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ADDENDUM for HYDROGEN SULFIDE
Supplement to the 2006 Toxicological Profile for HYDROGEN SULFIDE

Background Statement

This addendum to the [Toxicological Profile for Hydrogen Sulfide](#) supplements the profile that was released in 2006.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised “no less often than once every three years.” CERCLA further states that the Administrator will “establish and maintain inventory of literature, research, and studies on the health effects of toxic substances” [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 2006.

Chapter numbers in this addendum coincide with the [Toxicological Profile for Hydrogen Sulfide \(2006\)](#). This document should be used in conjunction with the profile. It does not replace it.

2. RELEVANCE TO PUBLIC HEALTH

2.3 MINIMAL RISK LEVELS

Intermediate Inhalation MRL

An intermediate-duration inhalation MRL of 0.02 ppm for hydrogen sulfide was derived in ATSDR's 2006 *Toxicological Profile for Hydrogen Sulfide* (ATSDR 2006). This MRL was derived from a NOAEL of 10 ppm for olfactory neuron loss and basal cell hyperplasia in the nasal olfactory epithelium in rats following inhalation exposure to hydrogen sulfide 6 hours/day for 10 weeks (Brenneman et al. 2000).

The MRL derivation was based on the human equivalent NOAEL (NOAEL_{HEC}) of 0.46 ppm, calculated by dosimetric adjustment according to U.S. EPA methodology (1994b) for category 1 gases; the dosimetric model takes into account species differences in the surface area of the upper respiratory tract and inhalation rates. However, the model does not take into consideration differences in air flow patterns or the fact that, compared to humans, a larger portion of the rat nasal cavity is lined with olfactory epithelium (50% in rats compared to 10% in humans). A computational fluid dynamics (CFD) model of the rat nasal epithelium developed for hydrogen sulfide (Moulin et al. 2002) found a strong correlation between the amount of hydrogen sulfide reaching the olfactory tissue and the severity of the lesions. Thus, uncertainty remains regarding whether the dosimetric adjustment used to calculate the MRL overestimates or underestimates human risk.

Subsequently, to predict quantitatively localized hydrogen sulfide nasal tissue dose in rats and humans, Schroeter et al. incorporated tissue reaction kinetics into nasal CFD models of rat and human nasal passages (Schroeter et al. 2006a; Schroeter et al. 2006b). Assuming that equivalent hydrogen sulfide flux values will induce similar responses in the olfactory region of rats and humans, a NOAEL_{HEC} was estimated at 5 ppm (Schroeter et al. 2006b). But here again, uncertainty remains, this time regarding the 5 ppm-NOAEL_{HEC}. Fiedler et al. (2008) reported increased anxiety symptoms in young, healthy persons exposed at 5 ppm for 2 hour sessions in three consecutive weeks. Fiedler and colleagues also reported a 0.05 ppm threshold for declined verbal-learning task performance.

In view of these uncertainties, we currently propose no change to the 0.02 ppm intermediate inhalation MRL for hydrogen sulfide.

3. HEALTH EFFECTS

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

3.2.1 Inhalation Exposure

3.2.1.2 Systemic Effects

Respiratory Effects

Community residents living near industrial hog operations in eastern North Carolina exhibited acute physical symptoms related to air pollutants comprised mostly of hydrogen sulfide and lower levels of other atmospheric sulfides and amines. Odor and hydrogen sulfide were associated with respiratory symptoms and with eye irritation; PM_{2.5} was associated with wheezing, breathing difficulty, burning eyes, and nasal irritation; endotoxin was associated with increased sore throat, chest tightness, and nausea (Schinasi et al. 2011).

Heaney et al. (2011) studied residents in a community bordering a landfill. Heaney and colleagues found a strong association of odor with average hourly hydrogen sulfide concentrations, and found that the odor was strongly associated with mucosal irritation and upper respiratory symptoms.

Hydrogen sulfide in ambient air from geothermal sources has been associated with the need for anti-asthma drugs in Reykjavik, Iceland's adult population, indicating poor respiratory health (Carlsen et al. 2012). A positive association with particulate pollution (PM₁₀) levels related to traffic and naturally occurring sandstorms was also reported. The 3-day moving average of hydrogen sulfide and PM₁₀ levels was positively associated with the number of persons who were dispensed drugs at 35 days lag, corresponding to a 2.0% (95% CI 0.4,3.6) and 0.9% (95% CI 0.1, 1.8) per 10 µg/m³ pollutant concentration increase, respectively.

3.2.1.4 Neurological Effects

When 74 young, healthy, educated adults were exposed to hydrogen sulfide for 2 hours at 0.05, 0.5 and 5 ppm at random order over three consecutive weeks, they reported increased anxiety and compromised verbal learning performance (Fiedler et al. 2008). Increased anxiety was related to irritation due to odor, and during exposures to 5 ppm, anxiety symptoms increased. With a threshold effect level of 0.05 ppm, Fiedler and colleagues also observed declined verbal learning, probably due to fatigue or attention lapses during exposure.

Malodor, hydrogen sulfide, and semivolatile PM₁₀ were related to stress and negative mood in communities near industrial hog operations in eastern North Carolina (Horton 2009). Stress or

annoyance was associated with increasing levels of hydrogen sulfide. Hydrogen sulfide was also associated with nervous or anxious feelings.

A study of residents in a community bordering a landfill reported strong association of odor with average hourly hydrogen sulfide concentrations; the odor was strongly associated with alteration of daily activities and negative mood states (Heaney et al. 2011).

Environmental exposure to hydrogen sulfide from living near one or multiple sources (sour gas/oil fields) for years impaired neurobehavioral function, disturbed moods and increased frequencies of irritation, indigestion, respiration, moods, sleep, balance, memory and limbic system symptoms (Kilburn et al. 2010).

Air monitoring of communities in swine production areas reported essentially the same average hydrogen sulfide concentrations in exposed communities (1.1 – 1.6 ppb) and non-exposed communities (1.1-1.5 ppb). The average ammonia concentrations in the exposed communities were 8.9 – 18.3 ppb compared with 6.9 – 12.6 ppb in non-exposed communities. The median log of the odor intensity value in the exposed communities (2.07) was twice the non-exposed communities (1.11). Community members who detected odors also reported symptoms such as headaches, runny nose, cough, and vomiting (Godbout et al. 2009).

3.3 GENOTOXICITY

At concentrations (250 – 2000 μM) – similar to concentrations found in the large intestine - hydrogen sulfide is genotoxic in human intestinal cells. Attene-Ramos et al. (2010) observed an increase in peroxide synthase COX-2 gene expression in hydrogen sulfide nontransformed human intestinal epithelial cells (FHs 74 Int cells) at both 30 minutes and 4 hours. Hydrogen sulfide also affected cellular homeostasis in the colonic mucosa and triggered both inflammatory and DNA repair responses.

Hydrogen sulfide caused DNA damage to nuclei from Chinese hamster ovary cells treated with Na_2S at concentrations as low as 1 $\mu\text{M}/\text{L}$ (Attene-Ramos et al. 2007). This genotoxicity is suggested to be associated with free radicals. Roberts et al. (2008) exposed 10-week old male Sprague-Dawley rats to 200 ppm hydrogen sulfide for 3 hours per day for 1 day or 5 days. Twenty-four hours after exposure, expression of genes associated with cell proliferation, cell cycle control, cytoskeleton organization and biogenesis was altered in those nasal respiratory epithelial cells. However, gene expression of cytochrome oxidase did not change following similar H_2S exposure.

H_2S activated a stress response and proinflammatory genes in lung and liver tissues of mice exposed to hydrogen sulfide (~5 ppm) containing atmosphere of sulfur baths for 8 hours (Stuhlmeier et al. 2012).

3.4 TOXICOKINETICS

3.4.3 Metabolism

3.4.3.1 Inhalation Exposure

Stein et al. (2012) found that breathing 80 ppm hydrogen sulfide in 10.5% O₂ for 6 hours induced hypometabolism in rats. Although this hydrogen sulfide-mediated hypometabolic state could have potential therapeutic applications, under these conditions the hydrogen sulfide caused tissue injury to the lung and heart.

3.7 CHILDREN'S SUSCEPTIBILITY

Although a fair amount of data are available on hydrogen sulfide toxicity in humans, very little data are available to judge the effects of hydrogen sulfide exposure in infants and children. Animal data suggest that following hydrogen sulfide exposure via inhalation, the respiratory tract - particularly the nasal olfactory epithelium - could be the most sensitive target. Preliminary results using nasal computational fluid dynamics (CFD) modeling suggest that differences in nasal anatomy and ventilation among adults and children do not significantly affect the hydrogen sulfide tissue dose in the olfactory region (Schroeter et al. 2010).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

3.8.2 Biomarkers Used to Characterize Effects Caused by Hydrogen Sulfide

Hydrogen sulfide poisoning also caused discoloration of the skin and brain (Milroy and Parai 2011).

4. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

No updated data.

6. POTENTIAL FOR HUMAN EXPOSURE

6.2 RELEASES TO THE ENVIRONMENT

Effective with the 2012 TRI reporting year, EPA reinstated hydrogen sulfide Toxics Release Inventory (TRI) reporting requirements. The first reports for the 2012 TRI reporting year are due from facilities by July 1, 2013 (EPA 2011).

6.2.1 Air

Air monitoring of communities in swine production areas (151 Animal Units of pig/Km²) reported ranges of average hydrogen sulfide concentration of 1.1 – 1.6 ppb, compared to 1.1 – 1.5 ppb in non-exposed communities; the difference in range of hydrogen sulfide concentrations between the two types of communities was not significant (Godbout et al. 2009).

Additionally, the cobalt sulfide manufacturing process releases hydrogen sulfide (Gangopadhyay and Das 2007), as do hydraulic fracturing (“fracking”) sites for natural gas production (Weinhold 2012).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

The U.S. Consumer Product Safety Commission conducted an emission and corrosion study of 51 homes. Indoor air concentrations of hydrogen sulfide was significantly higher in homes reporting drywall related complaints with a mean concentration of 0.66 ppb (0.19 – 2.23 ppb) compared with a mean concentration of 0.45 ppb (0.2 – 2.23 ppb) in non-complaint homes (CPSC 2010).

6.4.4 Other Environmental Media

The body produces small amounts of hydrogen sulfide endogenously. Enzymes cystathionine β -synthase (CBS) and cystathionine γ -lyase (CSE) can produce hydrogen sulfide directly, and 3-mercaptopyruvate sulfur transferase (3MST) can produce hydrogen sulfide indirectly. The liver, the kidney and many other tissues express CBS and CSE. CBS and 3MST are located primarily in the brain (Shibuya et al. 2009). Endogenous hydrogen sulfide may function as a signal molecule with many physiologic processes. Hydrogen sulfide in the cardiovascular system helps to control blood pressure (Wang 2010; Yang et al. 2008). H₂S relaxes vascular smooth muscle by opening ATP-dependent K⁺ channels (Zhao et al. 2001). In the brain, free hydrogen sulfide is maintained at low levels (<9.2 μ M) in the basal condition, and some of the H₂S produced may be stored as bound sulfur which releases H₂S when cells receive an appropriate signal (Ishigami et al. 2009). Endogenous hydrogen sulfide protects neurons from oxidative stress by enhancing

glutathione production (Kimura 2010). In the intestine hydrogen sulfide is important in the regulation of intestinal motility and ion secretion. In the upper and lower gastrointestinal tract hydrogen sulfide protects tissue from damage induced by non-steroidal anti-inflammatory drugs and ischemia/reperfusion (Cipiriani and Mencarelli 2011). In the liver, hydrogen sulfide regulates hepatic arterial buffer capacity (Siebert et al. 2008) and portal flow (Fiorucci et al. 2005).

7. ANALYTICAL METHODS

No updated data.

8. REGULATIONS AND ADVISORIES

Table 8-1 Regulations and Guidelines Applicable to Hydrogen Sulfide

Agency	Description	Information	Reference
<u>NATIONAL</u>			
Regulations and Guidelines:			
Air			
ACGIH	TLV (8-hour TWA)	1 ppm	ACGIH 2010
STEL		5 ppm	
NHSRC	PAL 1 ^a 24 hours	1.2 ppm	Marshall et al 2009
	PAL 1 30 days	0.85 ppm	
	PAL 1 90 days	0.85 ppm	
	PAL 2 ^b 24 hours	7 ppm	
	PAL 2 30 days	3 ppm	
	PAL 2 90 days	3 ppm	
	PAL 3 ^c 24 hours	27 ppm	

Provisional Advisory Levels (PALs): Developed by National Homeland Security Research Center (NHSRC). PALs are tiered temporary values that will be neither promulgated, nor formally issued as regulatory guidance. Their intended use is at the discretion of risk managers in emergency situations (Adeshina et al. 2009).

a. PAL 1: The assumed continuous exposure concentration of a chemical in air or drinking water above which changes from baseline of specific biomarkers or physiological responses could have adverse health effects in the general population. Adverse health effects are not expected when concentrations are at or below PAL 1.

b. PAL2: The assumed continuous exposure concentration of a chemical in air or drinking water above which serious, irreversible, or escape-impairing effects could result.

c. PAL 3: The assumed continuous exposure concentration of a chemical in air or drinking water above which lethality in the general population, including all ages and sensitive subpopulations, could occur.

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