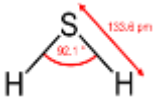
Substance name: Hydrogen Sulfide **DRAFT as of 12/12/2017**

CAS: 7783-06-4 **MW: 34.076**
Synonyms: Hydrosulfuric acid

Molecular formula: H_2S Structural formula: 

1 ppm to 1.4 mg/m^3 conversion factors at 25 ^oC and 760 mm/Hg:

GHS Classification
Signal: Danger
GHS Hazard Statements
H220: Extremely flammable gas [Danger Flammable gases - Category 1]
H280: Contains gas under pressure; may explode if heated [Warning Gases under pressure - Compressed gas, Liquefied gas, Dissolved gas]
H319: Causes serious eye irritation [Warning Serious eye damage/eye irritation - Category 2A]
H330: Fatal if inhaled [Danger Acute toxicity, inhalation - Category 1, 2]
H370: Causes damage to organs [Danger Specific target organ toxicity, single exposure - Category 1]
H400: Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard-Category 1]
H410: Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard - Category 1]

Physical characteristics at room temp: Colorless gas with a strong odor of rotten eggs.
Special physical characteristics if any: Heavier than air.

Flammability and other hazards: Extremely flammable. Corrosive. Reacts with strong oxidants.

Upper Explosive Limit 44% **Lower Explosive Limit 4.0%**

Major commercial form(s): Gas

Uses/applications: Main use is as precursor of elemental sulfur. Also as precursor of other chemicals used in paper manufacture, and in analytical chemistry

Occupations with Potential Exposure to Hydrogen Sulfide

Occupational exposures to hydrogen sulfide occur in such industries as animal husbandry and animal product production; sugar production; sewage, pipeline and other excavation trades; fermentation process industries; gas and petroleum production and pipeline maintenance; geothermal energy production; chemical production and processing; paper manufacture; synthetic fiber manufacture and metallurgy.

Occupational Exposure Limits

Title 8 PEL (1992): 10 ppm Ceiling 50 ppm STEL 15 ppm
OSHA PEL (1971) Ceiling 20 ppm, one-time 10 minute peak 50 ppm
ACGIH TLV (2010): 1 ppm STEL 5 ppm
NIOSH REL: 10 ppm10 minute Ceiling (1977) 100 ppm IDLH(1994)
Other OELs (WEEL, MAK, etc.):
MAK (2006): 5 ppm, 7.1 mg/m^3
WEEL (2013): Hydrogen Sulfide ERPG1: 0.1 ppm ERPG-2 30 ppm ERPG-3:100 ppm

Other recommendations:

Source and date	Findings/Recommendations	Basis/source/ref(s)	Discussion and Assessment
OEHHA REL	Acute: 42 µg/m^3 (30 ppb) Chronic: 10 µg/m^3	A: human volunteers exposed to increasing H2S until odor detected. C: 90-day inhalation study in mice, CIIT 1983c	A critical effect: Headache, nausea, physiological responses to odor C critical effect: Nasal lesions of the mouse olfactory mucosa
HESIS PEL 2017	Recommended PEL-TWA 0.27 mg/m^3 (194 ppb)	Nasal lesions of the olfactory mucosa (Brenneman et al., 2000).	Male rats exposed to hydrogen sulfide by inhalation for 10 weeks were examined for nasal lesions of olfactory mucosa as the critical effect to identify a NOAEL which is used to derive PEL-TWA following application of a total UF of 10 to account for subchronic (√10) and interspecies (√10) extrapolation.
Prop 65	Not listed		
NTP	Not studied.		
EPA	IRIS RfC: 2.0 µg/m^3	Nasal lesions of the olfactory mucosa	Relevancy to humans of the olfactory lesions seen in rodents is suggested by reports of decreased persistent olfactory function in workers exposed chronically to hydrogen sulfide
IARC	Not classified		
EU	5 ppm TWA 10 ppm STEL	SCOEL/SUM/124 June 2007	An uncertainty factor of 2 used to account for differences in exposure pattern (sub-chronic vs. chronic) and limited dataset for pathological findings.

Peer-reviewed journal articles used for proposed PEL

Respiratory

Bhambhani 1991; Bhambhani 1994; Bhambhani 1996; Bhambhani 1997

This series of studies on the physiological effects in controlled human exposure found metabolic effects from short-term exposure starting at 0.5 ppm H_2S that, while causing no clinical effect in the subjects, did result in altered enzymatic levels consistent with the accepted mode of action of H_2S toxicity. This toxic mode of action is considered to be the impairment of mitochondrial respiration by inhibition of cytochrome oxidase, thereby reducing energy production.

Study type: human volunteer
Method: Healthy male and female volunteers were exposed to 0.5 - 10 ppm H_2S for 30 minutes while operating a cycle ergometer at different energy intensities over the course of several studies. During these studies, metabolic and cardiovascular measurements were monitored at submaximal and maximal reference points so that H_2S -induced effects could be associated with moderate exercise and associated cardiac changes. Real-time physiological and perceptual responses were monitored and blood samples and muscle tissue biopsies obtained.

Results:
Bhambhani 1991
30-minutes exposures at 0, 0.5, 2.0 and 5.0 ppm H2S. 16 males, age: 25.2 ± 5.5. Physiological measurements at submaximal and maximal exercise were obtained. There was a tendency for oxygen uptake to rise with increasing H_2S concentrations at all three exercise durations. Heart rate and expired ventilation were unaffected by H_2S concentration. Only at the maximum exercise level at 5.0 ppm was a significant difference in oxygen uptake observed between controls and H_2S exposed subjects. Blood lactate concentrations increased in each exposure group at each exercise intensity but only lactate increases in the 5.0 ppm exposed group were significantly different from controls. Maximal power output of this exposed group was not significantly different from controls.

Bhambhani 1994
30-minutes exposures at 50% aerobic power to 0 and 5.0 ppm H_2S. 13 males, age: 24.7 ± 4.6; 12 females age: 22.0 ± 2.1. There were no significant differences between the two exposures for metabolic, cardiovascular, arterial blood and perceptual measures in either sex. Blood lactate concentrations in exposed men and women were not significantly different from controls, although 70% of men and 83% of women had elevated lactate compared to controls.

Bhambhani 1996
30-minutes exposures at 50% aerobic power to 0 and 5.0 ppm H_2S. 13 males, age: 24.7 ± 4.6; 12 females age: 22.0 ± 2.1. Immediately following exercise, muscle biopsies were obtained and analyzed for markers of aerobic and anaerobic metabolism. Multiple measures of markers of energy metabolism determined by enzymatic activity of the muscle tissues obtained during exposure/exercise were mostly not significantly different from controls. Specifically, cytochrome oxidase activity, the putative enzyme associated with H_2S toxicity, was not significantly different between exposed men and women and controls. Citrate synthase decreased significantly ($p=0.006$) in exposed men and there was a tendency for cytochrome oxidase to

decrease in exposed men but not significantly. In this study negative correlations were observed between aerobic capacity and muscle lactate concentrations, leading the authors to suggest that the healthy capacity of the subjects was a factor in attenuating the effects of 5 ppm H_2S.

Bhambhani 1997
30-minutes exposures at 50% aerobic power to 0 and 10.0 ppm H_2S. 15 males, age: 24.7 ± 4.6; 13 females age: 22.0 ± 2.1. Cardiorespiratory measurements were monitored as well as the other endpoints. A significant decrease in oxygen uptake and a significant increase in blood lactate was observed in exposed men and women. No significant differences were observed in arterial blood parameters and cardiovascular responses. The biochemical markers of energy production in muscle biopsies were not significantly different between controls and exposed subjects however there was a tendency for muscle lactate to increase and citrate synthase activity to decrease in both genders when exposed to 10.0 ppm H_2S.

P Jappinen, 1990

Study type: cross-sectional
Methods: 26 male pulp mill workers (mean age 40.3) with a daily exposure to H_2S in the workplace (mean 4.5, range 1-11 ppm), and 10 volunteers, who had asthma (mean age 42.4) exposed to 2 ppm H_2S in a laboratory setting. The respiratory function of the pulp mill workers was monitored by measuring forced vital capacity (FVC), forced expiratory volume in one second (FEV1) at least one day off work and at the end of a workday. Bronchial responsiveness was determined by administering histamine diphosphate aerosol at increasing concentrations until a fall of 15% in FEV1 was achieved or the maximum histamine diphosphate concentration of 3 2% was reached. Likewise, bronchial responsiveness was determined after at least one day off work and at the end of a workday. The 10 asthmatic subjects were exposed to 2 ppm of H_2S for 30 minutes in an exposure chamber. Airway resistance (Raw) and specific airway conductance (SGaw) were assessed by a body plethysmograph, and the ventilatory capacities were measured with a flow volume spirometer. Values derived from a Finnish general population were used as predicted normal values for FEV1, FVC, Raw, and SGaw.
Results: No significant changes in respiratory function or bronchial responsiveness related to exposure to hydrogen sulfide in the pulp mill workers were found. Similarly, no significant changes were observed in subsets of workers (workers exposed to at least 1 ppm, workers who smoked, exposed workers who had previous allergies or bronchial asthma, and five atopic subjects with a positive reaction in the skin prick test. There were no significant changes in the mean FVC, FEV1, and forced expiratory flow values after exposure to H_2S in subjects with asthma. In two asthmatics, changes in Raw and SGaw were over 30% in indicating clinical bronchial obstruction.

Brenneman et al. (2000)

Study type: sub-chronic inhalation in rats
Method: 10-week-old male CD rats (12/ group) were exposed to 0, 10, 30, or 80 ppm (0, 13.9, 42, or 111 mg/m^3) H_2S for 6 hr/day, 7 days/week, for 10 weeks. Due to the complexity of the rat nasal cavity, animal noses were dissected and examined for lesions and neuronal effects at 6 levels.
Results: an array of effects at different concentrations were observed at the different levels of the olfactory region. No effects were observed in the control or 10 ppm exposure animals that were considered treatment-related. Nasal lesions of the olfactory mucosa were observed in the 30 and 80 ppm exposure animals mostly in a dose dependent manner. Basal cell hyperplasia was observed in both exposure groups at one level of the nasal cavity but was more pronounced in the 30 ppm exposure group. Olfactory neuronal loss and basal hyperplasia occurred at 2 of the 6 nasal levels from exposure to 30 ppm H_2S.

Ocular/ Irritation

Vanhoorne, 1990

Study type: Cross sectional; rayon "spinners" concurrently exposed in H_2S and CS_2 compared to non-exposed workers.
Method: 123 male viscose rayon workers in 17 different job categories exposed to hydrogen sulfide (H2S) and/or carbon disulfide (CS_2) and 67 referents not exposed to either of these chemicals answered questions on eye irritation complaints in a self-administered questionnaire.
Results: Personal exposure varied from 4 to 112 mg/m^3 for CS_2 and from 0.2 to 8.9 mg/m^3 (0.14 – 6.39 ppm) for H_2S. A combined exposure measure was calculated using principal component analysis. When categorized into exposure groups (H_2S: 0, 0-5, >5 mg/m^3; CS_2: 0, 1-30, 31-90, >90 mg/m^3), eye symptoms in exposed workers were significantly different from controls only in the highest exposure categories (H2S > 5; CS_2> 90). It was not possible to discern what chemical caused the eye effects observed in this study however a NOAEL for the combined gas exposure was 5/90 mg/m^3 H_2S /CS_2.

Fiedler, 2008.

Study Type: human volunteers exposed in test chamber.
Methods: 74 healthy subjects [35 females, 39 males; mean age (± SD) = 24.7 ± 4.2) were exposed to 0.05, 0.5, and 5 ppm H_2S. During each 3-hour exposure session, subjects completed ratings and tests before H2S exposure (baseline, first hour) and during the final hour of the 2-hr exposure period. Subjects completed analog scales to rate pleasantness, intensity, and irritation of the H_2S odor, and to evaluate environmental qualities. Behavioral (odor ratings, symptoms and sensory function) and cognitive measures (visual acuity and visual contrast sensitivity, simple reaction time, finger tapping and symbol-digit substitution) were evaluated.
Results: Dose–response relationships between a reduction in air quality and increases in ratings of odor intensity, irritation, and unpleasantness were observed. After controlling for baseline, a significant exposure × time interaction for odor ratings, irritation, intensity and unpleasantness was observed at the start of exposure. After 2 hours, only the 5 ppm scores were significantly different from the other 2. Total symptom severity was not significantly elevated across any exposure condition, but anxiety symptoms were significantly greater in the 5-ppm than in the 0.05-ppm condition. No dose–response effect was observed for behavioral or cognitive measures. Verbal learning was compromised during each exposure condition.

Reproductive/Developmental

Dorman 2000

Study type: sub-chronic rat study, pre-mating, gestational and postnatal exposure
Method: SD male and female rats exposed for 4 weeks prior to mating for 6h/day, 7/day week to 0, 10, 30 and 80 mg H_2S mg/m3. Exposure continued to GD 19 and until PND 18. Offspring were evaluated using motor activity, passive avoidance, functional observation battery, startle response and neuropathology (PND 22 and 60).
Results: There were no effects on reproductive performance based on mating success and several litter characteristics. There was a nonsignificant higher incidence of testicular tubular degeneration at the highest dose.

Skrajny 1992

Study type: sub-chronic rat study, gestational and postnatal exposure

Method: exposed groups of 20 pregnant Sprague-Dawley rats to 0, 28, or 105 mg/m^3 (0, 20, or 75 ppm) H_2S 7 hours/day from day GD 5 through PND 21.

Results: Increased ($p < 0.05$) serotonin levels were observed in the frontal cortex on day 21 postpartum of pups exposed to 20 ppm hydrogen sulfide, whereas increased ($p < .01$) serotonin levels were observed in both the cerebellum and frontal cortex on postpartum days 14 and 21 in pups exposed to 75 ppm hydrogen sulfide. Norepinephrine levels were increased ($p < .05$) at 75 ppm in the cerebellum at postpartum days 7, 14, and 21, whereas norepinephrine levels were significantly increased in the frontal cortex only at day 21 postpartum. At 20 ppm H_2S, frontal cortex norepinephrine levels were decreased compared to controls on days 14 and 21.

Hayden 1990

Study Type: sub-chronic rat study, gestational and postnatal exposure

Method: pregnant SD rats exposed to 28, 70 0r 110 mg/m^3 for 7 hr/day on GD 6 until PPD 21.
Results: Dose – dependent increase in mean parturition time and difficult delivery of 10, 20 and 42% over matched controls. No statistical analysis presented but parturition time in controls (82.5 - 124 min) was considered too variable for statistical comparison with treated groups (105-148). No difference in maternal body weight gain between two groups. Maternal liver cholesterol content was elevated significantly on day 21 postpartum following exposure to 75 PPM H_2S each day for 6 weeks.

<u>Neurological</u>

Roth 1995

Study Type: sub-chronic rat study, gestational and postnatal exposure
Method: SD rat dams exposed to 28 -70 mg 7 hr/day from GD5. Pups born to treated dams were exposed perinatally up to PND 21. Morphological analysis of one cerebellar Purkinje cell per pup was performed. A quantitative analysis of dendritic growth was conducted to distinguish random versus nonrandom growth.
Results: Cells from H_2S-exposed rats underwent a significant amount of nonsymmetrical or nonrandom growth, suggesting that H_2S affected the branching pattern. The resulting alterations in dendritic arborization appeared to be in response to H_2S exposure at the 20 and 50 ppm (28 or 70 mg/m^3) levels such that the 20 ppm (28 mg/m^3) level may be considered a low-effect rather than a no-effect level.

Hannah 1989

Study Type: sub-chronic rat study, gestational and postnatal exposure
Methods: Rats exposed from GD5 to PND 21 to 75 ppm H2S for 7 hours/ day.
Results: Brain levels of aspartate, γ-aminobutyric acid (GABA), glutamate, and taurine were significantly depressed, but no follow-up studies were conducted to determine if these changes affected behavioral or structural development

Population Studies

Ecological investigations – community-based studies of low level H_2S exposure (ppb) - are difficult to evaluate for relevance to occupational exposure analysis. Many factors – continuous exposure to very low concentrations, confounders, lack of exposure measurements – limit the applicability of some studies to interpreting occupational exposures. There are unique studies of H_2S exposure from geothermal sources that do show little or no effect of H_2S exposure in the ppb range.

Bates 1998

Study Type: case-control
Methods: Cancer registry and hospital morbidity data were obtained from 1981 – 1990 for community adjacent to a geothermal H_2S and compared with non-exposed communities. Standardized incidence ratios (SIR) were calculated comparing the two groups. Diagnostic categories were based on known targets of H_2S toxicity – the respiratory, neurological and ocular systems.
Results: The exposed population had an elevated nasal cancer rate but cases were limited (4). For a subset of women, the SIR cancers of the trachea, bronchos and lung was 1.48 (1.03 – 2.06). For morbidity, diseases of the nervous system and the eye showed elevated SIR.

Bates 2015

Study Type: Ecological, cross-sectional
Methods: 1637 adults living 3 years or longer (median = 18 years) with low-level H_2S exposure from geothermal sources were randomly selected from high medium and low H_2S exposure areas. The median residential H_2S concentration was 20.3 ppb and the median workplace concentration 26.4 ppb. Spirometry testing was obtained of the participants and compared with were compared with predicted population values. Departures from the predicted value were outcomes for linear regression models using quartiles of the H_2S exposures. Separate models examined participants with and without asthma or COPD and never- and ever-smokers.
Results: None of the exposures were associated with lung function decrement. No evidence that long-term H_2S is associated with increased asthma or COPD risk.
Discussion: For all participants and sub-groups there was no evidence of an adverse association between ambient H_2S and any spirometric measures. More significantly, there was no evidence of an association between H_2S and COPD which might be expected from long-term exposure to a reactive, irritant gas. Potential exposure misclassification may have attenuated any actual exposure- response relationships but no effect was seen across 4 subgroups.

Bates 2017

Study Type: Ecological
Methods: 1637 adults living 3 years or longer (median = 18 years) with low-level H_2S exposure from geothermal sources were randomly selected from high medium and low H_2S exposure areas. The median residential H_2S concentration was 20.3 ppb and the median workplace concentration 26.4 ppb. Participants underwent comprehensive ophthalmic examination including pupil dilation and lens photography to capture evidence of any ocular opacities. Data analysis examined associations between the degree of opacification/nuclear color/cataract in relation to H_2S exposure.
Results: No associations were found between estimated H_2S exposures and any of the 4 opthalmic outcome measures.

Reed 2014.

Study Type: ecological
Methods: 1637 adults living 3 years or longer (ages 18-65, median residence time = 18 years) with low-level H_2S exposure from geothermal sources were randomly selected from high medium and low H_2S exposure areas. H_2S exposure at the time of participation and past exposure were calculated from data obtained from H_2S monitoring stations and exposure metrics were created for contemporary and the prior 30 years. Neuropsychological tests of visual and verbal memory, attention, fine motor skills, psychomotor speed and mood administered to participants were reported as being affected by H_2S or relevant to neurotoxic assessment. Association between cognition and measures of H_2S exposure were investigated with multiple regression while covarying demographics and factors known to be associated with cognitive performance.
Results: No association was found between H_2S exposure and neuropsychological and psychomotor assessments.

Finnbjornsdottir 2016

Study type: Ecological, urban population exposed to H_2S from geothermal energy plant.
Methods: Hospital data from patient- and population-registers on heart disease, respiratory disease and stroke from an acute care institution in the study area were obtained from 1 January, 2007 and 30 June, 2014. The population was geocoded into 5 areas within the H2S plume and the total number of individuals in each area calculated within age groups (18-59, 60-72, 73-80, and 81 and older) and gender. A national registry was used to count the total number of people at risk in the area according to the gender and age groups. Exposure estimates were modeled and exposure calculated by different percentiles 50% (2.46 µg/m3), 60% (3.16 µg/m3), 70% (4.14 µg/m3), 80% (5.74 µg/m3), 85% (7.00 µg/m3), 90% (8.80 µg/m3) and 95% (11.68 µg/m3). A generalized linear model assuming Poisson distribution was used to investigate the association between emergency hospital visits for each disease endpoint and H2S exposure.

Results: The total number of emergency hospital visits was 32961 with a mean age of 70 years. In fully adjusted un-stratified models, H_2S concentrations exceeding 7.00µg/m3 were associated with increases in emergency hospital visits with heart disease as primary diagnosis (RR): 1.067; 95% confidence interval (CI): 1.024–1.111). Among males an association was found between H_2S concentrations exceeding 7.00µg/m3, and heart disease (RR: 1.087; 95% CI: 1.032–1.146) and among those 73 years and older (RR: 1.075; 95%CI: 1.014–1.140).

HEAC Health-based assessment and recommendation

Few occupational studies are available to assess the effect of H_2S. Many studies are of workers exposed to multiple irritant chemicals and the exposure are not well-characterized. Most H_2S measurements in Jappinen were between 2 and 7 ppm and in Vanhoorne H2S concentrations ranged from 0.2 and 11.8 ppm so are comparable to those in the volunteer studies. No respiratory effects were observed and irritation only observed at > 5.0 ppm. Jappinen raises the concern of a healthy worker effect in that study however the lack of any differences in the 4 subgroups undergoing histamine challenge suggests that H_2S did not have respiratory impacts at 5.0 ppm.

The volunteer studies by Bhambhani demonstrate that effects of short-term exposure to H_2S can be detected in humans at 5 ppm. The potential for H_2S to inhibit mitochondrial respiration is a function of several factors of exposure and physiology. When H_2S is inhaled, it is absorbed into the bloodstream, where it is detoxified primarily by oxygen bound to hemoglobibn and in the process is oxidized into a sulfate or a thiosulfate that is excreted by the kidneys. The anionic moiety of H_2S (HS^-) is known to form a complex with the ferric heme group of methemoglobin in a 1:1 stoichiometric ratio. A minor portion of the inhaled H_2S can enter the musculature, where it undergoes a similar fate because of the presence of oxygen in the form of oxymyoglobin. Trace amounts of the gas that are unoxidized are eliminated by the lungs as dissolved H_2S. This detoxification process takes place very rapidly and therefore H_2S does not act as a cumulative toxin. However, if the dose of H_2S exceeds the detoxification capacity, it can then impair mitochondrial respiration by inhibiting the activity of the enzyme cytochrome oxidase (c and aa3) in the various tissues, thereby reducing overall energy production. Because of the rapid speed of these reactions, the the extent of cytochrome oxidase inhibition is greatest under constant and sustained concentrations of H_2S. Interindividual variability in blood oxygen levels is also a factor in H_2S detoxification.

One result of inhibition of cytochrome oxidase (CO) is the accumulation of lactic acid (LA) in the muscle and blood. CO is the terminal enzyme in aerobic respiration and its inhibition requires the cell to utilize anaerobic respiration to meet energy needs. LA is the final product in this anaerobic metabolism and LA levels rise naturally under exertion as supplied oxygen and aerobic respiration cannot meet the need for energy production. Above a certain concentration, H_2S augments this rise in LA by inhibiting CO, resulting in greater dependence in anaerobic metabolism. The Bhambhani papers show this effect with direct and indirect measures of inhibition – changes in blood and muscle lactate (the clinical measure of lactic acid) levels and aerobic enzyme activity (Table 1). The most consistent effect seen across the studies is the rise in blood lactate. At 5 ppm under increasing exercise (test 1) and at 5 and 10 ppm under fixed exercise (tests 2 and 3) in men and women, lactate levels in H_2S-exposed subjects were significantly higher than controls in most cases. Results for muscle lactate and aerobic enzymes (CO and citrate synthetase) were mixed but trended as expected with dose (Muscle lactate ↑; enzymes ↓).

Table 1: Summary of Bhambhani H2S Studies

Test	**TEST CONDITIONS** PPM/WL/N/VO_{2max}	VO_2, L/min (0/0.5/2/5 ppm)	Change in Blood lactate from Controls (mM/L) (↑)	Muscle Lactate (mmol/kg) (↑)	Cytochrome Oxidase (↓)	Citrate Synthetase (↓)
1	0, 0.5, 2, 5 Increasing exercise to VO2max; N = 16/- M: 41.5 ± 6	V1: 1.59/1.65/1.69/1.71 V2: 2.54/2.62/2.62/2.7 V3: 3.11/3.25/3.25/**3.39***	V1: 0.0/0.2/**1.5*** V2: 0.2/0.9/**2.7*** V3: 0.4/1.2/**4.5***	ND	ND	ND
2	0, 5 30 min 50% exercise; N = 25 (13/12) M: 51.2 ± 7.4 W: 40.3 ± 6.4	M: 0: 1.71 ± 0.28 5: 1.75 ± 0.27 W: 0: 1.36 ± 0.22 5: 1.34 ± 0.23	M: 0: 2.13 ± 0.83 5: 2.34 ± 1.09 W: 0: 2.18 ± 1.56 5: 2.46 ± 1.34 NOTE: 70% men and 83% women showed elevated lactate compared to control	M: 0: 1.60 ± 1.22 5: 1.98 ± 1.12 W: 0: 1.59 ± 0.72 5: 1.52 ± 0.27	M: 0: 4.85 ± 3.1 5: 4.47 ± 1.9 W: 0 3.26 ± 2.3 5: 4.01 ± 1.5 NOTE: 54% of men and 58% of women showed a decrease in CytOx compared to control	M: 0: 14.9 ± 4.3 **5: 12.0 ± 4.1*** W: 0: 12.6 ± 5.0 5: 10.2 ± 4.4 NOTE: 93% of men ($p< 0.05$) and 75% of women ($p=0.18$) showed decrease in CS compared to control
3	0, 10 30 min 50% exercise; N = 28 (15/13) M: 54.2 ± 8.4 W: 41.8 ± 4.5	M: 0: 1.96 ± 0.35 **10: 1.80 ± 0.36 *** W: 0: 1.34 ± 0.23 **10: 1.21 ± 0.24 ***	M: 0: 0.73 ± 0.43 **10: 1.82 ± 1.12 *** W: 0: 0.86 ± 0.65 **10: 1.48 ± 1.05 ***	M: 0: 1.81 ± 0.99 10: 2.41± 1.20 W: 0: 1.84 ± 1.19 10: 2.13 ± 1.26	M: 0: 6.51 ± 2.17 10: 5.44 ± 1.59 W: 0: 4.61 ± 1.25 10: 5.16 ± 2.34	M: 0: 13.7 ± 2.5 10: 12.8 ± 2.4 W: 0: 11.8 ± 3.4 10: 10.5 ± 3.3

Studies designed so that each subject served as own control. Changes in lactate and enzymes determined in same person under exercise at 0 ppm (control) and 5 (test 2) or 10 (test 3) ppm. In test 1, subjects put through a range of exercise; tests 2 and 3 conducted as 50% exercise for each subject as determined by their performance in test 1.

STUDY: 1: Range finding study – work load (WL) systematically increased until subjects ceased by volition or Vo2 increased no further; V1, V2 and V3 represent three ventilatory thresholds during the WL test (see Bhambhani, 1991); Change in blood lactate represent change from control (0 ppm) at different thresholds. (↑ or ↓) indicates expected change in value. Significant differences in red; * ≤ 0.05. 2: 30 min exposure to 0 and 5 ppm using 50% WL for each subject. Aerobic capacity substantially higher in male subjects than #1. Muscle lactate, cytochrome oxidase and CD are values obtained after subject exercised at 50% WL for 30 min at 0 or 5 ppm. Significant decrease in male CS. 3. 30 min exposure to 0 and 10 ppm using 50% WL for each subject. Significant decrease in VO_2 and lactate in men and women.

While H_2S clearly resulted in a rise in blood lactate levels in the short-term, this result produced no adverse effects in the subjects - measures of respiratory and pulmonary function in exposed subjects were not significantly different from controls. The one exception is the decline in ventilation rate at 10 ppm, which while significant, did not lead to a reduction in the maximum power achieved by subjects exposed to this concentration. In response to progressive, incremental exercise, blood LA increases gradually at first and then more rapidly as the exercise becomes more intense. The work rate beyond which blood LA increases exponentially is known as the lactate threshold (LT)] and is considered a better predictor of performance than V˙O2max and a better indicator of exercise intensity than heart rate. A fixed blood LA of 4 mM is widely recognized as the onset of blood LA accumulation and attainment of LT (Goodwin 2007). Variability among individuals is such that LT may vary between individuals from as low as 1.5 m*M* to as high as 7.5 m*M*.

The Bhambhani tests were conducted under increasing exercise until fatigue (1) or at 50% exercise, characterized as that level at which oxygen consumption was 50% of maximum, (2,3) for 30 minutes. Either condition is not likely to be sustainable over an 8-hr workday, though in tests 2 and 3 no significant changes in respiratory or cardiac measures were observed after 30 minutes. In test 1, the lactate threshold was exceeded after 16 minutes by controls and at all H_2S concentrations (figure 1) while in tests 2 and 3 lactate levels rose in all groups but not above 4 mM at 30 minutes for any group (table 1).

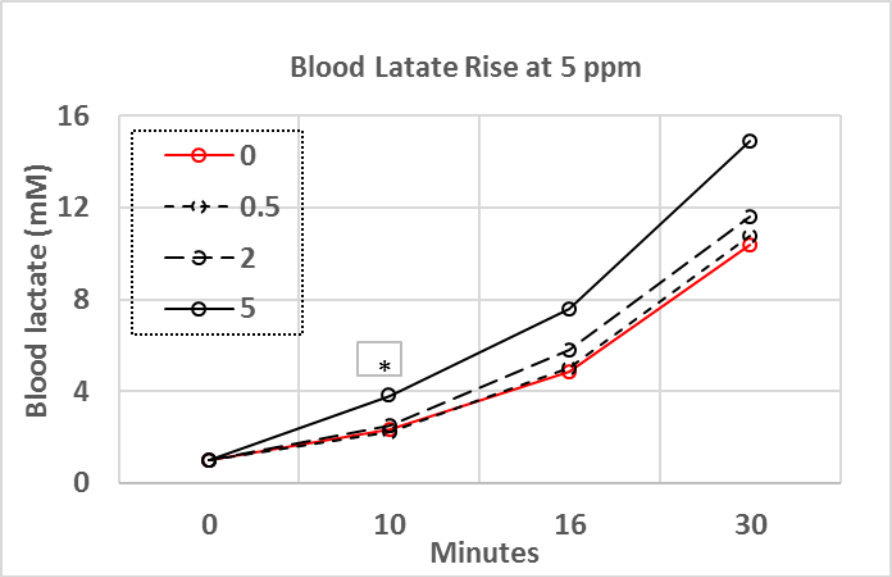


Figure 1

The utility of the Bhambhani studies for estimating potential human effects is to understand how the increase in LA levels relate to workplace exertion levels and the duration of that exertion. Using the data from test 1, a simple linear extrapolation of lactate levels for longer exposure at 5 ppm can be conducted. Multiplying the rate of lactate increase per minute achieved by the V1 threshold (10 minutes) by exposure time provides an estimate at longer duration. Using this extrapolation, Figure 2 shows that by 16 minutes, 5 ppm H2S produces lactate levels above the lactate threshold and by 60 minutes produces lactate levels considered intolerable at 30 minutes in test 1. Estimating for the controls, the lactate threshold is reached by 30 minutes but lactate levels never rise to a level considered intolerable by the subjects at 30 minutes. This extrapolation suggests that exposure to 5 ppm H_2S for 60 minutes under mild exercise induces lactate increases that may be associated with discomfort and fatigue not anticipated under no exposure. There may be a level of exercise at which 5 ppm does not increase blood lactate above the lactate threshold but that cannot be determined from the Bhambhani studies.

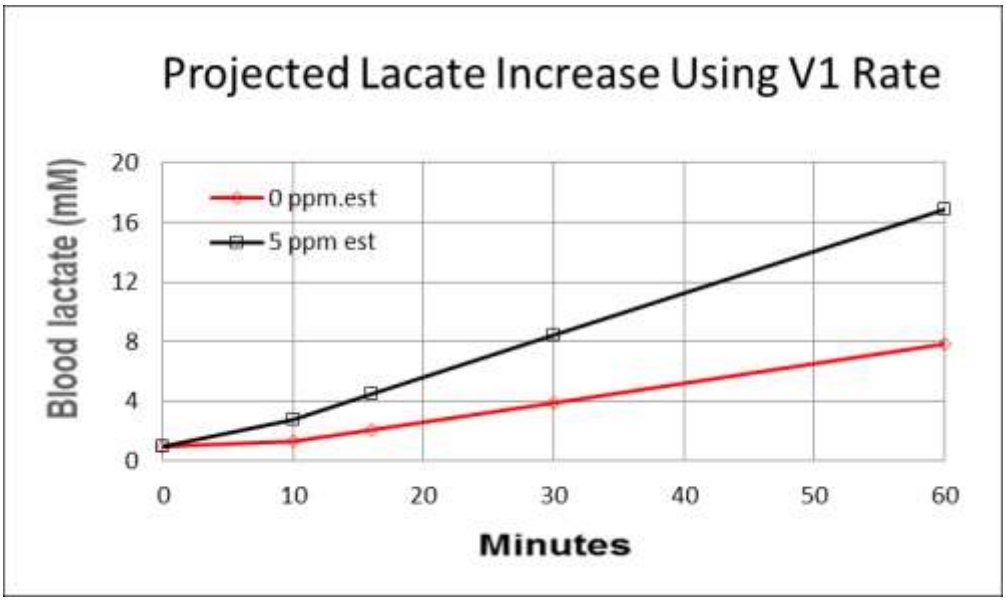


Figure 2:

One potential explanation for the discrepancies in the Bhambhani studies is subject variability in the amount of oxygen the blood can hold at maximum activity, VO_{2max}. VO_{2max} is related to physical health and gender and is typically directly related to the subject's exercise capacity. Bhambhani found an inverse correlation between VO_{2max} and blood lactate changes in the subjects in test 1 (Bhambhani, 1991). The mean value for VO_{2max} for the 16 male subjects in test 1 was 41.5 ± 6 while for test 2 and 3 were 51.2 ± 7.4 and 54.2 ± 8.4 (Column 2, table 1), a 20% difference in oxygen capacity. On average, workers have an estimated VO_{2max} of around 40 ml/kg/min (Lewis, 2011). Using data from the 1999 -2004 NHANES survey, Lewis reported that the survey-adjusted means (SE) for estimated VO_{2max} for total sample, males, and females were 40.4 ml/kg/min (SE = 0.3), 43.8 ml/kg/min (SE =0.3), and 35.9 ml/kg/min (SE = 0.3), respectively. The lowest average estimated VO_{2max} value was found for farm operators, managers, and supervisors in both males (M = 37.7 ml/kg/min, SE = 1.8) and females (M = 27.4 ml/kg/min, SE = 0.9). The highest average estimated VO_{2max} values were found for male and female construction laborers (M = 49.5 ml/kg/min, SE = 2.2; W = 44.9 ml/kg/min, SE = 6.4). VO_{2max} was estimated by extrapolation using measured heart rate responses to prescribed exercise workloads assuming a linear relationship between HR and oxygen consumption during exercise.

The developmental/neurological differences observed in rats at 20 ppm H_2S and above in Skrajny, Roth and Hannah are difficult to apply to the assessment of H2S for a number of reasons. The toxicological significance of the neurochemical levels (Skrajny and Hannah) and morphological differences (Roth) have not been determined nor have they been repeated in additional studies. A mechanism of action of H2S for these effects has not been identified. The biochemical and physiological role of H_2S is currently the subject of great interest as it was recently identified as a messenger molecule for a wide variety of cellular processes so new information about its neurological role will assist interpretation of these results at a later date.

The risk-based estimate for H_2S (HESIS PEL2017) applies duration adjustments for human equivalent exposure that may not be appropriate for occupational exposure. The conditions of that study (Brenneman, 2000; 10 weeks, 6 hours/day, 7 days/week) can be adjusted to an occupational exposure rather than a continuous exposure. Converting the NOAEL (30.5) to the human equivalent 8-hr occupational exposure and applying an RGDR of

0.159 results in a human equivalent dose of 5.1 ppm (30.5 x 6/8 x 7/5 x 0.159). Dividing by a total uncertainty factor of 10 (3 for sub-chronic study and 3 for intraspecies uncertainty) gives a PEL of 0.51 ppm. An alternate approach to determining the RfC for the olfactory lesions observed in Brenneman utilized a fluid dynamic model (CFD) of the rat and human nose and a PBPK rat model to determine deposition and kinetics of H_2S in the rodent olfactory region (Schroeter 2006). PBPK parameters from this study were scaled to human correlates based on an allometric scaling that was adjusted to account for the relative differences in nasal surface area between species. Using the 99th percentile olfactory flux values predicted by the human nasal CFD model, the study found that an H_2S exposure concentration of ~21 ppm will result in olfactory flux (and toxicity) equivalent to the rat exposed to 30 ppm. A $NOAEL_{[HEC]}$ for occupational exposure of 22.5 ppm can be calculated by adjusting to 8 hours (6/8) and 5 day (7/5) exposure conditions. Dividing by an uncertainty factors of 10 (3 for sub-chronic study and 3 for intraspecies uncertainty) gives a PEL of 2.25 ppm.

Recommendation: A PEL of 1 ppm is recommended based on the studies of Bhambhani (1991, 1994, 1996, 1997) and the risk-based estimates based on the Brenneman 2000 study. In the Bhambhani studies, non-adverse effects were observed in this healthy study population after 30 minute exposure to 5 ppm H2S under moderate exercise. The biochemical changes observed in these studies are in agreement with the inhibition of aerobic metabolism that is considered to be the toxic mode of action of H_2S. Extended to 8 hours, these changes could result in discernible fatigue, a symptom that has been reported in multiple occupational studies of H_2S, and possibly other effects. The risk-based estimates address potential nasal effects observed at 30 ppm in rodents. As these observation were obtained from a sub-chronic study (10 weeks) it is advisable to utilize uncertainty factors to estimate safe human exposure.

Lowering the 15-min STEL to 10 ppm is proposed. H_2S does not accumulate in the body and is rapidly cleared from blood and tissues so a sustained inhibition of respiration would not be expected from a short-term exposure to 10 ppm. The basis for the STEL is eye irritation between 10 – 20 ppm reported in multiple workplace investigations. These observations were obtained over longer exposure intervals (hours) however there is evidence that the threshold for H_2S eye irritation is lowered with co-exposure to other irritants so setting the STEL at 10 ppm will provide a margin of safety for this effect. No change to the 50 ppm Ceiling is proposed.

Usage information: EPA TSCA Chemical Data Reporting (CDR), EPA Toxics Release Inventories (TRI)), other sources:

In 2015, there were 27 TSCA CDR records for hydrogen sulfide (usage in excess of 25,000 lbs) in U.S. Of these, 2 were in California. In 2016 there were 519 TRI records for hydrogen sulfide of which 20 were in California.

Measurement/Implementation Feasibility

	OSHA Method ID 141 (validated)	NIOSH Method 6013
Estimated LOD/LOQ	**0.4/0.9 ppm (2 liters)**	**11 µg/ 17 µg**
Measurement issues	**silver nitrate impregnated filter**	**activated charcoal tube -some lots high S-**

Both NIOSH and OSHA methods are adequate to detect at the respective Ceiling Limits. The OSHA method is adequate to detect the TLV of 1 ppm. An issue with the OSHA method is that cassettes would have to be changed each hour at the minimum flow rate of 0.1 L/min if concentrations were near the OSHA Ceiling Level. Another issue is handling of the impregnated filter with forceps is necessary, and the impregnated filters are light sensitive so the cassettes must be shielded with aluminum foil or black tape during storage and transport. Store in a dark environment.

Economic Impact Analysis/Assessment

The Division has made a determination that this proposal is not anticipated to result in a significant, statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states. This proposal will not have any effect on the creation or elimination of California jobs nor result in the creation or elimination of existing businesses or affect the expansion of existing California businesses. The Division anticipates that any potential costs will be balanced by avoiding or minimizing the costs inherent in workers' compensation claims, lost work time, and productivity losses that would have been caused by exposure related illness of employees.

The PEL proposed is consistent with recent scientific findings, of which professional health and safety staff and consultants of these employers and others with significantly exposed employees should be aware. Many of these entities already seek to control employee exposures to substances to levels below existing PELs in the interest of business continuity and minimization of tort and workers compensation liability.

Setting a Permissible Exposure Limit for hydrogen sulfide that is up-to-date and consistent with current scientific information and state policies on risk assessment will send appropriate market signals to employers with respect to the costs of illness and injury, which chemicals can impose on workers and their families, the government, and society at large. With appropriate market signals, employers may be better able to protect employees from hydrogen sulfide exposures in the workplace and impose less of a burden on workers and society. There are no anticipated benefits to the state's environment. The economic benefits from the proposed PEL will result primarily from reduced health risk among exposed workers.

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