December 8, 2017

Dr. Garrett Keating, Staff Toxicologist
Division of Occupational Safety and Health
1515 Clay Street, Suite 1901
Oakland, CA 94612

Re: DOSH Documentation for Hydrogen Sulfide (H_2S)

Dear Dr. Keating:

The above-named organizations (collectively named the Coalition) represent businesses with employees that have potential exposure to H_2S. We are greatly concerned about the proposal to reduce the H_2S Permissible Exposure Limit ("PEL") from 10 ppm to 1 ppm (an 8-hour time-weighted-average intended to prevent material health impairment caused by chronic exposure). Some of the working environments of these industries have background levels possibly exceeding 1 ppm. A PEL lowered to that extreme must protect against a real threat based on sound science. The proposed PEL of 1 ppm does not meet this test.

As you know, H_2S is a byproduct in the natural degradation of organic matter. As such, exposures to H_2S have been common and unavoidable throughout history. For the coalition members, H_2S is not an ingredient or process chemical purchased for use. The widely recognized concerns are paralysis of the central nervous system (CNS) leading to loss of breathing resulting from concentrations of H_2S above 100 ppm as well as eye

damage occurring in the 50 to 100 ppm range from relatively high short-term exposures. Consequently, CNS and eye damage outcomes are addressed in California by a Ceiling Limit of 50 ppm. The irritation endpoint is addressed by a Short Term Exposure Limit ("STEL") of 15 ppm. The health endpoints noted in the DOSH documentation (discernible fatigue and discomfort) and assumed to justify lowering the PEL are not specifically observed in our industries, despite the fact such health effects would be evident on a daily basis should they exist. These endpoints are denoted by changes in the following: oxygen uptake, blood lactate, muscle lactate, lactate dehydrogenase, cytochrome oxidase, and citrate synthase. Note that in the relevant studies, there was an occasional increase or decrease in these endpoints. However, the majority of comparisons were not statistically significant. The DOSH H_2S documentation states, "Extended to 8 hours, these changes could result in discernible fatigue and discomfort…" This statement is linked to the working hypothesis for the toxic mode of action (MOA) of H_2S is the impairment of mitochondrial respiration by inhibition of cytochrome oxidase, thereby reducing energy production. However, it is clear in this set of studies and is stated in the documentation that "the putative enzyme associated with H_2S toxicity, was **not** significantly different between exposed men and women and controls." This lack of association and the fact that the subjects were not subject to a decrease in power output during exposure results in a conclusion that reducing the PEL to 1 ppm is not substantiated and does not meet the hurdle of material impairment.

The proposal to decrease the H_2S PEL from 10 ppm to 1 ppm is based largely on the studies of Bhambhani, Jappinen and Fiedler. DOSH has over interpreted the utility of these studies for generating an appropriate PEL. The available data in the scientific literature support maintaining the existing PEL. Importantly, the studies relied upon by DOSH do not meet the threshold of material impairment of health or functional capacity, as required by Labor Code Section 144.6:

> "In promulgating standards dealing with toxic materials or harmful physical agents, the board shall adopt that standard which most adequately assures, to the extent feasible, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to a hazard regulated by such standard for the period of his working life. Development of standards under this section shall be based upon research, demonstrations, experiments, and such other information as may be appropriate. In addition to the attainment of the highest degree of health and safety protection for the employee, other considerations shall be the latest available scientific data in the field, the reasonableness of the standards, and experience gained under this and other health and safety laws. Whenever practicable, the standard promulgated shall be expressed in terms of objective criteria and of the performance desired."

The Science Supports the Existing PEL of 10 ppm

The PEL rationale drafted by DOSH for the Health Experts Advisory Committee ("HEAC") relies on human studies rather than animal studies in determining the PEL. We agree with this preference and note it is consistent with past work by DOSH and the HEAC. In that vein, the body of our comments on the science are focused on the relevant human studies. As a footnote, we believe that the animal studies also support the existing PEL of 10 ppm[1].

There are many human studies in the literature that either point to or support the existing PEL of 10 ppm. They show that the most sensitive endpoint that may be considered a "material impairment" from chronic exposure is eye irritation. The effect is manifested at concentrations greater than 10 ppm. Of course, there is a continuum of this effect with mild irritation appearing around 10 ppm while eye damage are noted by several investigators to occur at 50 ppm and above. A short summary of these studies is presented below.

Barthelmey (1939) – Typical concentrations of 9 to18 ppm H_2S were not associated with eye complaints

Bhambhani et al. (1991, 1994, 1996, 1996, and 1997): Studies with exercising healthy volunteers have shown that inhalation at a concentration of 10 ppm resulted in no effects in men or women on FVC, FEV_1, peak expiratory flow rate, forced expiratory flow rate, or maximal ventilation volume

Jappinen (1990) – In pulp mill workers, no change in FVC, FEV_1, and FEF at a mean concentration of 4.5 ppm, range 1-11 ppm

Nesswetha (1969) – The first symptoms of eye irritation after 6-7 h of exposure to 11 ppm H_2S and "eye diseases" (likely increasing irritation) developed after 4-5 h at 14 ppm. On the basis of the data, the NRC, 2009, noted that it is unlikely that eye irritation worsens with time

Vanhoorne (1990) – NOEL >5ppm H_2S; >90 ppm carbonyl sulfide for eye complaints in rayon workers

The National Academy of Sciences (2008) has reviewed these data on H_2S and states in their review of Bhambhani et al., 1991, 1994, 1996, 1997, and Fiedler et al, 2008 that the results of those studies do <u>not</u> indicate changes in healthy adults that signal the

[1] With regard to animal studies, we believe that studies showing nasal lesions in rodents at high concentrations show a lack of relevance at the lower concentrations that are important in generating a PEL. In contrast, maintaining the PEL at 10 ppm is further supported by studies at CIIT where rats and mice exposed to 10.1 and 30.5 ppm, 6 hours per day, 5 days per week for 90 days did not show ocular toxicity (1983).)1

initiation of a toxic response to H_2S at exposures up to 10 ppm. In this regard, toxic response and material impairment have similar attributes. “The magnitude of the few exposure-related changes that were observed, the sporadic occurrence of the changes, and the lack of a functional change in the cardiorespiratory system are not consistent with a conclusion that the effects constituted a toxic response.” With regard to Bhambhani, Table 1 provides a summary of the four studies that provide information on metabolic endpoints. While any one study may provide information on a statistically significant biomarker of exposure, when using a weight of the evidence evaluation we find that these studies provide little information on data consistency or dose response that would indicate material impairment (Table 1).

Table 1: Summary of Bhambhani, 1997, 1994, 1996, and 1991 reporting metabolic changes as reported in Bhambhani (1999)

	BIOCHEMICAL MARKERS SHOWING METABOLIC CHANGES (NOT MATERIAL HEALTH EFFECTS)					
3 Studies	$V0_2$	La	MLa	LDH	CyOx	CS
1997 10 ppm 15 Men 13 Women	↓	↑	↔	↔	↔	↔
1994, 1996 5 ppm 13 Men 12 Women	↔	↔	↔	↔	↔	↓ Men
1991 5 ppm 16 Men	↑	↑				

VO_2 = oxygen uptake
La = blood lactate
MLa = muscle lactate
LDH = lactate dehydrogenase
Cy0x = cytochrome oxidase
CS = citrate synthase

↔Indicates no statistically significant change

<u>The Scientific Literature Must Uphold the Proposed Mode of Action</u>

The DOSH documentation for H_2S notes that the toxic mode of action is considered to be the impairment of mitochondrial respiration by inhibition of cytochrome oxidase, thereby reducing energy production. However, neither inhibition of cytochrome oxidase nor the reduction of energy production have been observed in the Bhambhani studies with

any statistical relevance. Bhambhani (1991) notes that on the basis of the biological mode of action of H_2S that has been reported, it was hypothesized that inhalation of sufficient quantities would result in a significant increase in the blood lactate concentration at a given work rate, which would result in a reduction in the physical work capacity. While Bhambhani reports a significant increase in blood lactate concentrations (at least in some cases) he stated that "this could not be considered to be indicative of an increase in intramuscular lactate production." In addition he states that the results do not support the link between blood lactate accumulation and muscular fatigue. In the documentation, this admission is clearly noted in the statement, "Multiple measures of markers of energy metabolism determined by enzymatic activity of the muscle tissues obtained during exposure/exercise were mostly not significant." Finally, it is notable that the documentation states that "cytochrome oxidase activity, the putative enzyme associated with H_2S toxicity, was not significantly different between exposed men and women and controls."

The NAS review committee clearly embraced this important question on mode of action and stated that the results suggested that anaerobic metabolism is increased by the presence of the sulfide, but whether that is due to inhibition of cytochrome oxidase cannot be determined from the results. The fact that the critical enzyme in this mode of action is not statistically inhibited matched with no effect on power output challenge the assumption that this mode of action is operating at these low concentrations. Maintaining that blood lactate levels could somehow be associated with discernible fatigue without additional supporting data is speculative.

Regarding Fiedler, human volunteers were exposed to H_2S and evaluated for several endpoints including anxiety level, performance in sensory and cognitive tests, odor ratings, general symptoms, and environmental quality ratings. Both odor ratings and anxiety level increased with dose, with anxiety symptom severity being significantly different at 5 ppm only. However, as the authors note, the overall magnitude in increased anxiety symptom severity was 2 points on a scale of 100. All other neurological endpoints evaluated in this study were unaffected by exposure.

Also, the anxiety measurements were likely due to the odor of H_2S gas and not to irritation as was noted in the DOSH statement. Many studies that have attempted to maintain a separation of outcomes related to olfaction (first cranial nerve) and irritation (fifth cranial nerve) have failed unless an adequate experimental design was incorporated to overcome the confounding nature of olfaction. Generally, this employs using either nose clips and mouth-only breathing or an odorant gas such as phenyl ethyl alcohol that because it does not produce sensory irritation is used as a negative control. Also, these type of studies have reported a false positive rate of up to 30% of subjects exposed simply to filtered air (Golden, 2011). Based on these findings, Fiedler et al. (2008) concluded that the increase in anxiety symptom severity, "cannot be regarded as clinically significant."

Therefore, this study does not demonstrate an adverse effect on the central nervous system, and as such should not be used in deriving an occupational exposure limit for H_2S.

Jappinen et al. (1990) was not sufficiently conducted to conclude "serious respiratory effects"

DOSH also finds support for a lower PEL in a Jappinen study that showed changes in airway resistance (Raw) and specific airway resistance (sRaw) that were greater than 30% in two of ten individuals with asthma following exposure to H_2S at 2 ppm for 30 minutes. However, use of this study in support of the proposed PEL is unwarranted for two reasons: significant methodological limitations of the study and considerable uncertainties in the clinical relevance of the parameters measured (*i.e*., Raw and sRaw).

The most critical methodological limitation of is that the authors did not include an appropriate control (a filtered air exposure for comparison) in the study. Modern controlled human exposure studies generally use a randomized, crossover design with filtered air exposure as the control, which allows a direct estimation of effects from the exposure of interest while controlling for independent effects from the experimental procedures (Utell and Frampton, 2000; National Academies of Sciences, Engineering, and Medicine, 2017). Without comparing to effects after exposure to filtered air, it is difficult, at best, to determine whether the observed changes in Raw and sRaw in the two individuals were due to the exposure of H_2S or to artifacts from the testing procedure that were not related to the H_2S exposure. For example, the study participants should have avoided certain activities, such as smoking, consuming alcohol, performing vigorous exercise, eating a large meal, and wearing tight-fitting clothing, immediately before participating the study (Miller *et al*., 2005). If any of the volunteers in this study had engaged in any of the above activities, the observed responses following their exposures to H_2S could have been compromised. Despite the critical importance of these details, the Jappinen *et al.* (1990) study did not report on the preparation of study participants. Also, Jappinen did not provide details on the laboratory protocol, such as whether the study participants were exercising while being exposed to H_2S or were in a sedentary position, which could have impacted the observed effects following exposures.

Setting aside the methodological issues of Jappinen *et al*. (1990), there are considerable uncertainties regarding the clinical relevance of observed changes in Raw and sRaw (Robinson *et al*., 2015).

Jappinen indicated that two study participants had greater than 30% changes in Raw and sRaw, and that this suggests bronchial obstruction. However, the study did not compare numeric values of Raw and sRaw in these two subjects to the normative values for Raw and sRaw in adults (Goldman *et al*., 2005; Piatti *et al*., 2012). If the post-exposure values of Raw and sRaw in these two subjects were within the normal range, the observed changes should not be considered as an adverse effect.

Despite widespread use of these two measures for airway resistance in respiratory function laboratories, there are no formal standardization guidelines, and methodology varies greatly across laboratories with regard to commercial equipment, the reference equation to calculate the percentage predicted values, and testing protocols (Robinson *et al*., 2015).

There is also no consensus regarding the magnitude of changes in Raw and sRaw in pulmonary function testing that constitutes an indicator of airway responsiveness. In a joint statement by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), the use of a 40% increase in sRaw to define a positive response has been proposed for bronchial challenge tests in children (Beydon *et al*., 2007). Using this 40% cutoff, the changes in Raw and sRaw in the two study participants in Jappinen would not be considered as a positive response.

In comparison, a method of categorizing the severity of lung function impairment based on the FEV_1 predicted is provided in Table 2 (Pellegrino et al., 2005). It is similar to several previous documents prepared by the American Thoracic Society (1986, 1991) and the American Medical Association. The number of categories and the exact cut points are not considered bright lines.

Table 2: Severity of any spirometric abnormality based on the forced expiratory volume in one second (FEV_1)

Degree of severity	FEV_1 % predicted
Mild	70
Moderate	60-69
Moderately severe	50-59
Severe	35-49
Very severe	35

Finally, there is a lack of consistency in the Jappinen results. The DOSH summary notes that Jappinen found no significant changes in mean FVC, FEV_1, and FEF values after exposure to H_2S in subjects with asthma.

In conclusion, the studies that DOSH relies upon to lower the PEL for H_2S do not meet the definition of "material impairment." DOSH should reconsider the evidence for changing this legal benchmark. Please direct any correspondence on this matter to Dan Leacox at 916-832-5677 or dan@leacox.net.

Respectfully submitted,

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