HYDROGEN SULFIDE:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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A. Extended abstract

The current California Ambient Air Quality Standard (CAAQS) for hydrogen sulfide is 0.03 ppm (30 ppb, 42 μg/m^3) for one hour. The standard was adopted in 1969 and was based on the geometric mean odor threshold measured in adults. The purpose of the standard was to decrease odor annoyance. The standard was reviewed in 1980 and 1984 (CARB, 1984), and was not changed since no new relevant information had emerged. The U.S. EPA presently does not classify hydrogen sulfide as either a criteria air pollutant or a Hazardous Air Pollutant. However, several countries have short-term (usually 30 minute) standards for hydrogen sulfide, as well as long-term (24 hour) standards.

This report focuses on key studies in humans and animals bearing on the health-protectiveness of the CAAQS for hydrogen sulfide. It also includes a discussion of whether significant adverse health effects would reasonably be expected to occur, especially among infants and children, at exposure concentrations below the CAAQS of 30 ppb, based on the findings of published studies. Additional research on odor sensitivity in infants, children, and adults would be useful in evaluating the standard. This would include: (1) testing of the odor threshold for H_2S using the most current methodology among groups of healthy persons of both sexes in different age ranges; (2) odor testing of hydrogen sulfide in adolescents or younger children to determine their odor threshold for H_2S; (3) the identification of children hypersensitive to the odor of hydrogen sulfide; and (4) physiologic testing of anosmic (either specifically anosmic to H_2S or totally anosmic) children at the CAAQS to determine if adverse physiological symptoms occur in the absence of odor detection.

B. Background

The Mulford-Carrell Air Resources Act of 1967 directed the Air Resources Board to divide California into Air Basins and to adopt ambient air quality standards for each basin (Health and Safety Code (H&SC) Section 39606). The existing California state-wide ambient air quality standard (CAAQS) for hydrogen sulfide of 0.03 ppm (30 ppb, 42 $\mu g/m^3$), averaged over a period of 1 hour and not to be equaled or exceeded, protects against nuisance odor ("rotten egg smell") for the general public. The standard was adopted in 1969 and was based on rounding of the geometric mean odor threshold of 0.029 ppm (range = 0.012 – 0.069 ppm; geometric SD = 0.005 ppm) measured in adults (California State Department of Public Health, 1969). The standard was reviewed by the Department of Health Services in 1980 and 1984, and was not changed since no new relevant information had emerged. OEHHA (1999) formally adopted 30 ppb as the acute Reference Exposure Level (REL) for use in evaluating peak off-site concentrations from industrial facilities subject to requirements in H&SC Section 44300 *et seq*. OEHHA (2000) adopted a level of 8 ppb (10 $\mu g/m^3$) as the chronic Reference Exposure Level (cREL) for use in evaluating long term emissions from Hot Spots facilities. The cREL was based on a study demonstrating nasal histological changes in mice.

At the federal level, U.S. EPA does not currently classify hydrogen sulfide as either a criteria air pollutant or a Hazardous Air Pollutant (HAP). U.S. EPA has developed a (chronic) Reference Concentration (RfC) of 0.001 mg/m^3 (1 $\mu g/m^3$) for hydrogen sulfide (USEPA, 1999). The RfC is 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.

There are no international standards for H_2S. Many countries have "short-term" (usually 30 minute) standards, which range from 6 to 210 ppb (WHO, 1981). The World Health Organization (WHO) recommends that, in order to avoid substantial complaints about odor

annoyance among the exposed population, hydrogen sulfide concentrations should not be allowed to exceed 0.005 ppm (5 ppb; 7 μg/m^3), with a 30-minute averaging time (WHO, 1981; National Research Council, 1979; Lindvall, 1970). A very short-lived, peak concentration could also be annoying. Rule 2 of Regulation 9 of the Bay Area Air Quality Management District (BAAQMD) specifies that ambient ground level H_2S concentrations may not exceed 60 ppb averaged over 3 consecutive minutes. Regulating at averaging times less than 30 – 60 minutes may be difficult. Many countries have "long-term" (24 hour) standards (WHO, 1981).

NRC (1979), WHO (1981), Beauchamp *et al*. (1984), Reiffenstein *et al*. (1992), and ATSDR (1999) have published reviews of the health effects of hydrogen sulfide.

C. Principal sources/Exposure assessment

Hydrogen sulfide (H_2S) is used as a reagent and as an intermediate in the preparation of other reduced sulfur compounds (HSDB, 1999). It is also a by-product of desulfurization processes in the oil and gas industries and rayon production, sewage treatment, and leather tanning (Ammann, 1986). Geothermal power plants, petroleum production and refining, and sewer gas are specific sources of hydrogen sulfide in California. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Information and Assessment Act in California (H&SC Sec. 44300 *et seq*.), based on the most recent inventory, were estimated to be 5,688,172 pounds of hydrogen sulfide (CARB, 1999).

A specific concern in California has been schools located near workplaces emitting toxic substances. For example, the Hillcrest Elementary School in Rodeo (Contra Costa County; part of the BAAQMD) is adjacent to an oil refinery which, on occasion, has emitted enough malodorous sulfur compounds (including H_2S) for the school to close its doors and for the teachers and children to "shelter-in-place." Thus the school district has planned to relocate the school (West County Times, November 23, 1999). These compounds have also affected other schools in the area.

Hydrogen sulfide is produced endogenously in mammalian tissues from L-cysteine, mainly by two pyridoxal-5'-phosphate-dependent enzymes, cystathionine beta-synthetase and cystathionine gamma-lyase (Hosoki *et al*., 1997). Abe and Kimura (1996) suggested that hydrogen sulfide may be an endogenous neuromodulator in the hippocampus based on the high level of cystathionine beta-synthetase in the hippocampus and on experimental effects of activators and inhibitors of the enzyme.

D. Key studies of acute and chronic health impacts

D.1. Toxicity to Humans

D.1.1. Adults. Hydrogen sulfide is an extremely hazardous gas (ACGIH, 1991). Exposure to high concentrations of hydrogen sulfide is reported to be the most common cause of sudden death in the workplace (NIOSH, 1977). Estimates of the mortality resulting from acute hydrogen sulfide intoxication include 2.8% (Arnold *et al*., 1985) and 6% (WHO, 1981). While severe intoxication is especially of concern when exposure occurs in confined spaces, an accidental release of hydrogen sulfide into the ambient air surrounding industrial facilities can cause very serious effects. As a result of an accidental release of hydrogen sulfide due to a malfunctioning flare at an oilfield at Poza Rica, Mexico in 1950, 320 people were hospitalized and 22 died (WHO, 1981).

Most information on H_2S toxicity comes from studies that used levels of H_2S orders of magnitude above the standard of 0.03 ppm. Hazardtext (1994) reported an inhalation LC_{Lo} of 600 and 800 ppm (840 and 1,120 mg/m³) for 30 and 5 minutes, respectively. A lethal exposure was documented for a worker exposed to approximately 600 ppm H_2S for 5 to 15 minutes (Simson and Simpson, 1971). Inhalation of 1,000 ppm (1,400 mg/m³) is reported to cause immediate respiratory arrest (ACGIH, 1991). Concentrations greater than 200 ppm (280 mg/m³) H_2S are reported to cause direct irritant effects on exposed surfaces and can cause pulmonary edema following longer exposures (Spiers and Finnegan, 1986). The mechanism of H_2S

toxicity, cellular hypoxia caused by inhibition of cytochrome oxidase, is similar to that for cyanide. Toxicity can be treated by induction of methemoglobin or by therapy with hyperbaric oxygen (Elovaara *et al*., 1978; Hsu *et al*., 1987).

At concentrations exceeding 50 ppm (70 mg/m^3) H_2S, olfactory fatigue prevents detection of H_2S odor. Exposure to 100-150 ppm (140-210 mg/m^3) for several hours causes local irritation (Haggard, 1925). Exposure to 50 ppm for 1 hour causes conjunctivitis with ocular pain, lacrimation, and photophobia; this can progress to keratoconjunctivitis and vesiculation of the corneal epithelium (ACGIH, 1991).

Bhambhani and Singh (1985) reported that exposure of 42 individuals to 2.5 to 5 ppm (3.5 to 7 mg/m^3) H_2S caused coughing and throat irritation after 15 minutes. Bhambhani and Singh (1991) showed that 16 healthy adult male subjects (25.2±5.5 years old) exposed to 5 ppm (7 mg/m^3) H_2S under conditions of moderate exercise exhibited impaired lactate and oxygen uptake in the blood. Subsequently Bhambani *et al*. (1994) compared the effects of inhaling 5 ppm H_2S on physiological and hematological responses during exercise. Subjects were 13 men (mean±SD for age, height, and weight = 24.7±4.6 y, 173±6.6 cm, and 73.1±8.1 kg, respectively) and 12 women (mean±SD = 22.0±2.1 y, 165±8.2 cm, and 63.4±8.6 kg, respectively). Subjects completed two 30-minute exercise tests on a cycle ergometer at 50% of their predetermined maximal aerobic power, while breathing either air or 5 ppm H_2S. There were no significant differences between the two exposures for metabolic (oxygen uptake, carbon dioxide production, respiratory exchange ratio), cardiovascular (heart rate, blood pressure, rate pressure product), arterial blood (oxygen and carbon dioxide tensions, pH), and perceptual (rating of perceived exertion) responses. No one reported adverse health effects following H_2S exposure. The authors believe that healthy adults can safely perform moderate intensity work in environments containing 5 ppm H_2S.

Bhambhani *et al*. (1996) examined the acute effects of "oral" inhalation of 10-ppm H_2S, the occupational exposure limit, on lung physiology as measured by pulmonary function in nine men and ten women. The volunteers inhaled medical air or 10 ppm H_2S through the mouth for 15 minutes each during cycle exercise at 50% of their maximal aerobic power. Routine pulmonary function tests (FVC, FEV_1, FEV_1/FVC, PEFR, maximal ventilation volume, and DL_{CO}) were administered at rest and immediately after the two exposure conditions. There were no significant changes in any of the variables derived from the flow volume loop, maximum ventilation volume, and diffusion capacity of the lung for carbon monoxide (DL_{CO}) in both genders. No subject experienced any sign or symptom as a result of H_2S. The authors concluded that inhalation of 10 ppm H_2S through the mouth at an elevated metabolic and ventilation rate does not significantly alter pulmonary function in healthy people.

Jappinen *et al*. (1990) exposed ten adult asthmatic volunteers to 2 ppm H_2S for 30 minutes and tested pulmonary function. All subjects reported detecting "very unpleasant" odor but "rapidly became accustomed to it." Three subjects reported headache following exposure. No significant changes in mean FVC or FEV_1 were reported. Although individual values for specific airway resistance (SR_{aw}) were not reported, the difference following exposure ranged from –5.95% to +137.78%. The decrease in specific airway conductance, SG_{aw}, ranged from –57.7% to +28.9%. The increase in mean SR_{aw} and the decrease in mean SG_{aw} were not statistically significant for the entire group. However, markedly (>30%) increased airway resistance and decreased airway conductance were noted in two of the ten asthmatic subjects at 2 ppm, which indicated bronchial obstruction and may be clinically important. Two ppm is 67 times the CAAQS of 0.03 ppm.

Hydrogen sulfide is noted for its strong and offensive odor. The existing CAAQS of 0.03 ppm (30 ppb, 42 $\mu g/m^3$) for 1 hour is based on rounding the geometric mean odor detection threshold of 0.029 ppm (range = 0.012 – 0.069 ppm; GSD = 0.005 ppm). The threshold was

determined for a panel of 16 presumably healthy adults (California State Department of Public Health, 1969). No information on the sex or age of the panel members has been located. Amoore (1985) reviewed 26 studies, published between 1848 and 1979, all of which reported average odor detection thresholds for H_2S. The 26 studies seem to be mainly controlled exposures and used various measurement methods. They included (1) at least two studies using only one subject, (2) a study of a panel of 35 people testing odors in natural gas in Southern California, and (3) another study of 852 untrained young adults (age range = 17.5 – 22.4 years) tested at county and state fairs in the Northwest. The average odor detection threshold in the 26 studies ranged from 0.00007 to 1.4 ppm H_2S. The geometric mean of the 26 studies was 0.008 ppm (8 ppb), approximately one-fourth the value determined by the Department of Public Health and lower than the lowest individual threshold of 12 ppb measured in the California panel. Surprisingly the Department of Public Health panel study was not one of the 26 studies used by Amoore and was not even mentioned in his 1985 report to the ARB.

Venstrom and Amoore (1968) reported that, in general, olfactory sensitivities decrease by a factor of 2 for each 22 years of age above age 20. The conclusion was based on a study of 18 odorants in 97 government laboratory workers, ages 20 through 70. Hydrogen sulfide was not tested. The geometric mean odor threshold of 8 ppb for H_2S from the 26 studies is based on an average age of 40 (possibly assumed to be the age of an average adult). Amoore (1985) estimated that an 18-year-old person would have a threshold of 4 ppb H_2S, while a 62-year-old person was predicted to have a threshold of 16 ppb. Amoore also stated that there was no noticeable trend of odor sensitivity between young adults and children down to 5 years but did not present specific data to support the statement.

Concentrations, which substantially exceed the odor threshold for, result in the annoying and discomforting physiological symptoms of headache or nausea (Amoore, 1985; Reynolds and Kauper 1984). The perceived intensity of the odor of H_2S depends on the longevity of the concentration, and the intensity increases 20% for each doubling of the concentration (Amoore,

1985). Several studies have been conducted to establish the ratio of discomforting annoyance threshold to detection threshold for unpleasant odors (Winkler, 1975; Winneke and Kastka, 1977; Hellman and Small, 1974; Adams *et al.,* 1968; and NCASI, 1971). The geometric mean for these studies is 5; therefore an unpleasant odor should result in annoying discomfort when it reaches an average concentration of 5 times its detection threshold. (Two studies that tested only H_2S had a geometric mean of 4.) Applying the 5-fold multiplier to the mean detectable level of 8 ppb results in a mean annoyance threshold of 40 ppb. Amoore (1985) estimates that at 30 ppb, the CAAQS, H_2S would be detectable by 83% of the population and would be discomforting to 40% of the population (Table 1). These "theoretical" estimates have been substantiated by odor complaints and reports of nausea and headache (Reynolds and Kauper 1984) at 30 ppb H_2S exposures from geyser emissions.

In order to avoid substantial complaints about odor annoyance among the exposed population, the World Health Organization (WHO) recommends that hydrogen sulfide concentrations should not exceed 0.005 ppm (5 ppb; 7 $\mu g/m^3$), with a 30-minute averaging time (WHO, 1981; National Research Council, 1979; Lindvall, 1970). The WHO task group believed that 5 ppb averaged over 30 minutes "should not produce odour nuisance in most situations."

Table 1. Predicted effects of exposure to ambient H_2S. (Adapted from Amoore, 1985)

H_2S (ppb)	% able to detect odor[a]	Perceived odor intensity[b] (ratio)	Median odor units[c]	% annoyed by odor[d]
200	99	2.31	25	88
100	96	1.93	12	75
50	91	1.61	6.2	56
40	88	1.52	5.0	50
35	87	1.47	4.4	47
30 (CAAQS)	83	1.41	3.7	40
25	80	1.34	3.1	37
20	74	1.27	2.5	31
15	69	1.18	1.9	22
10	56	1.06	1.2	17
8	50	1.00	1.00	11
6	42	0.93	0.75	8
4	30	0.83	0.50	5
2	14	0.70	0.25	2
1	6	0.58	0.12	1
0.5	2	0.49	0.06	0

[a]Based on mean odor detection threshold of 8.0 ppb and SD±2.0 binary steps
[b] Based on intensity exponent of 0.26 (Lindvall, 1974).
[c]H_2S concentration divided by mean odor detection threshold of 8 ppb.
[d] Based on assumption that mean annoyance threshold is 5x the mean odor detection threshold, and SD±2.0 binary steps.

Kilburn and Warshaw (1995) investigated whether people exposed to sulfide gases, including H_2S, as a result of working at or living downwind from the processing of "sour" crude oil demonstrated persistent neurobehavioral dysfunction. They studied 13 former workers and 22 neighbors of a California coastal oil refinery who complained of headaches, nausea, vomiting, depression, personality changes, nosebleeds, and breathing difficulties. Neurobehavioral functions and a profile of mood states were compared to 32 controls matched for age and educational level. The exposed subjects' mean values were statistically significantly different (abnormal) compared to controls for several tests (two-choice reaction time; balance (as speed of sway); color discrimination; digit symbol; trail-making A and B; immediate recall of a story). Their profile of mood states (POMS) scores were much higher than those of controls. Test scores for anger, confusion, depression, tension-anxiety, and fatigue were significantly

elevated and nearly identical in both exposed residents and former workers, while the scores for controls equaled normal values from other published studies. Visual recall was significantly impaired in neighbors, but not in the former workers. Limited off-site air monitoring (one week) in the neighborhood found average levels of 10 ppb H_2S (with peaks of 100 ppb), 4 ppb dimethylsulfide, and 2 ppb mercaptans. On-site levels were much higher. The authors concluded that neurophysiological abnormalities were associated with exposure to reduced sulfur gases, including H_2S from crude oil desulfurization.

D.1.2. Children. In a case report Gaitonde *et al*. (1987) described subacute encephalopathy, ataxia, and choreoathetoid (jerky, involuntary) responses in a 20-month-old child with long term (approximately one year) exposure to hydrogen sulfide from a coal mine. Levels of up to at least 0.6 ppm (600 ppb) were measured and levels were possibly higher before measurements started. The abnormalities resolved after the emission source ceased operation.

As part of the South Karelia Air Pollution Study in Finland (Jaakkola *et al*., 1990), Marttila *et al*. (1994) assessed the role of long-term exposure to ambient air malodorous sulfur compounds released from pulp mills as a determinant of eye and respiratory symptoms and headache in children. The parents of 134 children living in severely polluted (n = 42), moderately polluted (n = 62), and rural, non-polluted (n = 30) communities responded to a cross-sectional questionnaire (response rate = 83%). In the severely polluted area, the annual mean concentrations of hydrogen sulfide and methyl mercaptan (H_3CSH) were estimated to be 8 $\mu g/m^3$ (6 ppb) and 2 - 5 $\mu g/m^3$ (1.4 – 3.6 ppb), respectively. The highest daily average concentrations were 100 $\mu g/m^3$ (71 ppb) and 50 $\mu g/m^3$ (36 ppb), respectively. The adjusted odds ratios (OR) for symptoms experienced during the previous 4 weeks and 12 months in the severely versus the non-polluted community were estimated in logistic regression analysis controlling for age and gender. The risks of nasal symptoms, cough, eye symptoms, and

headache were increased in the severely polluted community, but did not reach statistical significance (Table 2). In addition, OEHHA staff noted that the highest percentages of children with symptoms were in the moderately polluted community, not in the severely polluted community. The authors concluded that exposure to malodorous sulfur compounds may affect the health of children. The odor threshold for methyl mercaptan of 1.6 ppb (Amoore and Hautala, 1983) indicates that it also likely contributed to the odor and probably the symptoms.

Table 2. Symptoms Reported in Marttila *et al*. (1994)

Symptom	*Time*	*Odds Ratio*	*95% CI*	*Time*	*Odds ratio*	*95%CI*
nasal symptoms	4 weeks	1.40	0.59-3.31	12 months	2.47	0.93-6.53
cough	4 weeks	1.83	0.75-4.45	12 months	2.28	0.95-5.47
eye symptoms	NR	NR	NR	12 months	1.15	0.43-3.05
headache	NR	1.02	0.36-2.94	12 months	1.77	0.69-4.54

NR = not reported

Studies of controlled exposures in children to study H_2S odor detection have not been located. A recent report studying children concluded that children aged 8 to 14 years have equivalent odor sensitivity to young adults (Cain *et al*., 1995), although children lack knowledge to identify specific odors by name. Koelega (1994) found that prepubescent children (58 nine-year-olds) were inferior in their detection of 4 of 5 odors compared to 15-year-olds (n = 58) and 20-year-olds (n = 112). Schmidt and Beauchamp (1988) have even tested 3-year-olds (n = 16) for sensitivity to noxious chemicals, such as butyric acid and pyridine.

In March-April 1983, 949 cases (including 727 in adolescent females) of acute non-fatal illness consisting of headache, dizziness, blurred vision, abdominal pain, myalgia, and fainting occurred at schools on the West Bank. However, physical examinations and biochemical tests were normal. There was no common exposure to food, drink, or agricultural chemicals among those affected. No toxins were consistently present in patients' blood or urine. The only environmental toxicant detected was H_2S gas in low concentrations (40 ppb) in a schoolroom at

the site of the first outbreak (from a faulty latrine in the schoolyard). The illness was deemed to be psychogenic and possibly triggered by the smell of H_2S (Landrigan and Miller , 1983; Modan *et al*., 1983).

D.1.3. Development. Xu *et al*. (1998) conducted a retrospective epidemiological study in a large petrochemical complex in Beijing, China in order to assess the possible association between petrochemical exposure and spontaneous abortion. The facility consisted of 17 major production plants divided into separate workshops, which allowed for the assessment of exposure to specific chemicals. Married women (n = 2,853), who were 20-44 years of age, had never smoked, and who reported at least one pregnancy during employment at the plant, participated in the study. According to their employment record, about 57% of these workers reported occupational exposure to petrochemicals during the first trimester of their pregnancy. There was a significantly increased risk of spontaneous abortion for women working in all of the production plants with frequent exposure to petrochemicals compared with those working in non-chemical plants. Also, when a comparison was made between exposed and non-exposed groups within each plant, exposure to petrochemicals was consistently associated with an increased risk of spontaneous abortion (overall odds ratio (OR) = 2.7 (95% confidence interval (CI) = 1.8 to 3.9) after adjusting for potential confounding factors). Using exposure information obtained from interview responses for (self-reported) exposures, the estimated OR for spontaneous abortions was 2.9 (95% CI = 2.0 to 4.0). When the analysis was repeated by excluding 452 women who provided inconsistent reports between recalled exposure and work history, a comparable risk of spontaneous abortion (OR 2.9; 95% CI = 2.0 to 4.4) was found. In analyses for exposure to specific chemicals, an increased risk of spontaneous abortion was found with exposure to most chemicals. There were 106 women (3.7% of the study population) exposed only to hydrogen sulfide; the results for H_2S (OR 2.3; 95% CI = 1.2 to 4.4) were statistically significant. Unfortunately H_2S exposure concentrations were not reported.

D.2. Effects of Animal Exposure

D.2.1. Adult/mature animals. A median lethal concentration (LC_{50}) in rats exposed to H_2S for 4 hours was estimated as 440 ppm (616 mg/m³) (Tansy *et al*., 1981). An inhalation LC_{Lo} of 444 ppm for an unspecified duration is reported in rats, and a lethal concentration of 673 ppm (942 mg/m³) for 1 hour is reported in mice (RTECS, 1994). In another study, mortality was significantly higher for male rats (30%), compared to females (20%), over a range of exposure times and concentrations (Prior *et al*., 1988). A concentration of 1,000 ppm (1,400 mg/m³) caused respiratory arrest and death in dogs after 15-20 minutes (Haggard and Henderson, 1922). Inhalation of 100 ppm (140 mg/m³) for 2 hours resulted in altered leucine incorporation into brain proteins in mice (Elovaara *et al*., 1978). Kosmider *et al*. (1967) reported abnormal electrocardiograms in rabbits exposed to 100 mg/m³ (71 ppm) H_2S for 1.5 hours.

Khan *et al*. (1990) exposed groups of 12 male Fischer 344 rats to 0, 10, 50, 200, 400, or 500-700 ppm hydrogen sulfide for 4 hours. Four rats from each group were euthanized at 1, 24, or 48 hours post-exposure. The activity of cytochrome c oxidase in lung mitochondria, a primary molecular target of H_2S, was significantly ($p<0.05$) decreased at 50 ppm (15%), 200 ppm (43%), and 400 ppm (68%) at 1-hour post-exposure compared to controls. A NOAEL of 10 ppm for inhibition of cytochrome c oxidase was identified in this study.

Fischer and Sprague-Dawley rats (15 per group) were exposed to 0, 10.1, 30.5, or 80 ppm (0, 14.1, 42.7, or 112 mg/m^3, respectively) H_2S for 6 hours/day, 5 days/week for 90 days (CIIT, 1983a,b). Measurements of neurological and hematological function revealed no abnormalities due to H_2S exposure. Histological examination of the nasal turbinates also revealed no significant exposure-related changes. A significant decrease in body weight was observed in both strains of rats exposed to 80 ppm (112 mg/m^3).

In a companion study, the CIIT conducted a 90-day inhalation study in mice (10 or 12 mice per group) exposed to 0, 10.1, 30.5, or 80 ppm (0, 14.1, 42.7, or 112 mg/m^3, respectively) H_2S for 6 hours/day, 5 days/week (CIIT, 1983c). Neurological function was measured by tests

for posture, gait, facial muscle tone, and reflexes. Ophthalmologic and hematologic examinations were also performed, and a detailed necropsy was included at the end of the experiment. The only exposure-related histological lesion was inflammation of the nasal mucosa of the anterior segment of the noses of mice exposed to 80 ppm (112 mg/m^3) H_2S. Weight loss was also observed in the mice exposed to 80 ppm. Neurological and hematological tests revealed no abnormalities. The 30.5 ppm (42.5 mg/m^3) level was considered to be a NOAEL for histological changes in the nasal mucosa. (Different adjustments were made to this NOAEL by U. S. EPA to calculate the RfC of 1 μg/m^3 and by OEHHA to calculate the chronic REL of 10 μg/m^3 (8 ppb).)

Hydrogen sulfide (0, 10, 30, or 80 ppm) was administered via inhalation (6 h/d, 7 d/wk) to 10-week-old male CD rats (n = 12/group) for 10 weeks (Brenneman *et al*., 2000). Histological evaluation revealed that rats exposed to 30 or 80 ppm had significant increases in lesions of the olfactory mucosa but not other tissues. Multifocal, rostrocaudally-distributed olfactory neuron loss and basal cell hyperplasia were seen. The dorsal medial meatus and the dorsal and medial portions of the ethmoid recess were affected. The lowest dose (10 ppm) was considered a no observed adverse effect level for olfactory lesions.

Fischer F344 rats inhaled 0, 1, 10, or 100 ppm hydrogen sulfide for 8 hours/day for 5 weeks (Hulbert *et al*, 1989). No effects were noted on baseline measurements of airway resistance, dynamic compliance, tidal volume, minute volume, or heart rate. Two findings were noted more frequently in exposed rats: (1) proliferation of ciliated cells in the tracheal and bronchiolar epithelium, and (2) lymphocyte infiltration of the bronchial submucosa. Some exposed animals responded similarly to controls to aerosol methacholine challenge, whereas a subgroup of exposed rats were hyperreactive to concentrations as low as 1 ppm H_2S.

Male rats were exposed to 0, 10, 200, or 400 ppm H_2S for 4 hours (Lopez *et al.*, 1987). Samples of bronchoalveolar and nasal lavage fluid contained increased inflammatory cells,

protein, and lactate dehydrogenase in rats treated with 400 ppm. Later Lopez and associates (1988) showed that exposure to 83 ppm (116 mg/m^3) for 4 hours resulted in mild perivascular edema.

D.2.2. Developing animals. Saillenfait *et al.* (1989) investigated the developmental toxicity of H_2S in rats. Rats were exposed 6 hours/day on days 6 through 20 of gestation to 100 ppm hydrogen sulfide. No maternal toxicity or developmental defects were observed.

Hayden *et al*. (1990) exposed gravid Sprague-Dawley rat dams continuously to 0, 20, 50, and 75 ppm H_2S from day 6 of gestation until day 21 postpartum. The animals demonstrated normal reproductive parameters until parturition, when delivery time was extended in a dose-dependent manner (with a maximum increase of 42% at 75 ppm). Pups exposed in utero and neonatally to day 21 postpartum developed with a subtle decrease in time of ear detachment and hair development, but with no other observed change in growth and development through day 21 postpartum.

Hannah and Roth (1991) analyzed the dendritic fields of developing Purkinje cells in rat cerebellum to determine the effects of chronic exposure to low concentrations of H_2S during perinatal development. Treatment of timed-pregnant female Sprague Dawley rats with 20 and 50 ppm H_2S for 7 hours per day from day 5 after mating until day 21 after birth produced severe alterations in the architecture and growth characteristics of the dendritic fields of the Purkinje cells. The architectural modifications included longer branches, an increase in the vertex path length, and variations in the number of branches in particular areas of the dendritic field. The treated cells also exhibited a nonsymmetrical growth pattern at a time when random terminal branching is normally occurring. Thus, developing neurons exposed to H_2S may be at risk of severe deficits. However, the lower level of 20 ppm for 7 hours is nearly 2 orders of magnitude above the present one-hour standard.

Dorman *et al*. (2000) examined the effect of perinatal exposure of H_2S on pregnancy outcomes, offspring development, and offspring behavior in rats. Male and female Sprague-

Dawley rats (12 rats/sex/concentration) were exposed to 0, 10, 30, or 80 ppm H_2S 6 h/day, 7 days/week for 2 weeks prior to breeding. Exposures continued during a 2-week mating period and then from Gestation Day (GD) 0 through GD 19. Exposure of rat dams and their pups (eight rats/litter after culling) resumed between postnatal day (PND) 5 and 18. Adult males were exposed for 70 consecutive days. Offspring were evaluated using motor activity (assessed on PND 13, 17, 21, and 60±2), passive avoidance (PND 22±1 and 62±3), functional observation battery (FOB) (PND 60±2), acoustic startle response (PND 21 and 62±3), and neuropathology (PND 23±2 and 61±2). No deaths occurred and no adverse physical signs were seen in F_0 males or females. There were no statistically significant effects on the reproductive performance of the F_0 rats as assessed by the number of females with live pups, litter size, average length of gestation, and the average number of implants per pregnant female. Exposure to H_2S did not affect pup growth, development, or performance on any behavioral test. The authors conclude that H_2S is neither a reproductive toxicant nor a behavioral developmental neurotoxicant in the rat at occupationally relevant exposure concentrations (i.e., at 10 ppm, the current occupational daily average exposure limits - TLV and PEL; however, the ACGIH is considering lowering the TLV to 5 ppm). The lowest level tested (10 ppm) is more than 300-fold higher than the CAAQS of 0.030 ppm.

E. Interactions between hydrogen sulfide and other pollutants

Ethanol can potentiate the effects of H_2S by shortening the mean time-to-unconsciousness in mice exposed to 800 ppm (1,120 mg/m³) H_2S (Beck *et al*., 1979).

Endogenous hydrogen sulfide may regulate smooth muscle tone in synergy with nitric oxide (Hosoki *et al*., 1997).

Hydrogen sulfide is often accompanied by other malodorous sulfur compounds, such as methyl mercaptan, dimethyl sulfide, and dimethyl disulfide. Some of these have odor thresholds

lower than that of hydrogen sulfide. The complex mixture is often referred to as TRS (total reduced sulfur).

Lindvall (1977) reported that the perceived odor strength of H_2S is increased by the simultaneous presence of 600 ppb nitric oxide (600 ppb nitric acid is imperceptible by itself).

F. Conclusions

The current standard of 0.03 ppm (30 ppb) hydrogen sulfide for one hour based on odor is well below NOAEL levels from animal experiments where exposure lasted weeks to months, including the period of intrauterine development. However, it is greater than OEHHA's chronic Reference Exposure Level (REL) of 8 ppb, which is based on histological changes in the nasal area of mice. (The chronic REL is compared to the annual average H_2S concentration.) Ideally neither of these two benchmark levels should be exceeded by the properly averaged concentration.

Additional research might help reduce uncertainties regarding the impacts of hydrogen sulfide on the health of infants and children. This would include:

a. Odor testing of hydrogen sulfide in adolescents or younger children, if ethically permissible, to determine their odor threshold. Current data on odor detection in children are not consistent. Data on H_2S odor detection in children under controlled exposure are lacking.

b. The identification of children hypersensitive to the odor of hydrogen sulfide. While the odor from very low level H_2S would not itself threaten their physical health, the odor might be alarming to hypersensitive children. Psychosomatic complaints might be more confusing to children than to adults.

c. Physiologic testing of anosmic (either specifically anosmic to H_2S or totally anosmic) children at the CAAQS would be useful in determining whether if adverse physiological symptoms occur in the absence of odor detection.

d. Testing of the odor threshold for H_2S using the most current methodology among groups of healthy persons of both sexes in different age ranges. Data from such testing would likely be an improvement over the use of either the mean of 16 people (California Department of Public Health, 1969) or the mean from 26 studies, conducted over a period of 130 years, which found thresholds spanning a 20,000 fold range, from 0.07 ppb to 1400 ppb (Amoore, 1985). (If the highest and lowest values of the range in Amoore (1985) are dropped as outliers - Amoore (1985) stated that these two studies seemed to involve only one subject - the range would be 0.43 ppb to 190 ppb, a 440-fold range).

e. Further research is needed on the topic of when odor is an adverse health effect and how much consideration should be given to psychosomatic complaints accompanying odor annoyance (Dalton *et al*., 1997; ATS, 2000). A recent American Thoracic Society position paper titled “What Constitutes an Adverse Health Effect of Air Pollution?” (ATS, 2000) indicates that air pollution exposures, which interfere with the quality of life, can be considered adverse. This suggests that, for the purpose of setting a standard, odor-related annoyance should be considered adverse, even if nausea or headache or other symptoms are not present.

G. References

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