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Via Electronic Mail

Ms. Esther Barajas-Ochoa
Associate Governmental Program Analyst
Office of Environmental Health Hazard Assessment
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Re: Comments on Notice of Proposed Rulemaking: Amendment to Section 25705 Specific Regulatory Levels Posing No Significant Risk (Antimony Oxide)

Dear Ms. Barajas-Ochoa:

Keller and Heckman is pleased to provide the following comments in response to the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) Notice of Proposed Rulemaking to amend Title 27, California Code of Regulations, Section 25705(b), Specific Regulatory Levels Posing No Significant Risk: Antimony Trioxide. We submit these comments on behalf of a multinational corporation that produces textiles that ultimately will be used by its customers for flame-retardant apparel and related applications.

In keeping with California's Safe Drinking Water and Toxic Enforcement Act of 1986 (otherwise known as Proposition 65[1]), OEHHA has proposed to adopt a No Significant Risk Level (NSRL) for antimony trioxide of 0.13 micrograms per day. While we recognize the need for a standard NSRL for antimony trioxide and acknowledge that the method utilized to develop the proposed NSRL is compliant with the regulatory requirements of the Act, our client is concerned that specific aspects related to the proposed derivation of the NSRL will inappropriately impact how the safe harbor level may be applied in practice. These concerns are detailed as follows.

[1] Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et seq.

I. Implied Specificity of the Derived NSRL

Antimony trioxide is recognized as a suspected carcinogen by the inhalation route only. Early occupational monitoring showed workers in the industry had higher rates of pulmonary cancers compared to control populations.[2] Cancers related to other routes of exposure such as dermal or incidental ingestion have not been associated with occupational exposure to antimony trioxide.[3]

In their 2017 study, the National Toxicology Program (NTP) concluded that "[t]here was clear evidence of carcinogenic activity in female B6C3F1/N mice based on increases in the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma of the lung and on increased incidences of malignant lymphoma" as the result of inhalation of particulate antimony trioxide.[4] It was the combined deep pulmonary cancer rate that was used in OEHHA's Initial Statement of Reasons to develop the NSRL for the compound.[5] As a result, our client respectfully submits that the quantification of the carcinogenicity of antimony trioxide must be considered specifically and exclusively with regard to the exposure of pulmonary tissues from respirable particulate through the route of inhalation.

The designation of route-specific NSRLs is not unusual under Proposition 65. Currently, there are thirteen other NSRLs listed under 27 CCR §25705 that are specific to the inhalation route only. It is our client's view that this is a particularly important consideration in this case. There is no evidence that the application of an NSRL of 0.13 µg/day for *ingestion* of antimony trioxide would result in an increased cancer rate of 1:100,000. This calls into question whether the proposed NSRL is compliant with 27 CCR §25703(b).

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[2] ATSDR. 2019. Toxicological profile for antimony and compounds. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, Atlanta, GA.

[3] IARC (International Agency for Research on Cancer). 1989. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 47, Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting. IARC, World Health Organization, Lyon, France.

[4] NTP. 2017. Toxicology and Carcinogenesis Studies of Antimony Trioxide (CAS No. 1309-64-4) in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N Mice (Inhalation Studies). NTP Technical Report Series No. 590. National Toxicology Program, US Department of Health and Human Services, Research Triangle Park, NC.

[5] OEHHA. 2022. Initial Statement of Reasons, Title 27, California Code of Regulations Proposed Amendment to:

Section 25705(B), Specific Regulatory Levels Posing No Significant Risk Antimony Trioxide. California Office of Health Hazard Assessment, Cal EPA, Sacramento, CA.

The same is true of dermal exposure. In 2003, the World Health Organization (WHO) considered the carcinogenicity of antimony compounds. In this assessment, WHO concluded that carcinogenicity of the compounds was related to the inhalation route and that there was a lack of appropriate data to evaluate the cancer risks associated with oral antimony exposure. In addition, WHO reported that therapeutic doses of an antimony(V) compound, meglumine antimoniate, does not represent any mutagenic or carcinogenic risks to humans.[6] Further, the proposed NSRL represents exposure that is much lower than antimony trioxide that is naturally occurring.

Antimony trioxide is a solid under conditions of possible human exposure, with limited aqueous solubility (approximately 0.37 µg/ml). As a result, inhalation exposure must be in the form of a suspended particulate that is capable of being inhaled by humans. When characterizing exposure to airborne solids, the physical form of the material can be equally relevant as the concentration of the carcinogen within it.[7] It has been demonstrated that, for solid particulates, size impacts not only the distribution and transport of the toxicant, but also its surface efficacy.[8]

It is well documented that the deposition of particulate within the human airway is a function of the size of the particulate.[9] In ranges between 10 and 2 µm in aerodynamic diameter, the smaller the particle size, the greater proportion of the particulate will be deposited in the deep or acinar portion of the lung (Figure 1). Increasing the size of the particulate will reduce the proportion of the inhaled particles that reach the deep pulmonary; instead, these particles are expected to be deposited in the nasopharyngeal region or in the upper bronchia where it is subject to clearance via the mucociliary escalator.[10] In the NTP inhalation study that OEHHA relied upon to develop the NSRL, antimony trioxide was administered in a particle size of between 1-2 µm in aerodynamic diameter. This was intentional and intended to "maximize deposition in the lower respiratory tract."[11]

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[6] WHO. 2003. Antimony in drinking-water – background document for development WHO Guidelines for Drinking-water Quality. Geneva.

[7] Morawska L, and G Buonanno. 2021. The physics of particle formation and deposition during breathing. Nature Reviews: Physics. 3:300-301.

[8] Sturm R. 2020. Modelling the deposition of fine particulate matter (PM2.5) in the human respiratory tract. AME Med J. 5:14.

[9] Hofmann W. 2011. Modelling inhaled particle deposition in the human lung—A review. Journal of Aerosol Science 42:693–724.

[10] Brown JS, T Gordon, O Price, and Asgharian B. 2013. Thoracic and respirable particle definitions for human health risk assessment. Part Fibre Toxicol. 10:12.

[11] NTP. 2017.

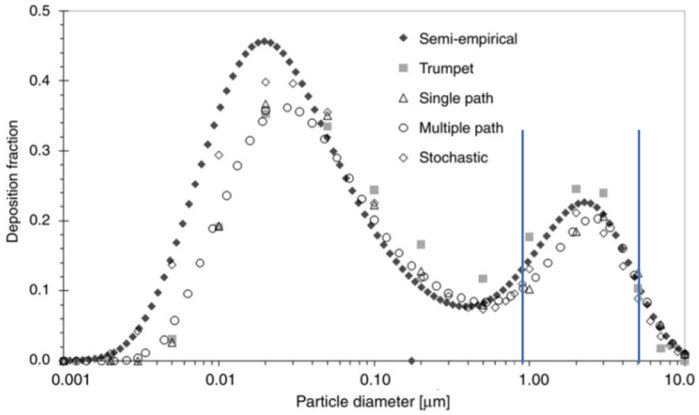


Figure 1: Comparison of model predictions of acinar deposition for unit density particles ranging from 1 nm to 10 µm under nasal sitting breathing conditions, applying 5 different deposition models: semi-empirical, trumpet, single path, multiple path, and stochastic.[12] Vertical lines represent the mass median aerodynamic particle diameter used in the NTP study.

To develop the NSRL, OEHHA relied on a multistage cancer model to derive a cancer potency estimate. This is consistent with the approach that Armitage proposed[13] and is in keeping with the risk assessment procedures set forth at 27 CCR §25703. The multistage model derives a regression relation based on the air borne concentration of antimony trioxide and the proportional response of the female mice. However, what the model does not account for is the nature of the particulate, specifically with respect to size, and how this size may impact the efficacy of antimony trioxide as a carcinogen. This is an artefact to OEHHA's multistage procedure upon which the NSRL is based. Accordingly, the NSRL derived using the multistage cancer model reflects a prediction of the potency of antimony trioxide with a mass median aerodynamic particle diameter from 0.9 to 1.5 µm and a geometric standard deviation from 1.7 to 2.2 across exposure concentration and time. Studies indicating pulmonary carcinogenicity to antimony oxide to particles with a larger average particulate size also had much larger variation in particle size distributions suggesting that exposures still involved administration of respirable particulate.[14] As such, our client respectfully asserts that the NSRL for antimony trioxide must be qualified to represent a safe harbor for this specific type of antimony oxide particle. In other words, the safe harbor level for antimony trioxide should only be

[12] International Commission on Radiological Protection (ICRP). 1994. Human Respiratory Tract Model for Radiological Protection. ICRP Publication 66, Annals of ICRP 24, Nos. 1–3. Oxford: Pergamon Press.

[13] Armitage P. 1985. Multistage models of carcinogenesis. Environ Health Perspect. 63:195–201.

[14] ATSDR 2019.

applied where exposure to antimony trioxide is as a respirable particulate defined by the US Environmental Protection Agency as having an aerodynamic diameter equal to or less than 2.5 µm.[15]

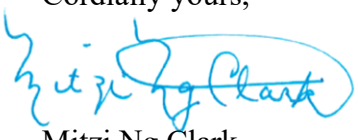
II. Conclusion

In summary, we respectfully submit that, given the particle size of the antimony trioxide that is subject to the NTP study, and that the NTP data primarily confirm the effects of the substance where inhaled as very fine particles, the NSRL of 0.13 µg/day should be limited to inhalation routes of exposure of standard respirable size of ≤ 2.5 µm. Such action would reflect a more realistic approach to evaluating carcinogenic risk of the compound in humans.

* * *

We appreciate the opportunity to comment on this proposed rule and look forward to working with OEHHA to ensure that the antimony trioxide NSRL is appropriate and reasonable. If you have any questions or concerns regarding these comments, or if we can provide additional information regarding any of the above points, please do not hesitate to contact us.

Cordially yours,



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[15] U.S. EPA. 1997. National ambient air quality standards for particulate matter; final rule. Fed Reg. 1997;62(July 18):38652–38752.