Hydrogen sulfide
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Risk Analysis Documentation

Summary of the toxicity assessment of hydrogen sulfide conducted by the Secretary's Scientific Advisory Board on Toxic Air Pollutants

Abstract
The Secretary's Scientific Advisory Board on Toxic Air Pollutants (SAB) evaluated the toxicity of hydrogen sulfide (H_2S) in response to a request made by DENR. The current H_2S Acceptable Ambient Level (AAL) guideline, based on acute irritancy, was established in 1986. At that time the North Carolina Academy of Sciences commented that the "issue of chronic effect needs to be resolved." H_2S is a malodorous compound that is emitted in significant quantities in North Carolina. It is an ocular and respiratory irritant that can prove fatal at sufficiently high exposure levels. Its odor is universally considered unpleasant and commonly referred to as "rotten-egg odor." H_2S is also a neurotoxin, capable of causing nerve paralysis in the nose during inhalation exposure leading to a loss of odor perception at high level exposures. Recent publications in the toxicological literature have studied adverse effects resulting from low level exposures to H_2S. In laboratory animals repeated exposure to H_2S resulted in damage to the tissues lining a specific portion of the nose. In humans, effects on metabolic enzyme levels were seen in one group of exposed individuals. In another study, some asthmatics experienced a strong bronchoconstrictive response to controlled H_2S exposures. Workers exposed to hydrogen sulfide in the viscose rayon industry experienced higher rates of eye pain than non-exposed workers. The SAB considered these and other published studies and listened to several expert presentations on the chemical and toxicological features of this compound before issuing their recommendations. The SAB's recommendations for H_2S are based on several health endpoints, including nasal toxicity in exposed rodents and respiratory and ocular effects in exposed humans. The final recommendations were generated by applying a set of safety factors to identified effect levels to account for various residual uncertainties including effect levels for sensitive individuals, non-continuous exposure scenarios and differences between species. The exposure level recommendations range from 0.083 ppm using rat nasal lesions as the basis to 0.023 ppm based on human eye effects. The recommendation based on asthmatic response (0.040 ppm) would be associated with a 1-hour AAL guideline, while the other two recommendations are based on long-term exposure and would necessitate 24-hour guidelines. These recommendations are meant to provide a choice to risk managers faced with implementation of resulting rule changes. Only one alternative involving a 24-hour guideline should be chosen for final rule development. The recommended 1-hour guideline could also be sent forward to replace the currently existing AAL.

Introduction

Most humans will recognize the distinctive rotten egg odor of H_2S when exposed at levels above the odor threshold. H_2S is a common degradation byproduct of organic materials and exposures are commonplace in agricultural and waste treatment environments. Some industrial operations including gasoline refining, pulp and paper production and chemical manufacturing may also release large quantities of H_2S. In 1999 over 4,000,000 pounds of H_2S was released from industrial point sources in North Carolina (DAQ, 1999).

The North Carolina Division of Air Quality maintains an AAL guideline of 1.5 ppm under its toxic air pollutants regulatory program. This guideline, established in 1986 by the North Carolina Academy of Sciences (NCAS), is based on the recommended Short Term Exposure Limit for occupational settings (15 ppm). A safety factor of 10 was utilized, in accordance with guidelines set up by the NCAS. The health basis for the original AAL was acute irritant effects including respiratory irritation and eye effects. The NCAS also commented that "the issue of chronic effect needs to be resolved" (NCAS 1987).

In response to rising concerns over environmental exposures to H_2S in North Carolina the Division of Air Quality asked the Scientific Advisory Board to recommend new health-based guidelines for H_2S. In the 15 years since the issuance of the original AAL recommendation several important papers have been published in the scientific literature examining the adverse health effects of H_2S exposure. These studies were scrutinized closely by the SAB during their deliberations and form the basis for their recommendations. Although H_2S is a potent odorant and well established as a cause for nuisance complaints, the SAB was explicitly directed by the Division of Air Quality not to use odor as the basis for any AAL recommendation. The Division feels that recent odor nuisance regulations will serve to protect citizens impacted by industrial emissions of H_2S and other odor-causing chemicals.[1] For more information on the adverse physiological effects arising from exposure to objectionable odors, readers are encouraged to refer to a recent summary document released by the North Carolina Department of Health and Human Services (McBride 1998).

Toxicity Assessment

Several documents have been published summarizing the chemical and toxicological features of H_2S (Beauchamp 1984, Guidotti 1996, ATSDR 1999). Readers are encouraged to refer to these documents for a more comprehensive survey of the characteristics of H_2S and its effects on exposed individuals. A brief summary of critical studies considered by the SAB follows.

[1] 15A NCAC 2D.1806

Human Health Effects: H_2S is a leading cause of occupational mortality. Many papers have been published describing accidental lethal or incapacitating exposures to H_2S. Exposure levels in most studies are poorly characterized but it has been estimated that levels above 500 ppm are responsible for death or unconsciousness (Beauchamp 1984). Recovery may occur following exposure-induced unconsciousness but in some cases long-term or permanent neurological effects have been seen. These effects may be complicated by hypoxia concurrent with H_2S exposure.

Pulmonary edema and olfactory paralysis have been noted following exposure to 50 to 250 ppm H_2S. The loss of smell associated with these exposures can compound the risk for incapacitation. Below 50 ppm H_2S is associated with a very strong, unpleasant odor that may induce nausea. H_2S is perceived to carry an unpleasant odor at all detectable levels. Both published and anecdotal reports suggest that H_2S odor perception is highly variable within the human population (Beauchamp 1984, Schiffman, personal communication). Collins and Lewis estimated that 50% of humans could detect the odor of H_2S at 8 ppb, while over 90% could detect the odor at 50 ppb and virtually everyone could detect H_2S at 200 ppb. They also estimated that exposures as low as 0.5 ppb H_2S might be detectable by a limited number of people (Collins and Lewis 2000).

Environmental exposures to H_2S have been described in several publications. Many of these cohorts involved individuals exposed as a result of working for or living downwind from industrial processes that emitted large quantities of H_2S. Accurate measurement of H_2S exposure is difficult and often confounded by concomitant exposure to other irritants and odor-causing compounds such as sulfur dioxide and mercaptans. Symptoms such as headache, nausea and eye and throat irritation are described in "downwind" communities at levels as low as 7 to 10 ppb with periodic fluctuations over an order of magnitude higher (Jaakola 1990, Marttila 1995, Kilburn 1995). Outcomes of several neuropsychological and neurophysiological tests exhibited impairment in exposed individuals (Kilburn 1995). In addition to H_2S, sulfur dioxide and mercaptans were also measured at these locations.

Occupational exposure to H_2S is common in several industrial settings including oil and gas refineries and pulp and paper mills. Workers commonly report many of the same symptoms experienced by nearby residents including headache and nausea. Occupational exposure limits for H_2S have ranged from 10 to 20 ppm over the past several decades (ACGIH 1992). Ocular toxicity including keratitis is generally associated with repeated exposures above 50 ppm. In viscose rayon plants exposure to hydrogen sulfide, carbon disulfide and sulfuric acid may occur. The calculated geometric mean H_2S exposure from one study involving workers complaining of eye pain was 6.4 ppm (Van Hoorne 1991)[2].

[2] A 10 ppm arithmetic mean exposure was calculated for the exposed "spinners" group.

Controlled exposures to H_2S have been carried out under a number of scenarios including using healthy exercising volunteers and a small cohort of asthmatics. Bhambani and colleagues carried out and published results from a series of studies involving healthy men and women. Endpoints monitored included pulmonary function, biochemical changes in skeletal muscle, cardiovascular effects and metabolic indicators. Inhalation exposures ranged from 0.5 to 10 ppm H_2S and from 15 to 60 minutes during exercising conditions. Pulmonary tests at 10 ppm were negative (Bhambani 1996). At 5 ppm and under light exercising conditions no significant change in metabolic, cardiovascular or arterial blood indicators was seen (Bhambani 1994). Under higher intensity exercise conditions, exposure to 5 ppm H_2S resulted in significantly higher blood lactate levels and decreased respiratory exchange ratios (Bhambani 1991). Buildup of lactate in muscle tissue could lead to muscular fatigue during exercise. These effects may be related to the inhibitory effect of H_2S on the enzyme cytochrome oxidase. No significant effect was seen at 0.5 or 2.0 ppm in this study.

In another study, controlled exposure of a small group of asthmatics to 2 ppm H_2S was carried out to study the effect on airway resistance and conductance (Jappinen 1990). While no overall effect was seen when comparing the total cohort to a group of control subjects, two of the ten asthmatic individuals in the study exhibited a pronounced response. Airway resistance and conductivity were both altered by greater than 30%, suggesting significant bronchial obstruction. Patients with "severe" asthma were not included in this study. Participants in the study were asked to refrain from taking asthma medications for two days prior to challenge testing.

Effects in Experimental Animals: H_2S has been studied extensively in laboratory rodents. Both acute and subchronic inhalation studies have been conducted using several species of laboratory animals. Many of the effects in animals are similar to those experienced by humans. Acute exposures to 500 ppm H_2S or more results in death within minutes to hours. Cytotoxicity and respiratory tract histological changes have been noted in rats following 4-hour exposures to 83 to 400 ppm H_2S. Short-term exposures have also resulted in ocular irritation, metabolic changes and cardiovascular effects in rabbits and guinea pigs. These studies are summarized in recent publications (ATSDR 1999).

While no chronic exposure studies have been performed using H_2S, results from several recent studies involving subchronic 90-day inhalation exposures have been published. Dorman, et al examined whether exposures at 10, 30 or 80 ppm would have any effect on fertility or developmental outcomes in Sprague-Dawley rats. Developmental landmarks were monitored and behavioral tests conducted on pups during the first 2 months after birth. Histopathological examination of brains from controls and high-dose offspring was conducted. Reproductive organs from the parent animals were also examined and a complete necropsy was carried out on all animals in the study. No adverse effects on

fertility or neurodevelopment were seen in parent or offspring rats at any dose level studied (Dorman 2000).

Examination of nasal tissues from the exposed adult rats in this study highlighted olfactory neuron loss and basal cell hyperplasia in the olfactory epithelium. Dose-dependent increases in incidence and severity of effect were seen beginning at 30 ppm H_2S. "Exposure-related olfactory changes were readily detectable with exposure to 30 and 80 ppm H_2S and affected approximately 50% and 70%, respectively, of the olfactory mucosa at these exposure concentrations" (Brenneman 2000). Dose-dependent effects were generally limited to the olfactory epithelium, which may be a reflection of airflow in the nose and resultant delivered dose, or alternatively could be due to distinctive tissue metabolism. The distribution of cytochrome oxidase and H_2S detoxification enzymes in the rat nasal cavity has not been well characterized but may explain the unique distribution of histological changes arising from H_2S exposure (Brenneman 2000). The no-effect level for H_2S in this study was 10 ppm.

Additional Information

Areas unaffected by natural or anthropogenic releases contain less than 1 ppb H_2S in ambient air (EPA 1993). Because gaseous reduced sulfur species are natural byproducts of the degradation of sulfur-containing organic material, measurable quantities of H_2S may be found in pristine settings such as wetlands and forests. Cooper, et al reported levels short-term readings as high as 62 ppb H_2S in Florida wetlands (Cooper 1987). Widely varying values have been reported at sites influenced by local source emissions. In the South Karelia, Finland air pollution study, air in the neighborhood of a pulp mill demonstrated an average level of 3 ppb H_2S, with a maximum 4-hour measurement of 40 ppb (Jaakkola 1990). Kilburn reported an average and peak measurements of 10 and 100 ppb H_2S in a neighborhood study near a large oil refinery. Preliminary data from an ambient air study in central North Carolina indicate that normal H_2S levels are below 1 ppb and transient fluctuations possibly associated with local emission sources are generally below 20 ppb H_2S. It is difficult to meaningfully compare results from the various studies examining H_2S levels in air because of variability in measurement methodologies. Often, measurements of total reduced sulfur (TRS) compounds are reported. In addition to H_2S this would include methyl mercaptan, dimethyl sulfide and dimethyl disulfide, compounds which could result in similar health effects upon exposure.

H_2S is produced endogenously by living organisms, including human beings, through the normal digestion and metabolism of sulfur containing materials. H_2S and other reduced sulfur gases produced in the gut may subsequently be exhaled or released in flatus. An average level of 25.5 ppmv has been reported in human flatus. The degree of malodor is positively associated with the concentration of H_2S in the passed gas.

H_2S is believed to be partially responsible for bad breath and halitosis. H_2S and other reduced sulfur gases are produced both in the gut as well as the mouth and can vary depending on several factors including diet and oral hygiene. Several dental research papers have reported results on measurements of sulfur gases on human breath (Rosenberg 1992, Suarez 1999, 2000). Similar to the situation with measurements of H_2S in ambient air, inconsistencies with measurement methodologies and incomplete description of results plague this field of research. Studied populations commonly include both patients complaining of bad breath as well as patients with normal breath. Shimura reported mean results of 13.2 ppb and 177.6 ppb H_2S on the breath of normal patients and those suffering from halitosis, respectively (Shimura 1996). No in-depth discussion of variability was included and raw data were not provided. Rosenberg authorized a summary paper on oral malodor in which he describes the intraday variability as measured by volatile sulfides. Daytime levels are predominantly less than 50 ppb but at night and in the early morning levels approached 300 ppb. A recent paper by Suarez et al used GC-MS to distinguish and measure the levels of reduced sulfur compounds on human breath upon waking (Suarez 2000). Subjects were free of periodontal disease and did not report problems with bad breath. Measurements of H_2S exhibited "enormous individual variability." The average value for eight subjects measured on six separate occasions (48 total samples) was 525 ppb H_2S. A handful of readings exceeded 1.0 ppm H_2S but the majority of readings appear to fall in a range between 0 and 500 ppb H_2S.

The studies outlined above focused on H_2S measurements in mouth air. The toxicological measurement of import for exposure to H_2S is alveolar H_2S. Suarez (1999) showed that increases in mouth H_2S did not lead to increases in alveolar H_2S above background levels, implying that even with high concentrations in the mouth, actual inhaled quantities of H_2S can be quite low. A similar situation is seen with mercury exposure from dental amalgams. This may be a reflection of the insignificant volume of air in the mouth relative to the volume of air inhaled during normal breathing. Normal breathing of ambient air could thus be a far greater contributor to lower airway exposures. Any exposure to H_2S in ambient air will contribute to the overall burden of exposure resulting from natural processes.

There is evidence to suggest that low levels of H_2S may act as a neuromodulator. H_2S may be produced endogenously through the metabolism of L-cysteine in selective areas of the brain. It is not currently known what effect external exposures to H_2S might have on this process.

Risk Assessments

SAB risk assessments for H_2S are summarized in the attached tables. Three assessments are presented, based on nasal toxicity in experimental animals (Table 1), human respiratory effects in exposed asthmatics (Table 2) and human eye irritation (Table 3). Justifications for safety factors are included in each summary table. In general, larger

uncertainty factors reflect greater uncertainty about the health effect being considered or a greater severity of effect.

Conclusion

The SAB concluded their review of H_2S at the June 19, 2001 meeting. Risk estimates have been provided based on results from experimental animal tests and documented human health effects. The SAB agreed to bring forward several risk estimates as a fulfillment of the recommendation by the Air Toxics Working Group that they forward a range of risk estimates rather than one single estimate (ATWG 1997). The SAB cannot state with certainty which toxicologic endpoint is more relevant. However, adopting the lowest concentration value (in this case 0.023 ppm) would be the most conservative choice and would theoretically also protect against other, less sensitive health endpoints.

- Option 1: Nasal toxicity in exposed rats, 0.083 ppm.
- Option 2: Respiratory effects in exposed asthmatics, 0.040 ppm.
- Option 3: Eye irritation in exposed workers, 0.023 ppm.

AALs are intended to be *incremental* exposure values. They represent exposure values that would *add to* the "background" exposures that occur as a result of other natural or man-made processes.

For a sense of comparison, H_2S health guidelines from other State and Federal regulatory agencies are provided. The California state-wide ambient air quality standard for H2S is 30 ppb, averaged over an hour and not to be equaled or exceeded. It was designed to protect against nuisance odors for the general public. California also has a chronic guideline for their Hot Spots regulatory program of 8 ppb, designed to protect against long-term effects such as nasal lesions. The current USEPA reference concentration for H2S is 0.7 ppb, based on adverse effects such as nasal lesions following chronic exposure. The reference concentration is defined 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." The reference concentration will likely be updated during 2001 to reflect the latest science. The USEPA also recently developed acute exposure guidelines (AEGLs) for H_2S, based on the aforementioned Jappinen study. The recommended values range between 250 ppb and 110 ppb, over 10 minute to 8 hour exposures. The AEGLs are meant to represent "short-term threshold or ceiling exposure values intended for the protection of the general public, including susceptible or sensitive individuals, but not hypersensitive or hypersusceptible individuals." The North Carolina AALs, by contrast represent average, and not peak, concentrations. Finally, the Agency for Toxic Substances and Disease Registry (ATSDR) maintains two "Minimum Risk Level" (MRL) guidelines for H2S: 70 ppb for acute duration exposures (1 to 14 days) and 30 ppb for intermediate duration exposures (15 - 364 days). The MRL is

defined as "an estimate of daily human exposure to a dose of a chemical that is likely to be without appreciable risk of adverse noncancerous effects over a specified duration of exposure." MRLs are generally used as screening values by ATSDR health assessors in exposure situations.

Averaging Times

The Division of Air Quality recommends that a 1-hour averaging time be used in conjunction with the SAB recommendation based on asthmatic response. The other two recommendations should carry 24-hour averaging times. These recommendations are consistent with guidelines detailed by the North Carolina Academy of Sciences prescribing 1-hour averaging times for acute exposure effects and 24-hour averaging times for chronic non-carcinogenic health effects.

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Table 1: Subchronic Rat Inhalation Exposure		
Variable	**Value**	**Notes**
Starting Point	10 ppm (NOAEL)	Nasal lesions in olfactory mucosa of rats following 10-week exposure to 30 and 80 ppm but not at 10 ppm H_2S (Brenneman, et al). Lack of significant reproductive or behavioral effects and lack of gross body weight changes and organ pathology at 10 and 30 ppm in Sprague-Dawley rats (Dorman, et al).
Time Factor Adjustment	24/6	Acute effect at 400 ppm for 4 hours but not 200 ppm suggests subchronic effects at lower levels are due to cumulative dose or delayed sequela (Brenneman). H_2S is a direct acting toxicant but it remains unknown whether threshold dose-response pattern exists.
Interspecies variability	3	Rat nasal anatomy may predispose this species to greater toxicity due to enhanced deposition of inhaled gases on the nasal tract. Rats are also obligate nose-breathers. However, nasal toxicity has not been characterized in humans and precise factors influencing toxicity (i.e. metabolism vs. anatomy) have not been clearly defined.
Interindividual variability	10	Possible variability in human nasal anatomy or toxification/detoxification steps which are as yet incompletely defined. Variability in odor detection circumstantial evidence.
Composite Uncertainty Factor	120	
Final Value	**10 ppm/120 = 0.083 ppm (0.12 mg/m^3)**	**Based on sub-chronic nasal toxicity in rats (Brenneman).**

Table 2: Human Respiratory Effects		
Variable	**Value**	**Notes**
Starting Point	2 ppm (LOAEL)	Significant change in airway resistance and conductivity in 2/10 asthmatics exposed to 2 ppm H_2S, headaches experienced by 3/10 at this level (Jappinen). (Also: 2 ppm NOAEL for physiological responses in Bhambani, et al (1991). Significant increase in blood lactate levels at 5 ppm, slight increase at 2 ppm.)
NOAEL/LOAEL	5	Reduced uncertainty factor due to relatively low response rate (2/10) in the principal study. Also, the short 2-day recovery period from asthma medication may have masked effects in some participants (Stopford). Lack of dose-response information prohibits further reduction of uncertainty factor.
Time Factor Adjustment	1	Not applicable. Acute effect occurring following short-term exposures (up to 30 minutes).
Interindividual variability	10	In Jappinen study, patients with "severe" asthma were excluded. Additionally, the results suggested that 2 of the 10 asthmatics included in the study did experience bronchoconstriction, illustrating varied susceptibility. (Bhambani study excluded individuals who were classified as "high risk.")
Composite Uncertainty Factor	50	
Final Value	**2 ppm/50 = 0.040 ppm (0.056 mg/m^3)**	**Based on triggering of asthma symptoms following exposure to 2 ppm H_2S (Jappinen).**

Table 3: Human Keratitis		
Variable	**Value**	**Notes**
Starting Point	9.8 ppm (13.7 mg/m^3) (LOAEL)	Eye pain and visual disturbances in viscose rayon workers exposed to H_2S (Vanhoorne). Increased incidence of symptoms in spinners exposed to arithmetic mean value of 13.7 mg/m^3 H_2S.
Time Factor Adjustment	4.2	Chronic exposure effect not detected in acute exposure scenarios. Workers in spinning area presumed to work full-time. 40 hrs exposure/(168 hrs/wk).
NOAEL/LOAEL	10	Full uncertainty factor for conversion to NOAEL. Lack of meaningful data to determine dose-response curve for this health effect. Study data showed slight increase in effect in moderately (1 - 5 mg/m^3) exposed group.
Interindividual variability	10	Full uncertainty factor. Lack of data to suggest whether the studied population could be considered "sensitive" or to determine range of interindividual sensitivity. Prior corneal disease state or use of contacts could predispose exposed individuals to ocular toxicity.
Composite Uncertainty Factor	420	
Final Value	**(9.8 ppm)/420 = 0.023 ppm** **(0.033 mg/m^3)**	**Based on eye pain and visual disturbances caused following chronic exposure to H_2S (Vanhoorne).**