concentrations of the chemical with the exposed populations and AEGL values to determine appropriate responses. Three levels (AEGL-1, AEGL-2 and AEGL-3) have been developed for each of five exposure periods (10 and 30 min, 1 hr, 4 hr, and 8 hr) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

- AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure. AEGL-1 ranges from 0.33 ppm to 0.75 ppm for averaging

times ranging from 8 hr to 10 min, respectively. These values are derived from a human study of headaches among asthmatics (Jappinen et al. 1990).

- AEGL-2 is the airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-2 ranges from 17 ppm to 41 ppm for averaging times ranging from 8 hr to 10 min, respectively. These values are derived from rat studies of perivascular edema (Khan et al.1991; Green et al. 1991).
- AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death. AEGL-3 ranges from 31 ppm to 76 ppm for averaging times ranging from 8 hr to 10 min, respectively. These values are derived from a rat study of mortality following a 1-hour exposure (MacEwen and Vernot 1972).

As the AEGL program notes, “AEGLs have been developed primarily to provide guidance in situations where there can be a rare, typically accidental exposure to a particular chemical that can involve the general public. They, therefore, differ from PELs, TLVs, WEELs, RELs or MAK values, etc. in that they are based primarily on acute toxicology data and not subchronic or chronic data. The guidance therefore does not reflect the effects that could result from frequent exposure. Also, they are designed to protect the general population including the elderly and children, groups that are generally not considered in the development of workplace exposure levels.” An advantage of AEGLs is that they account for exposure time. AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses. It is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

The current AEGLs for H_2S were published on April 11, 2002, and remained “interim” AEGLs until 2012 when they were accepted by the AEGL Subcommittee to become “Final” for use by public and private organizations. The Subcommittee states that interim AEGLs represent “the best efforts of the AEGL Committee to establish exposure limits, and the values are available for use as deemed appropriate on an interim basis by federal and state regulatory agencies and the private sector” (NRC 2001). Shortly after approving the AEGLs, the Subcommittee disbanded. The AEGLs have not been revised subsequently.

4.4 Summary of Exposure Recommendations and Regulatory Levels

Guidelines and standards for continuous exposure to H_2S in community and occupational settings address short-term, intermediate, and long-term duration of exposure to a range of concentrations that, for the most part, exceed the background levels that communities experience on a regular basis. For shorter term exposures, the ATSDR has recommended a MRL of 0.07 ppm with a LOAEL of 2 ppm for exposures lasting ≤14 days and the WHO published a guidance value of 0.1 ppm with a LOAEL of 15 ppm for exposures lasting 24 hrs. For intermediate exposure duration (15 – 365 days), the ATSDR set a MRL of

0.02 ppm with a NOAEL of 30.5 ppm. For long-term, even lifetime, exposure duration, the EPA set an RfC of 0.0015 ppm with a LOAEL of 30 ppm and a NOAEL of 10 ppm. The California OEHHA set an inhalation REL of 0.008 ppm with a NOAEL of 30.5 ppm. In terms of occupational guidelines and standards, STELs of 5 ppm, 10 ppm, and 50 ppm were established by ACGIH, U.K. OES, and OSHA, respectively; TWAs of 1 ppm, 5 ppm, and 10 ppm were set by ACGIH, U.K. OES, and OSHA, respectively; Ceilings of 10 ppm and 20 ppm were established by OSHA and NIOSH, respectively. The OSHA exposure limits are higher than those set by other agencies and have not been updated in 40 years. Additional standards for emergency response situations (AEGLs and ERPGs) exist but are not intended to address chronic, low-level exposures. As previously discussed, occupational and community air standards are different for valid reasons. Workers are, on average, healthier and exposed to less toxic agents than would be a community member. Protective community standards must consider people of all ages with underlying health conditions, odor sensitivities, or other vulnerabilities, and who are likely exposed to a more complex mixture of agents.

For short, intermediate, and long-term exposures, community standards identify exposure to H_2S concentrations between 0.0015 and 0.1 ppm and above as potentially dangerous to human health. At first glance, a long term community standard set in the vicinity of 0.01 ppm may seem protective of public health given the H_2S levels reported in most of the epidemiological studies that used objective measures of H_2S concentrations. Most of these studies used an averaging period of at least one year, notably longer than the time period considered by all of the occupational standards, as well as by most of the community standards. However, local sources of H_2S in community settings that result in low (<0.01 ppm) long term exposure can and frequently do produce much higher concentration short-term peaks (lasting minutes to hours); these peaks may far exceed the odor detection threshold and may be associated with irritation and other adverse health effects. This highlights the need for both chronic and acute exposure limits.

Finally, as noted throughout this review, community exposure to H_2S typically occurs as a mixture of pollutants that depends on the source (e.g., CAFO, wastewater, landfill, oil and gas facility). Given the difficulty and expense of monitoring all components in the mixture, the H_2S (or total reduced sulfur) concentration may serve as a surrogate or indicator of exposure. While this does not affect the H_2S-health response relationship, it may require additional interpretation and adjustment as a community standard. Specifically, a lower standard may be required if the co-pollutants in the mixture have synergistic effects or increase the toxicity when H_2S is at low levels. Unfortunately, relatively few studies adequately characterize co-pollutants, much less their interactions.

5 Conclusion

Increased large scale food production and shifts in the fossil fuel sector, specifically the development and expansion of CAFOs and hydraulic fracturing, have spurred the growth of industries that emit H_2S. In turn, elevated emissions of H_2S in the U.S. and elsewhere has increased the likelihood of low level but widespread and chronic community exposure to this toxic gas. Acute exposure to high H_2S concentrations can produce morbidity and

death with a well-understood dose-response relationship, based primarily on a large body of occupational studies. In contrast, effects of chronic and low-level exposure of H_2S, defined here as concentrations below 0.1 ppm, in both occupational and community settings is much less well understood.

This review has synthesized the literature since 2004, which includes over 100 studies addressing toxicology, controlled human studies, and observational human studies, with a focus on community impacts. We have not attempted a risk assessment of H_2S exposure. Most of the recent literature continues to focus on naturally occurring geothermal and volcanic H_2S sources and on industrial sources such as CAFOs, pulp and paper mills, and wastewater treatment facilities. The epidemiological studies in these settings are limited by several challenges. First, the exposure assessments have frequently used spatial proxies of H_2S, or spatially and temporally sparse point measurements, both with potentially large and generally unknown exposure measurement error. This is significant given considerable uncertainty and variability in H_2S emissions and concentrations, perhaps especially around CAFOs. Second, H_2S emitted by both natural and industrial sources typically occurs as part of a mixture with other pollutants; this mixture can include other reduced sulfur compounds released from many sources, as well as ammonia, dust, bacteria, insecticides, and mold from CAFOs, and SO_2, other combustion products and VOCs from industrial sources such as paper and pulp mills and oil and gas facilities. This leads to the potential for confounding by co-pollutants, particularly in chronic studies where the spatial and temporal variation of exposures is large. Third, the epidemiological literature is not conducive to formal meta-analyses given its diversity in terms of population studied, exposure conditions, and study design. However, it is primarily the potential for exposure measurement errors and confounding that limits the strength of the association between low level H_2S exposure and adverse health effects. Despite such limitations, chronic community exposure to H_2S at average concentrations below 0.01 ppm and peak (short-term) exposures roughly an order of magnitude higher has been associated with a spectrum of adverse health effects, most notably odor aversion, irritation, and ocular, nasal, respiratory, and neurological effects. It is likely that susceptible and vulnerable populations, including individuals with underlying health conditions such as asthma, may be particularly at risk. Several of the observational studies, particularly those with larger sample sizes and longitudinal designs, have greater sensitivity and have shown effects for changes in H_2S levels in the 0.001 ppm range. While the possibility of confounding by co-pollutants cannot be completely ruled out in each study, effects of low level chronic exposure are seen in different settings and across H_2S sources (CAFOs, landfills, geothermal, volcanic, pulp mills) where pollutant mixtures will vary significantly. Collectively, the epidemiological evidence supports the finding that adverse health impacts are caused by exposure to H_2S at low levels, defined here as below 0.1 ppm.

Our findings should be confirmed and extended by larger and more comprehensive epidemiological studies that incorporate susceptible populations, address a wider variety of industrial sectors, and assess multiple outcomes, including neurological, cardiovascular, reproductive/developmental, immune, and carcinogenic endpoints. These studies should be methodologically robust, measuring co-pollutants, accounting for multicollinearity, and employing objective exposure assessment techniques that include long-term continuous sampling to determine annual, daily and hourly average H_2S concentrations, mapping of

exposures, hybrid modeling. Study designs using larger samples sizes, longitudinal models with repeated observations or using case-crossover techniques may prove particularly sensitive and robust. In addition, researchers should consider measuring indoor air concentrations or individual exposures using personal air monitors, while weighing the feasibility of associated costs and participant burdens.

To date, few studies have focused on the oil and gas extractive industries, or the chemical and petroleum industries, which collectively emit about one-third of total U.S. H_2S emissions. Understanding the health impacts of fracking is particularly important given its recent and rapid growth and its potential to emit significant levels of H_2S during well development and potentially other phases, though we recognize the potential for co-exposure to diesel particulate matter, NO_x and potentially other pollutants in such studies. National or state H_2S emissions tracking programs can help to identify the relative contributions of industrial sectors and the potential impact of imposing stricter regulations. Industry emissions data can help inform the design of community-based exposure assessment and health studies, although these data may not be adequate and reliable.

Long-term epidemiological studies with large sample sizes and objective exposure measures also are needed to confirm and expand upon findings of neurological effects starting at long-term mean concentrations of 0.007 ppm, and eye irritation, nasal irritation and harmful respiratory effects starting at 0.0003 ppm. As research expands to include susceptible populations and a wide range of adverse health effects, agencies will need to ensure that their guidelines are sufficiently protective of community-wide releases of H_2S.

The adverse health impacts associated with low-level chronic exposure shown in many of the reviewed studies, combined with the continuing and possibly increasing emissions in some sectors, suggest the need for additional emission standards, administrative and/or engineering controls on agricultural and industrial facilities, and enforcement of protective exposure standards or guidelines. In the USA, community guidelines of 0.0015 and 0.020 ppm were set by the EPA (RfC) and ATSDR (Intermediate MRL) in 2003 and 2006, respectively. The lower EPA guideline is more protective in part as it considers subchronic and lifetime exposures; the intermediate ATSDR guideline considers exposure durations up to one year. Although both agencies stated that these levels consider sensitive populations, they were developed from rat inhalation studies that may not be sufficiently protective to protect susceptible populations, even after adjusting for uncertainty factors. Further, these guidelines do not account for odor aversion, irritation, and ocular, nasal, respiratory and neurological effects that epidemiological studies suggest can occur at low exposure levels. Compared to community guidelines, occupational guidelines permit considerably higher exposure concentrations, namely, 1 and 10 ppm, as established by the ACGIH (TLV-TWA) and OSHA (PEL-TWA) in 2010 and 1989, respectively, and should not be applied as community guidelines.

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List of abbreviations and acronyms

This report uses the following abbreviations:

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Level
AER	Alberta Energy Regulator
AEUB	Alberta Energy and Utility Board
AH	Alberta Health
AIHA	American Industrial Hygiene Association
ATSDR	Agency for Toxic Substances and Disease Registry
BDI	Beck’s depression inventory
BHS	Beck’s hopelessness
CAAQS	California Ambient Air Quality Standard
CAFO	confined animal feeding operation
CC16	club cell protein 16
CDC	Centers for Disease Control and Prevention
CIIT	Chemical Industry Institute of Toxicology
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	computed tomography
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
ERPG	emergency response planning guideline
FEV_1	forced expiratory volume
FNBH	Finnish National Board of Health

FR	Federal Register
FVC	forced vital capacity (measure of lung volume)
H_2S	hydrogen sulfide (gaseous air pollutant)
HEC	human equivalent concentration
ICAM-1	intercellular adhesion molecule 1
IDLH	Immediately Dangerous to Life and Health
IL-8	interleukin 8
IQR	interquartile range
JEM	job-exposure matrix
LOAEL	lowest observed effects level
MIP	macrophage inflammatory protein
MRI	magnetic resonance imaging
MRL	minimal risk levels
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effects level
NO_x	nitrogen oxides (gaseous air pollutant)
NRC	National Research Council
O_3	ozone
OEHHA	California Office of Environmental Health Hazard Assessment
OEL	Occupational Exposure Limit
OES	Occupational Exposure Standard
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
PK-CFD	pharmacokinetic computational fluid dynamics
$PM_{2.5}$	particulate matter under 2.5 μm dia. Also, PM_{10} for 10 μm diameter
ppb	parts per billion (volume-type pollutant concentration unit)
ppm	parts per million (volume-type pollutant concentration unit)
R_{aw}	airway resistance

RADS	reactive airways distress syndrome
RBC	red blood cell
REF	reference exposure level
REL	reference exposure levels (used by State of California)
RfC	reference concentration
SG_{aw}	specific airway conductance
sIgA	secretory immunoglobulin A
SO_2	sulfur dioxide (gaseous air pollutant)
SpD	surfactant protein D
TLV	Threshold Limit Values
TRI	Toxic Release Inventory, part of the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 toxic chemical release reporting requirements
TRS	total reduced sulfur (gaseous air pollutant)
TSP	total suspended particulate (particulate air pollutant)
TWA	time weighted average
$\mu g/m^3$	micrograms per cubic meter (density type pollutant concentration unit)
WHO	World Health Organization
WTP	water treatment plant
WWTP	wastewater treatment plant

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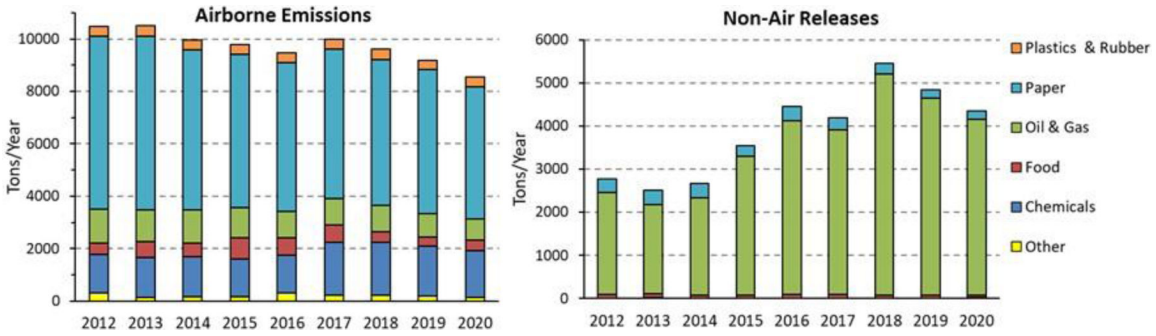

Figure 1.

H_2S emissions reported in the U.S. Toxics Release Inventory (TRI) to air and other media by the top emitting industry sectors, 2012–2020. “Oil & gas” includes releases from petroleum refineries, bulk plants and terminals, and NAICS industry code 999 (primarily oil and gas extraction); “Paper” includes pulp mills; “Other” includes primary metals, nonmetallic mineral products, water, wastewater, beverages, electric utilities, hazardous waste, wood products, leather, poultry and egg production, machinery, furniture, transportation equipment, and metal mining.

Table 1.

Summary of health symptoms and effects for concentrations and exposure durations of H_2S reported in the cited studies. Co-exposures and concentration range and study population size shown, when available. Adapted in part from ACGIH (2001) and Skrtic (2006).

Concentration (ppm)	Exposure Duration	Effect	Source	Exposure group	H_2S exposure range	Co-exposure (average, range, SD)
5000 ppm	Immediate	Death	Fuller and Suruda 2000	Occupational	0.2–5000 ppm	None
1000 – 2000 ppm	NA but very short term	Loss of consciousness, collapse, paralysis of respiration, possible death	ACGIH 2001	Occupational based on rat and human studies	0.0002–2000 ppm	None
			Fuller and Suruda 2000	Occupational	0.2–5000 ppm	None
			Milby and Baselt 1999	Occupational	0.25–1000 ppm	Cl, NH_3, SO_2 noted, but not as co-exposures
500 – 1000 ppm	Acute	Serious respiratory, central nervous, and cardiovascular system effects, e.g., stimulation of respiratory response, hyperpnea, apnea, unconsciousness, death	ACGIH 2001	Occupational based on rat and human studies	0.0002–2000 ppm	None
			EPA 1993	Oil & gas production	0–2000 ppm	Reduced sulfur gases, organic sulfides noted
			Fuller and Suruda 2000	Occupational	0.2–5000 ppm	None
250 ppm	Acute and Intermediate	Pulmonary edema, risk of death	Milby and Baselt 1999	Occupational	0.25–1000 ppm	Cl, NH_3, SO_2 noted, but not as co-exposures
		Damage to organs, nervous system, depression of cellular metabolism	EPA 1993	Oil & gas production	0–2000 ppm	None
150 – 200 ppm	NA	Olfactory fatigue, paralysis	ACGIH 2001	Occupational based on rat and human studies	0.0002–2000 ppm	None
			EPA 1993	Oil & gas production	0–2000 ppm	None
100 ppm	NA	Headaches, dizziness, lethargy	ACGIH 2001	Occupational based on rat and human studies	0.0002–2000 ppm	None
50 – 100 ppm	Prolonged	Intense eye irritation, conjunctivitis, cornea scarring, olfactory fatigue	EPA 1993	Oil & gas production	0–2000 ppm	None
			Milby and Baselt 1999	Industrial	0.25–1000 ppm	Cl, NH_3, SO_2 noted, but not as co-exposures
50 ppm	Prolonged	Olfactory fatigue, ocular pain	OEHHA 2008	Workplace	0.00007–1000 ppm	None
4–50 ppm	Prolonged	Nasal bleeding, headaches, fatigue	Mousa 2015	Oil field workers	4–50 ppm	None
30 ppm	NA	Olfactory paralysis	Snyder et al. 1995	Occupational	30 - >700 ppm	None

Concentration (ppm)	Exposure Duration	Effect	Source	Exposure group	H_2S exposure range	Co-exposure (average, range, SD)
5 – 50 ppm	NA	Moderate irritation of the eyes, risk of pulmonary edema	ACGIH 2001	Occupational based on rat and human studies	0.0002–2000 ppm	Carbon disulfide
5 ppm	Immediate	Increase in anxiety	ATSDR 2006	Inhalation	0->500 ppm	NO_X, SO_2, CO, NH_3, methyl mercaptan, methyl sulfide
5 – 10 ppm	Immediate	Relatively minor metabolic changes in exercising individuals during short-term exposures.	ACGIH 2001	Occupational based on rat and human studies	0.0002–2000 ppm	None
<10 ppm	Various	Slowed development in infants, irritability, headache, fatigue.	EPA 1993	Oil & gas production	0–2000 ppm	None
5 ppm	Acute	Increase in anxiety symptoms (single exposure)	ACGIH 2001	Occupational based on rat and human studies	0.0002–2000 ppm	None
5 ppm	NA	Start of the dose-response curve (short term exposure':	ACGIH 2001	Occupational based on rat and human studies	0.0002–2000 ppm	None
<5 ppm	NA	Metabolic changes observed in exercising individuals, but not clinically significant	ACGIH 2001	Occupational based on rat and human studies	0.0002–2000 ppm	Methyl mercaptan, dimethyl sulfide
2 – 5 ppm	Acute	Higher oxygen intake	Bhambhani et al. 1996;	Inhalation with exercise	0–5 ppm	None
			Bhambhani and M. Singh 1991	Inhalation with exercise	0–5 ppm	SO_2, CO_2 noted, but not as co-exposures
			Jappinen et al. 1990	Pulp mill workers	1–11 ppm	SO_2 (0.03 ppm)
1 – 5 ppm	Acute to intermediate	Balance issues, delayed verbal recall, impaired color discrimination, decreased grip strength, reaction time impacts, recall issues	Kilburn 1999	4 exposure groups: (1) residents with soil gas exposure in California (N-24); (2) residents near refinery (N=35); (3) residents near refinery explosion (N=48); (4) refinery workers (N=16); Controls from 4 towns (N=357)	0.1 – 8.8 ppm (24-hr), other measurements to 20 ppm reported	Group 2: carbon oxide sulfide (2.6–52 ppm), mercaptans (1–21.1 ppm)
0.25 – 0.30 ppm	Chronic	Odor nuisance, nausea, disturbance to sleep	Milby and Baselt 1999	Industrial	0.25–1000 ppm	Cl, NH_3, SO_2 noted, but not as co-exposures
0.17 ppm	Chronic	Increase in mortality from transportation accidents	Lewis et al. 2003	Petroleum workers(N=25,292; Transportation accidents with N=15)	H_2S estimated for workers with transportation accidents (N=15); 0.01–0.60 ppm for larger group	Fuels (0.01–48 ppm), lubricants (0.1 – 289 ppm), coke/catalyst (0.03–84 μg/m^3), vinyl chloride monomer, asbestos; smoking status
0.020–0.027 ppm	Chronic	Slightly reduced prevalence of wheeze; no other effects on asthma or respiratory symptoms	Bates et al. 2013	Adults in Rotorua at residential & workplace locations (N=1637)	0–0.064 ppm	None

Concentration (ppm)	Exposure Duration	Effect	Source	Exposure group	H_2S exposure range	Co-exposure (average, range, SD)
0.02–0.13 ppm	Acute	Odor recognition	Costigan 2003	Oil and water treatment industry - review of studies	0–2000 ppm	SO_2, CS_2, H_2SO_4
0.03 ppm	Chronic	Aggravation of respiratory disease noted by increased hospital visits	Campagna et al. 2004	Unscheduled hospital visits for respiratory disease in Nebraska, USA near agricultural and tanning sources (Visits N=455 for asthma, N=5009 for all respiratory disease)	0.03 ppm	TRS, SO_2 (0.03 ppm)
0.03–0.05 ppm	Acute	Odor nuisance, headaches, nausea	Fiedler et al. 2008	Individuals exposed to low concentrations	0.05–5 ppm	None
			OEHHA 2008	Panel study (N=16)	0.00007–1,000 ppm	none - controlled study
			Reynolds and Kamper 1984	Sensitive population	0.012–0.069 ppm	CO_2, NO
0.008 ppm	Intermediate	Nasal histological change in mice	OEHHA 2008	90-day mouse exposure; N=10–12 for each of 4 exposure groups	0 – 80 ppm for 6 hr/day, 5 day/week for animals; 100-fold adjustments for humans	none - controlled study
0.007–0.027 ppm	Chronic	Neurophysiological abnormalities	Legator et al. 2001	Groups in Odessa, Texas (N=126) and Puna, Hawaii (N=97) compared to 170 controls	0.007–0.027 ppm (average); 0.5 ppm for max 8-hr in Odessa; 0.5 ppm for max 1-hr in Puna	None
0.007–0.096 ppm	Acute & Chronic	Eye irritation	Haahtela et al. 1992	Group near pulp mill during upset (N=60) and reference group (N=66)	0–0.096 ppm (4-hr)	SO_2 (2–3 μg/m^3, average); mesityl oxide
			Heaney et al. 2011	Adults living within 0.75 mile of landfills (N=23)	0–0.0023 ppm	None
			Kilburn 2012	Residents within 2.2 km of CAFO hog lagoons (N=25) in Ohio and unexposed individuals (N=22)	0–0.03 ppm (average); several measurements from 1–2.1 ppm	CO in expired air (0–27 ppm)
			Marttila et al. 1994	Children living near pulp mill (N=134)	0.0007–0.053 ppm average; 0.01–0.067 ppm 24-hr peaks (modeled)	CH_3HS (2–5 μg/m^3 average), SO_2 (2–3 μg/m^3 average)
			Schiffman et al. 2005	Volunteers in controlled tests (N=48)	0–0.024 ppm	NH_3 (0.046–0.817 ppm), PM_{10} (24 μg/m^3), endotoxin (7.4 EU/m^3)
			Schinasi et al. 2011	see Horton below	see Horton below	see Horton below
0.002 ppm (TRS)	Intermediate	Eye and nasal symptoms, cough, headache/migraine	Partti-Pellinen et al. 1996	Residents near pulp & paper mill and controls (N=336)	0.002 ppm average; 0–0.038 ppm for 24-hr; 0.104 ppm for 1-hr max (all as TRS)	SO_2 (average 1 μg/m^3; 24-hr from 0–24 μg/m^3; 1-hr maximum of 152 μg/m^3)

Concentration (ppm)	Exposure Duration	Effect	Source	Exposure group	H_2S exposure range	Co-exposure (average, range, SD)
Δ0.0067 ppm	Chronic	Asthma exacerbation, indicated by increase in medication dispensed	Carlsen et al. 2012	Adults in Rotorua, Iceland dispensed anti-asthma drugs (N=up to 192 per day)	0–0.062 ppm (24-hr)	PM_{10} (24-hr 23.2 ±17.8 μg/m^3); NO_2 (24-hr 21.9 ±14.5 μg/m^3); O^3 (8-hr 42.9 ±15.2 μg/m^3)
Δ0.005 ppm	Chronic	Respiratory hospitalizations and mortality	Nuvolone et al. 2019	Residents near geothermal electric power plants (N=33,804)	Model predicted 90-day maximum	PM, NO_2, O_3 noted as below limits
0.005 ppm	Acute effects (7.5 year long study)	Emergency room visits associated with heart disease	Finnbjornsdottir et al. 2016	Residents exposed to geothermal power plant plume in Reykjavik, Iceland (N=13,381 hospital patients)	0.005 ppm average: 0–0.047 ppm for 24-hr; plume model estimates	NO_2, O_3, PM_{10}, SO_2 noted; values not given
0.00022 ppb	Acute	Emergency room visits associated with heart disease	Heaney et al. 2011	Residents within 0.75 mile of municipal waste landfills (N=23)	0–2.3 ppb (1-hr)	None
0.0003–0.001 ppm *	Chronic (2-yr)	Stress and negative mood	Horton 2007	Residents within 0.2 – 1.4 miles of CAFO (swine) facility (N=101)	0.0003 ±0.00186 ppm (1-hr average); 0–0.0015 ppb (2-yr average across 16 areas)	Odor (1.3 ±1.88); $PM_{2.5}$ (10.9 ±5.6 μg/m^3); PM_{10} (19.4±11.8 μg/m^3), endotoxin
		Nose and eye irritation, difficulty breathing, wheezing	Schinasi et al. 2011			

'NA' means not available (not provided).'Δ' means change in concentration;

* analyzed a 0.001 ppm change in the exposure concentration.

Table 2.

Summary of existing H_2S exposure recommendations for the general public in the U.S. Derived and updated from Armstrong et al. (2004).

Parameter	EPA	California OEHHA	ATSDR	ATSDR	WHO
Standard or guideline	RfC	REL (inhalation)	Acute MRL	Intermediate MRL	Guidance value
Concentration (ug/m^3)	2	10	100	30	150
Concentration (ppm)	0.0015	0.008	0.070	0.020	0.101
Exposure period	continuous (lifetime)	continuous (i.e., 8 yrs)	continuous, acute duration (≤ 2 wks)	continuous, intermediate duration (≤1 yr)	24 hr
Target population	general population, including sensitive groups	general population	general population, including sensitive groups	general population, including sensitive groups	general population
LOAEL (ppm)	30	-	2	-	15
NOAEL (ppm)	10	30.5	-	30.5	NA
Critical study	subchronic rat study by Brenneman et al. 2000	subchronic mouse study by CIIT 1983	acute experimental human study by Jappinen et al. 1990	subchronic rat study by Brenneman et al. 2000	Savolainen et al. 1982 for ocular effects; Tenhunen et al. 1983 for haem synthesis
Critical effects	no destruction of olfactory neurons or inflammation/necrosis of nasal epithelium	no inflammation of nasal epithelium	increase in airway resistance	no inflammation of nasal epithelium	ocular irritation
Adjustments	intermittent = continuous exposure, rat = human, dosimetry, interspecies, sensitive humans, subchronic = chronic exposure	intermittent = continuous exposure, rat = human, dosimetry, interspecies, sensitive humans, subchronic = chronic exposure	LOAEL= NOAEL, interspecies sensitivity	intermittent = continuous exposure, rat = human, dosimetry, interspecies, sensitive humans	uncertainty factor due to steep dose-effect curve; also single report of haem synthesis impacts at 1.5 mg/m^3
Year developed	2003	2000, maintained in 2008	1999, maintained in 2016	2006, maintained in 2016	2000, maintained in 2003
Comments	RfCs can be derived for non-carcinogenic effects of known carcinogens and for non-inhalation routes.	same as ATSDR except for subchronic, chronic factor and rounding differences			Also recommends a 30-min mean exposure limit of 0.005 ppm or 7 μg/m^3 for odor annoyance.