Effect of environmental exposure to hydrogen sulfide on central nervous system and respiratory function: a systematic review of human studies

Eunjung Lim¹, Omar Mbowe¹, Angela S. W. Lee², James Davis¹

¹Biostatistics and Quantitative Health Sciences, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA, ²Health Sciences Library, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA

Background: Assessment of the health effects of low-level exposure to hydrogen sulfide (H₂S) on humans through experiments, industrial, and community studies has shown inconsistent results.

Objective: To critically appraise available studies investigating the effect of H₂S on the central nervous system (CNS) and on respiratory function.

Methods: A search was conducted in 16 databases for articles published between January 1980 and July 2014. Two researchers independently evaluated potentially relevant papers based on a set of inclusion/exclusion criteria.

Results: Twenty-seven articles met the inclusion criteria: 6 experimental, 12 industry-based studies, and 10 community-based studies (one article included both experimental and industry-based studies). The results of the systematic review varied by study setting and quality. Several community-based studies reported associations between day-to-day variations in H₂S levels and health outcomes among patients with chronic respiratory conditions. However, evidence from the largest and better-designed community-based studies did not support that chronic, ambient H₂S exposure has health effects on the CNS or respiratory function. Results from industry-based studies varied, reflecting the diversity of settings and the broad range of H₂S exposures. Most studies did not have individual measurements of H₂S exposure.

Discussion: The results across studies were inconsistent, justifying the need for further research.

Keywords: Hydrogen sulfide, Central nervous system, Respiratory function, Geothermal

Introduction

Hydrogen sulfide (H₂S) is produced naturally from the breakdown plant and animal material and from geothermal fields. It is also created via industrial sources such as rayon textile production, oil and gas refineries, and pulp and paper manufacturing.¹ The health effects of H₂S increase sharply with dose, ranging from a rotten egg smell (0.13–0.15 ppm), to respiratory, eye, and throat irritation (100 ppm), to olfactory nerve paralysis (150 ppm), and coma (1000 ppm).^{2–4} Exposure to high concentrations can be extremely hazardous and lead to immediate collapse or death. Most deaths have occurred in industrial settings.^{5–7}

Experimental studies examining the short-term effects of low H₂S level exposure (from 2 to 10 ppm) on healthy adults found that during exercise, ratings of odor intensity and irritation increased, and oxygen uptake decreased.^{8–12} However, no trends between dose, sensory

or cognitive measures, and respiratory function were described. Experimental studies suggest that short-term health effects are limited in healthy adults. Less certain are the health effects of low-level community exposures, in the range of 0.5 to 90 ppb, from industrial or natural sources of H₂S. Settings with ambient H₂S exposure include communities near commercial farming and volcanic or geothermal sources. The reported health effects of H₂S exposure in such settings have been inconsistent.^{13–15} This review examines published studies of respiratory and central nervous system (CNS) effects. Our review includes articles from both industrial and community studies examining the health effects associated with day-to-day variations in H₂S levels.

Methods

Eligibility criteria

We conducted a comprehensive systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁶ The initial

Correspondence to: James Davis, PhD, Biostatistics and Quantitative Health Sciences, John A. Burns School of Medicine, University of Hawaii, 651 Ilalo Street, BSB 211, Honolulu, HI 96813, USA. Email: jamesdav@hawaii.edu

eligibility criteria were developed by the authors to address the main question: What evidence is there of possible negative health effects in respiratory system and CNS from H₂S exposure? We included studies where the cohort or human subjects had low-level H₂S exposure in experimental setting, industry, or community. The inclusion criteria were studies (1) of neurological or respiratory symptoms, (2) English language, and (3) published in peer-reviewed literature from January 1980 to July 2014. The exclusion criteria were (1) review papers, (2) non-human studies, and (3) forensic or case-report studies.

Information source and literature search

The literature search was conducted between March and July 2014. Search terms included: H₂S, geothermal energy, and health effects. Although the terms H₂S and geothermal energy are well defined with few variant spellings or synonyms, the concept of health effects covers a range of topics. Thus, the authors agreed on “health effects” as the search phrase to encompass all the many alternative terms for neurological and respiratory functions. The search was broadened by including all pairs of the three major concepts (i.e. H₂S and geothermal; H₂S and health effect; geothermal and health effect) and other sources of H₂S (e.g. pulp mill, hog farm, refinery, sewer) and more specific terminologies indicating CNS and respiratory functions (e.g. brain, cognition, CNS, nervous system, neurological, breathing, lung, pulmonary, respiration, cardiovascular, circulatory).

Sixteen databases were extensively searched: CABI Environmental Impact, Cochrane Library, EMBASE, GeoBase, GeoRef, GreenFILE, Global Health Library (WHO), Google Scholar, National Technical Information Service, PsycINFO, PubMed/Medline, TOXNET, TRIP, SUMSearch, Web of Science, and WorldCat.

A sample search strategy from a PubMed/Medline search is provided below:

- (1) (H₂S OR hydrogen sulfide) AND (geothermal) AND (health effects OR health condition OR health status OR medical condition).
- (2) (H₂S OR hydrogen sulfide) AND (geothermal) AND (brain OR cognition OR CNS OR nervous system OR neurological OR breathing OR lung OR pulmonary OR respiration OR cardiovascular OR circulatory).

The results were transferred to the reference management software Endnote¹⁷ for easier management and retrieval of full-text articles. Two of the three authors (JD, EL, OM) determined the eligibility of each article. Differences of opinion were resolved by the third.

Risk of bias

The risk of bias was assessed based on the presence of three common study biases: information, selection, and confounding biases.^{18–21} To evaluate information bias, H₂S exposure levels were classified into individual or ecological measurement. Ecological measurements can come

from H₂S monitors placed around cities or workplaces, from using job titles as categories of exposure, and from employing geographical residence as a measure of exposure. Individual measurements can be obtained by having people wear a measuring instrument on their bodies. Alternatively, individual exposures may be estimated from calculations of H₂S exposure based on where people live and/or work. An example of confounding would be the association between H₂S exposure and respiratory function that might be distorted by exposure to SO₂.^{22,23} Studies were classified by whether or not they controlled for potentially confounding variables. Selection bias results from using a non-representative sample of the study population. People with both H₂S exposure and symptoms, for example, may join a study more often than people without symptoms. Studies were classified based on whether they used a “convenience sample.” Using people convenient to the researcher, such as volunteers or plaintiffs in lawsuits, can create a selection bias and misleading conclusions. Study assessments of the three biases were done independently by three of the authors (JD, EL, OM). Discrepancies were resolved by discussions.

Results

Study selection

Figure 1 shows a flow chart of the literature search. Three hundred and seventy-seven research articles were identified. After removing duplicate and ineligible articles, 27 articles remained for systematic review.

Study characteristics and risk of bias

Tables 1–3 summarize the study characteristics of the 28 eligible studies. One article included both experimental and industry-based studies. The tables provide information on study designs, inclusion of participants, and risk of bias. Table 1 summarizes experimental studies and Tables 2 and 3 summarize community and industry-based studies, respectively. Two (9%) of the non-experimental studies examined short-term exposure to H₂S such as a week or less, and the rest of non-experimental studied chronic exposures.

Results of experimental studies

Fiedler *et al.*⁸ examined the relationship between H₂S levels and cognitive test results before and after exposure. Ratings in odor intensity, irritation and unpleasantness increased with H₂S dose. No trends with exposure levels were observed for cognitive measures, including finger tapping and simple reaction time, but complex reaction time and verbal learning were significantly lower during exposure. However, the authors concluded that further investigation is needed to determine whether the significant effects are due to H₂S or subject fatigue. They also examined the effect of H₂S levels on respiratory function. The participants reported significantly greater upper respiratory symptoms (i.e. sneeze, nasal congestion, choking,

Figure 1 Literature search strategy and selection process for included studies.

throat irritation, or nose irritation) and/or lower respiratory symptoms (i.e. short of breath, wheezy, chest tightening, chest pain, or coughing) when exposed to 5 ppm H₂S, as compared to 0.5 ppm H₂S.

Other experimental studies investigated the effect of H₂S exposure on respiratory function. Jappinen *et al.*²⁴ exposed 10 asthmatic patients to H₂S concentration of 2 ppm for 30 min and compared respiratory function before and after exposure. They found no significant difference in pre- and post-exposure measures. However, they did report that 3 of the 10 asthmatic subjects developed headaches during the exposure. Bhambhani *et al.*^{9–12} also conducted experiments on the effects of low doses of H₂S on respiratory function. Although their early studies^{9,10,12} showed inhalation of lower H₂S doses had insignificant effects on respiratory function, in their latest study,¹¹ they found that a 10 ppm H₂S inhalation decreased oxygen uptake (VO₂) of healthy adults during exercise with a concomitant increase in blood lactate. The oxygen-carrying capacity of blood and oxygen transport was not affected. Based on this finding, they concluded that at 10 ppm H₂S, aerobic metabolism tends to be inhibited during exercise. As a result, they questioned the current occupational exposure limit for H₂S (i.e. 10 ppm).

Results of community-based studies

The most studied community is Rotorua, New Zealand, built on a geothermal field. Table 4 summarizes results of the Rotorua studies. The studies have varied widely in their designs, outcomes, and extent of associations of outcomes with H₂S exposure. Earlier studies used area-level assessments of H₂S exposure. The two most recent studies estimated the H₂S exposure of individual study participants, neither of which found significant associations between H₂S exposure and diseases of the CNS or respiratory systems.^{13,25,26} A third study with individual measurements was conducted by Inserra *et al.*²⁵ in Dakota City and South Sioux, Nebraska, communities with industrial sources of H₂S exposure. The study used kriging processes to generate an exposure map and classify residential areas as ≥90 ppb H₂S exposure and <50 ppb H₂S exposure. Residents were evaluated with a series of neurobehavioral tests. The authors reported that of a battery of 28 tests assessed, living in areas with the greater H₂S levels was associated with statistically insignificant albeit marginally poorer performance only on memory and grip strength tests. The authors concluded that the exposed and unexposed groups did not differ significantly in cognitive function.²⁵

Table 1 Experimental studies included in the systematic review

Author/ year	Study design			Participants/inclusion		Risk of bias		
	Type of study	Study region	Source of H ₂ S gas	Intervention and control groups/ population	Number of participants	Information	Confounding	Selection
Bhambhani <i>et al.</i> ¹²	Longitudinal	University of Alberta, Edmonton, Canada	Study personnel administered doses of H ₂ S (5 ppm for 30 min)	Healthy subjects	25 healthy volunteers (13 M and 12 F)	Individual	Controlled (subjects served as their own control)	Convenience
Bhambhani <i>et al.</i> ⁹	Longitudinal	University of Alberta, Edmonton, Canada	Study personnel administered doses of H ₂ S (5 ppm for 30 min)	Healthy subjects	25 healthy volunteers (13 M and 12 F)	Individual	Controlled (subjects served as their own control)	Convenience
Bhambhani <i>et al.</i> ¹⁰	Longitudinal	Not specified	Study personnel administered doses of H ₂ S (10 ppm for 15 min)	Healthy subjects	19 healthy volunteers (9 M and 10 F)	Individual	Controlled (subjects served as their own control)	Convenience
Bhambhani <i>et al.</i> ¹¹	Longitudinal	Not specified	Study personnel administered doses of H ₂ S (10 ppm for 30 min)	Healthy subjects	28 healthy volunteers (15 M and 13 F)	Individual	Controlled (subjects served as their own control)	Convenience
Fiedler <i>et al.</i> ²⁸	Longitudinal	UMDNJ-RWJ & Rutgers University Community surrounding New Jersey suburbs	Study personnel administered doses of H ₂ S (0.05, 0.5, and 5 ppm for 2 h per each ppm)	Healthy non-smokers from the study region	74 (35 F and 39 M)	Individual	Controlled (subjects served as their own control)	Convenience
Jappinen <i>et al.</i> ²⁴	Longitudinal (pre/post)	Finland	Administered doses of H ₂ S (2 ppm 30 min)	Asthmatic subjects	10 volunteer asthmatic subjects	Individual	Controlled (subjects served as their own control)	Other

Notes: Information bias was classified as “ecological” or “individual.” Individual = H₂S exposure was measured or estimated for each participant (e.g. by having people wearing a measuring instrument on their body). Ecological = H₂S exposure was measured or classified by group or area exposure levels (e.g. H₂S monitors placed around cities or workplaces, job titles, geographical residence).

Several studies investigated the relationship between day-to-day levels of H₂S and respiratory outcomes. A study by Carlsen *et al.*²⁷ in Reykjavik, Iceland, reported an increase in prescriptions for anti-asthma or adrenergic drugs three to five days following spikes in H₂S. The number of individuals who were dispensed anti-asthma drugs increased 2% (95% CI = 0.4–3.6) per µg/m³ in H₂S. The study monitored H₂S from a single, major traffic intersection.

Campagna *et al.*²⁸ examined daily hospital visits in Dakota City and South Sioux, Nebraska, on the day of and one and two days following measured H₂S levels. They observed no association between H₂S levels and hospital visits in adults for what they referred to as “all respiratory diseases including asthma.” At one of five H₂S outdoor monitoring stations, the study did observe an association between H₂S levels on the previous day and hospital visits for asthma. For children, hospital visits for all respiratory diseases including asthma significantly increased with H₂S

levels on the previous day at five monitoring stations (6 to 40% increases).

In an earlier study in Finland, Rossi *et al.*²⁹ measured pollutants including NO₂, SO₂, and H₂S using objective analyzers and computed correlations between number of hospital admissions for asthma and each chemical. They reported a significant correlation between hospital visits for asthma and H₂S levels monitored daily during a year (partial correlation = 0.26). The major sources of pollution were pulp mills, a chemical factory, and two heating plants.

Logue *et al.*³⁰ measured day-to-day H₂S levels in an investigation comparing a school with H₂S exposure from mushroom composting operations to a nearby control school. Outcomes were based on a self-reported health surveys. The study did not observe a consistent relationship between low levels of H₂S and health outcomes including respiratory symptoms (e.g. asthma, runny nose, and tightness in the chest).

Table 2 Community-based studies included in the systematic review

Study design			Participants/inclusion		Risk of bias				
Author/year	Type of study	Study region	Source of H ₂ S gas	Short-term exposure	Intervention and control groups/population	Number of participants	Information	Confounding	Selection
Bates <i>et al.</i> ⁴²	Cross-sectional	Rotorua, New Zealand	Geothermal field	No	Participants were obtained from Census Data for the years 1981, 1986, and 1991	Not reported, but results were based on the New Zealand census	Ecological	Controlled (age, calendar year, sex, ethnicity)	Other
Bates <i>et al.</i> ⁴³	Cross-sectional	Rotorua, New Zealand	Geothermal field	No	Based on census data for 1981, 1986, and 1991	Not reported, but results were based on the New Zealand census	Ecological	Controlled (age, calendar year, sex, ethnicity)	Other
Bates <i>et al.</i> ⁴⁴	Cross-sectional	Rotorua, New Zealand	Geothermal field	No	Residents of Rotorua stratified by residential census area units (CAUs)	Not reported, but results were based on the New Zealand census	Ecological	Controlled (age, sex, ethnicity)	Other
Bates <i>et al.</i> ¹³	Cross-sectional	Rotorua, New Zealand	Geothermal field	No	Residents of Rotorua, New Zealand	1,637 adults	Individual	Controlled (age, sex, smoking, education, employment status, income)	Other
Campagna <i>et al.</i> ²⁸	Longitudinal (time-series)	Dakota City and South Sioux City, Nebraska	Large beef slaughter, leather tanning facility with a liquid waste treatment complex	Yes	Patients who visited emergency or non-scheduled outpatient care from January 1998 to May 2000 at the two local hospitals (located in South Sioux City) and resided in zip codes 68776 or 68731	Not reported, but results were based on census numbers (455 Asthma, 5,009 all respiratory, 2,271 all digestive hospital visits)	Ecological	Controlled (time, temperature, humidity, weekend, holidays)	Other
Carlsen <i>et al.</i> ²⁷	Longitudinal (time-series)	Reykjavik, Iceland	Geothermal power plants	No	Adults 18 years and older living in Reykjavik	Population of Reykjavik (number not provided)	Ecological	Controlled (temperature, humidity, pollen count, influenza season)	Other
Durand & Wilson ⁴⁵	Cross-sectional (spatial)	Rotorua, New Zealand	Geothermal field	No	Residents of Rotorua stratified by census area units	Census numbers were not provided	Ecological	Controlled (age, ethnicity, smoking, deprivation)	Other
Inserra <i>et al.</i> ²⁵	Cross-sectional	Dakota City and South Sioux City, Nebraska	A large beef slaughter and leather tanning facility and a nearby sizable wastewater lagoon	No	The population was randomly selected from a census of households. Two eligibility criteria were ≥ 16 years of age and a 2-year residency	171 exposed and 164 unexposed group	Individual	Controlled (education, age, sex, language for testing, BMI, prior caffeine consumption, prior alcohol consumption, prior drug use, treatment for drug or alcohol use, job-related exposure)	Other
Legator <i>et al.</i> ³¹	Cross-sectional	Odessa, Texas and Puna, Hawaii (Exposed) and Midlothian and Waxahachie, Texas and Hilo, Hawaii (Unexposed)	Odessa, Texas: Industrial wastewater containing sulfate ions; Puna, Hawaii: geothermal plant	No	Participants who lived in the communities for at least 5 years	223 exposed (126 from Odessa, 97 from Puna) and 170 unexposed (58 from Midlothian, 54 from Waxahachie, and 58 from Hilo)	Ecological	Did not control (but smokers were removed from respiratory function outcome analyses)	Convenience

Table 2 Community-based studies included in the systematic review

Study design			Participants/inclusion		Risk of bias				
Author/year	Type of study	Study region	Source of H ₂ S gas	Short-term exposure	Intervention and control groups/population	Number of participants	Information	Confounding	Selection
Logue <i>et al.</i> ³⁰	Longitudinal	Chester County, Southeast Pennsylvania (Exposed)	Mushroom-composting operations	Yes	Students in an elementary school exposed to H ₂ S in Chester county in Pennsylvania and students in an elementary school where located five miles away from Chester county	Spring: 730 students (97%) in exposed school and 491 students (95%) from control school. Autumn: 674 students (86%) from exposed school and 454 students (87%) from control school	Ecological	Did Not Control	Other
Reed <i>et al.</i> ²⁶	Cross-sectional	Rotorua, New Zealand	Geothermal plant	No	Residents of Rotorua, New Zealand	1,637 adults residing for at least 3 years in Rotorua	Individual	Controlled (age, sex, education)	Other
Rossi <i>et al.</i> ²⁹	Longitudinal	Finland (industrial town from a pulp mill, a chemical factory producing fertilizers, and two heating plants)	Air pollution	No	All adult patients (aged 15–85 years) attending the emergency room at Oulu University Central Hospital for asthma attacks from 10/01/1985 to 09/30/1986	232 adult asthma patients	Ecological	Controlled (temperature, humidity, pressure, rainfall depending on outcomes)	Other

Notes: Short-term Exposure = acute or short-term exposure to H₂S such as a week or less. Information bias was classified as "ecological" or "individual." Individual = H₂S exposure was measured or estimated for each participant (e.g. by having people wearing a measuring instrument on their body). Ecological = H₂S exposure was measured or classified by group or area exposure level (e.g. H₂S monitors placed around cities or workplaces, job titles, geographical residence).

Among the community studies, Legator *et al.*³¹ was the only study using a convenience sample and the study did not adjust for confounding. They reported that CNS and respiratory diseases were strongly associated with chronic exposure to low levels of H₂S (CNS: odds ratio [OR] = 12.7, 95% CI = 7.59–22.09; respiratory diseases: OR = 11.92, 95% CI = 6.03–25.72). The study found significantly increased ORs that exceeded 3.0 in 9 out of 12 categories of self-reported health symptoms (e.g. respiratory, CNS, urinary). The wide-ranging associations suggest a possible selection bias of participants and by ongoing litigation. In addition, the compared communities differed in other respects (e.g. socioeconomic status) that render comparisons difficult to interpret.

Results of industry-based studies

Only one industry-based study measured H₂S on individual study participants. De Fruyt *et al.*³² explored neuropsychological effects, assessed by digit span tests and tests for auditory attention, visual attention, visual memory, and visual-constructive capabilities, from occupational exposure to H₂S and CS₂. Participants wore a device attached to their collars to monitor the two gases. The study did not find a significant effect on memory and attention from either gas.

A study of sewer maintenance workers in Egypt by Farahat and Kishk³³ investigated cognitive impairment such as simple reaction time, P300 latency, Mini Mental State Examination, digit forward and backward due to H₂S exposure. The average H₂S exposure level of the workers was 4.8 ppm (range = 5–6.6 ppm). They found that exposed workers had significantly prolonged reaction times and performed worse on neuropsychological tests compared to unexposed workers. However, other possible chemical exposures (e.g. chlorine dioxide, sodium nitrate) and biological hazards (e.g. bacteria) were not measured to control for potential confounding effects.^{34,35}

Richardson³⁶ compared the respiratory function, measured by FEV₁/FVC, of sewer workers exposed to H₂S to water treatment workers, who were assumed unexposed to H₂S. The study only observed a difference in respiratory function among non-smokers. Compared to water treatment plant workers, non-smoking sewer workers had a decrease of 3.1 in the FEV₁/FVC value (95% CI = (–5.8)–(–0.4)) and were more likely to have obstructive lung disease (OR = 21.0, 95% CI = 2.4–237.8) based on a physician review of the spirometry tests.

Jappinen *et al.*²⁴ by contrast did not find an association with H₂S exposure and respiratory function among pulp mill workers. This study compared the difference in respiratory function such as FVC, FEV₁, and PC15 (a test for evaluating bronchial responsiveness to histamine) comparing workers during the workweek to after at least one day off work.

Five industry-based studies used convenience sampling. Schinasi *et al.*³⁷ examined the associations of hog

Table 3 Industry-based studies included in the systematic review

Author/year	Study design	Participants/inclusion				Risk of bias				
		Short-term exposure	Source of H ₂ S gas	Intervention and control groups/population	Number of participants	Information	Confounding	Selection		
De Fruyt <i>et al.</i> ³²	Cross-sectional	No	Viscose rayon plant	Viscose rayon workers exposed to H ₂ S at least one year for exposed group and metal work, plastic processing and starch procession employees for unexposed group	120 exposed and 67 unexposed	Individual	Controlled (age, education, eye complaints, alcohol, medicine intake, test defensiveness, tremor, hand predominance)	Other		
Farahat & Kishk ³³	Cross-sectional	No	Sewage	Sewer workers in the Districts of El Manial, Misr el Kadema and Kasr el-Aini, Egypt	33 exposed and 30 unexposed	Ecological	Controlled (workers matched by age, education, and SES)	Other		
	Cross-sectional	No	Oil and natural gas exploration	Full-time male workers of Mobil Oil company and Esso resources in Drayton Valley/Cynthia area	14 knockdown, 51 gas exposure, and 110 unexposed	Ecological	Controlled (age, height, cigarette)	Other		
Jappinen <i>et al.</i> ²⁴	Longitudinal (pre/post)	No	Pulp mill	Male pulp mill workers and some volunteers who had asthma	26 exposed workers and 10 volunteer asthmatic subjects	Ecological	Controlled (workers served as their own control)	Other		
Kilburn ⁴⁰	Cross-sectional	No	Oil fields, refineries, sewage, and a chemical plant	Subjects reported as referred because of exposure to sour gas (H ₂ S and other gasses)	16 exposed and 353 controls	Ecological	Controlled (age, education, sex, height)	Convenience		
Kilburn ⁴¹	Cross-sectional	No	Various work sites such as oil field, cleaning, hog farm, papermill, glass, chemical explosion, refinery, sewage, etc.	10 patients exposed to H ₂ S at work and 9 exposed at home, and 202 unexposed. The reference subjects were picked at random from voter registration rolls of Wickenburg, Arizona	19 exposed and 202 unexposed	Ecological	Controlled (age, education, sex, height, weight)	Convenience		
Kilburn <i>et al.</i> ³⁹	Cross-sectional	No	Sour gas (sewage, natural gas desulfurization plant)/oil refinery fields	Volunteers in Lovington, community church members in Tatum in New Mexico; complainers to H ₂ S exposure in Artesia in New Mexico; random sample of Arizona adults	26 exposed from Lovington, 23 less exposed from Tatum, 11 from Artesia, and 42 unexposed from Arizona	Ecological	Controlled (age, education, sex, height, weight)	Convenience		
Kilburn ³⁸	Cross-sectional	No	Hog manure lagoon	People living close to hog manure lagoons (exposed) and living at least 3 km from lagoons and in Tennessee (unexposed)	25 exposed and 80 unexposed (22 living at least 3 km from lagoons and 58 in Tennessee)	Ecological	Controlled (age, sex, education depending on outcomes)	Convenience		
Richardson ³⁶	Cross-sectional	No	Sewage	All workers in sewage and water treatment plants	68 exposed (sewer workers) and 60 unexposed (water treatment workers)	Ecological	Controlled (age, height, race, smoking)	Other		
Schinasi <i>et al.</i> ³⁷	Longitudinal	No	Hog operations	Nonsmoking volunteers aged at least 18 years residing within 1.5 miles of at least one hog operation	101 adults	Ecological	Controlled (time of day)	Convenience		

Notes: Short-term Exposure = acute or short-term exposure to H₂S such as a week or less. Information bias was classified as "ecological" or "individual." Individual = H₂S exposure was measured or estimated for each participant (e.g. by having people wearing a measuring instrument on their body). Ecological = H₂S exposure was measured or classified by group or area exposure level (e.g. H₂S monitors placed around cities or workplaces, job titles, geographical residence).

Table 4 Summary of studies conducted in Rotorua, New Zealand

Study	Brief study description	Conclusion
Bates et al. ⁴²	<ul style="list-style-type: none"> Compared recorded mortality for selected diseases in the Rotorua geothermal area over the decade 1981–1990, comparing deaths to what would have been expected based on deaths in the rest of New Zealand over the same period 	<ul style="list-style-type: none"> Found no evidence of excess mortality related to exposure to H₂S for CNS diseases. For example, Rotorua did not have an increased mortality for inflammation of the CNS (SMR = 1.60, 95% CI = 0.69–3.14) Some respiratory diseases had elevated mortality rates associated with H₂S exposure including the diagnosis category of pneumonia and influenza (SMR = 1.20, 95% CI = 1.04–1.38)
Bates et al. ⁴³	<ul style="list-style-type: none"> Compared the hospitalization rates of residents of Rotorua to those of people living elsewhere in New Zealand to assess possible health risks from H₂S 	<ul style="list-style-type: none"> Found elevated rates in Rotorua for diseases of the nervous system and sense organs (SIR = 1.11, 95% CI = 1.07–1.15) and for diseases of the respiratory system (SIR = 1.01, 95% CI = 0.99–1.04)
Bates et al. ⁴⁴	<ul style="list-style-type: none"> Compared rates of hospital discharges after standardization by age, gender, and ethnicity (Maori and Other) among residents of Rotorua Conducted by first classifying census areas into low, medium, and high H₂S exposure based on the darkening of photographic paper from passive H₂S samplers 	<ul style="list-style-type: none"> High H₂S exposure areas had increased rates of hospitalizations for diseases of the nervous system and sense organs (SIR = 2.19, 95% CI = 1.99–2.41) and for respiratory diseases (SIR = 1.65, 95% CI = 1.51–1.79) The study had adjusted for age, gender, and ethnicity, but did not have information on smoking
Durand and Wilson ⁴⁵	<ul style="list-style-type: none"> Conducted spatial analyses in Rotorua to identify geographic associations with hospitalizations for respiratory conditions 	<ul style="list-style-type: none"> Found that non-infectious respiratory diseases clustered in census regions with the highest levels of H₂S. For instance, compared to other areas, the relative risk for chronic obstructive pulmonary disease was greater than fivefold higher in a cluster of census areas in or near the geothermal source field
Bates et al. ¹³	<ul style="list-style-type: none"> Conducted to investigate the associations between H₂S exposures and having asthma symptoms or a diagnosis of asthma H₂S concentrations was monitored at about 50 sites across Rotorua, and utilized a method known as kriging to create a geographic map of the levels of H₂S exposure. Individual exposures were calculated from estimated concentrations at home and work 	<ul style="list-style-type: none"> Found no evidence that the risk of asthma increases with H₂S exposure In fact, the authors noted that H₂S exposure might even reduce the risks of asthma and symptoms from asthma
Reed et al. ²⁶	<ul style="list-style-type: none"> Investigated the association between low-level H₂S exposure and diseases of the CNS for the same population as reported by Bates et al.¹³ 	<ul style="list-style-type: none"> Found no consistent association between H₂S exposure and tests of cognitive functions

Notes: CNS = central nervous system, CI = confidence interval, SMR = standardized mortality ratio, SIR = standard incidence ratio.

odor and air pollutants (i.e. H₂S, particulate matters (PMs), endotoxin) with two lung function tests (i.e. FEV₁ and peak expiratory flow rate (PEF)) and physical symptoms, including respiratory symptoms, irritation of the skin and eyes, gastrointestinal, neurologic, and other symptoms. Confounding was avoided by comparing participants against themselves instead of using a control group. The participants' outcomes on days with higher H₂S exposure were compared to their outcomes on days with lower H₂S exposure (a within-person analysis). They found that an increase in 12-h average H₂S was associated with having a runny nose and difficult breathing, but not with five other respiratory symptoms. Self-reported outcomes such as having a runny nose might be influenced by external factors such as odors and annoyance. Lung function measured by PEF and FEV₁ was not significantly associated with H₂S exposure.

The other convenience studies were conducted by Kilburn and co-investigators.^{38–41} These studies are largely based on the individuals who complained of symptoms from H₂S exposure. Kilburn³⁸ compared people living in an area neighboring manure lagoons and hog confinement

buildings to people living at least three kilometers away from these exposures. Participants underwent a battery of neurophysiological tests (e.g. simple reaction time, choice reaction time, body balance, blink reflex, hearing, color discrimination, visual fields performance, grip strength) and neuropsychological tests (e.g. verbal recall, cognition, moods), respiratory function (FVC, FEV₁, FEV₁/FVC), and symptom frequencies. Total abnormality was assessed using the sum of the results outside of the 95% CI of each test. This study found that people near the exposure sites averaged 4.3 neurological abnormalities (SD = 3.0), significantly higher than 2.5 (SD = 2.3) observed for local control populations and 2.3 (SD = 2.1) for out-of-state control populations. In a study of people exposed to H₂S by working in sewer plants, oil refineries, natural gas production plants, and cheese manufacturing plants, Kilburn *et al.*³⁹ conducted same battery of neurophysiological and neuropsychological tests. The study reported that people exposed in their work environments had significantly more abnormalities in neurobehavioral functions than control populations from the same town or a neighboring state. The exposed workers also had poorer results on a variety

of tests, including cognitive tests such as digit symbol, verbal recall, vocabulary, and long-term memory. In earlier studies, Kilburn *et al.*^{40,41} compared people exposed to H₂S by working in a variety of settings to unexposed populations on respiratory symptoms (e.g. short breath, wheezing), pulmonary functions (e.g. FVC, FEV₁), and neurobehavioral functions (e.g. simple reaction, balance sway speed). The studies consistently observed strong associations between H₂S exposure and CNS and respiratory outcomes. Some participants in these earlier studies were either identified as plaintiffs in lawsuits or randomly selected from a list of plaintiffs compiled by a legal firm conducting an H₂S-related community investigation.

Discussion

Summary of evidence

This systematic review found that studies measuring the association between H₂S and CNS and respiratory conditions were highly diverse in design, populations, sample sizes, and geographic settings. Drawing conclusions is difficult due to methodological differences and weakness including multiple chemical exposures (e.g. PM, SO₂, and CS₂), incomplete or no adjustment for confounding, and/or the use of volunteers or litigants who may have enrolled in studies because they suspected H₂S caused their health problems. Self-selection bias may have caused associations of H₂S with poor health outcomes.

The experimental studies examined the effects of H₂S levels of no greater than 10 ppm under controlled situations. The results were mixed in terms of effects, but statistically significant responses were reported. Some experiments found evidence of increased odor ratings, respiratory symptoms, and decreased oxygen uptake on exercise.

Much of what we know about health effects from chronic exposure in communities comes from studies of Rotorua, New Zealand. The earliest studies compared Rotorua to the rest of New Zealand assuming everyone in Rotorua was equally exposed to H₂S. With the development of passive samplers, studies assigned H₂S exposure more locally, at the census level. Studies using these approaches reported significant associations between H₂S exposure and hospital discharges for certain CNS and respiratory outcomes.^{42–44}

Recent studies in Rotorua on respiratory and CNS outcomes included estimates of individual exposure levels.¹³ Participants were selected by random sampling. The studies did not find significant associations between H₂S exposure and adverse health outcomes. Differences in methods may have contributed to the difference in findings between the recent and earlier studies. The outcomes, however, also differed. Recent studies used functional measures, whereas earlier studies used hospital discharges based on geographic area. A future study re-examining hospitalizations with individual hospitalizations and estimates of H₂S exposure could help clarify our understanding.

The study in Dakota City and South Sioux, Nebraska, used similar methods to the recent Rotorua studies and also failed to find consistent associations with cognitive outcomes.²⁵ Together, the Nebraska and Rotorua studies support the conclusion that chronic, low-level H₂S exposure is not associated with neurobehavioral performance.

Among industry-based studies, a study of viscose rayon workers found that H₂S exposure was not associated with effects on memory and attention.³² A study of pulp mill workers did not find associations between H₂S exposure and respiratory function.²⁴ In these work settings, the levels of H₂S may have been controlled sufficiently to avoid health effects. Control of H₂S exposure may be difficult in other work settings such as for sewer workers. Two studies of sewer workers reported significant deficits in neurological tests and FEV₁/FVC ratios, respectively.^{33,36} A study of workers extracting and processing oil and natural gas reported many workers had experienced symptoms from H₂S exposure.³⁶ Only the workers experiencing knockdowns, however, had persistent respiratory effects. A study of neighborhoods near hog operations reported some minor symptoms associated with H₂S exposure, but no association with respiratory symptoms.³⁷ Although hog operations are uncontrolled environments, the levels of H₂S released — such as from manure lagoons — may have limited health effects in adjacent neighborhoods.

The results from industrial studies suggest a range of health effects, varying in severity with the exposure dose. Workers exposed in industrial settings to H₂S, however, often are exposed to multiple chemical and other factors that may affect their health. Sewer workers as an example incur both chemical and bacterial exposures.^{34,35} One group of studies, however, has reported nearly uniformly strong associations. These are the studies using convenience samples such as volunteers and litigants. The studies may create a selection bias by disproportionately recruiting people exposed to H₂S and have symptoms. Other articles have specifically discussed concerns with the series of such studies by Kilburn and collaborators.^{5,26}

A number of studies examined the possibility of respiratory effects from short-term increases in H₂S emissions. The recent study by Carlsen *et al.*²⁷ from Reykjavik, Iceland, reported an increase in prescriptions for anti-asthma or adrenergic drugs three to five days following spikes in H₂S. A study among residents of Dakota City and South Sioux, Nebraska,²⁸ reported positive associations of day-to-day H₂S levels with hospital visits for respiratory diseases among children. An earlier study by Rossi *et al.*²⁹ in an industrial setting in Finland reported a significant association between daily H₂S levels and emergency room visits for asthma attacks. An early study by Jappinen *et al.*²⁴ among pulp mill workers, however, did not observe notable differences in respiratory function between work days and days off from work. The study of exposure to H₂S in neighborhoods adjacent to hog farms reported day-to-day variations in H₂S exposure associated with only a

subset of self-reported symptoms such as a runny nose.³⁷ Overall, the possibility that spikes in H₂S emissions may result in adverse health effects is unsettled, but has support from some studies.

Limitations

The small number of studies identified, and the even smaller number of high-quality studies, was a limitation of this systematic review. The diversity of the study designs did not allow us to conduct a statistical meta-analysis, which could have resulted in a more decisive conclusion. Although the systematic review searched 16 databases, we cannot rule out the possibility of having missed some relevant articles. This review did not include research articles that did not mention the source of pollutants or that lacked a description of how H₂S was measured.

Conclusions

We found a diverse literature in terms of populations, settings, study designs, and results. The number of studies was small considering the range of populations at risk from H₂S. Overall, the studies of the health effects from chronic H₂S exposure obtained mixed results. The studies with stronger designs did not find substantial health effects from low-level, chronic exposure. Some studies raised concerns, about the possible effects of acute H₂S exposure for vulnerable groups such as children with asthma. Additional studies of acute H₂S effects using carefully designed studies are warranted to clarify the short-term health effects, especially among vulnerable populations.

List of abbreviations

CS₂ carbon disulfide
FEV₁ forced expiratory volume in 1 s
FVC forced vital capacity
SO₂ sulfur dioxide

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Conflict of interests

None of the authors had any personal or financial conflicts of interest.

Disclosure statement

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