To: Esther Barajas-Ochoa
Office of Environmental Health Hazard Assessment
1001 I Street, 23rd Floor Sacramento, California 95814
Submitted via: https://oehha.ca.gov/comments

October 11, 2022

RE: Comments on No Significant Risk Level (NSRL) for antimony trioxide

Dear Ms. Barajas-Ochoa,

Thank you for the opportunity to provide comments on the No Significant Risk Level (NSRL) proposed for antimony trioxide. This letter is submitted on behalf of the undersigned public and environmental health organizations. The proposed NSRL of 0.13 micrograms per day is appropriate and based on established scientific methodologies, and we support the proposed NSRL to be adopted under Proposition 65.

Basis for Antimony Oxide's inclusion in Proposition 65 is appropriate

Antimony has in fact been listed as a Proposition 65 chemical since 1990, on the basis of determination of carcinogenicity by the The World Health Organization's International Agency for Research on Cancer (IARC), an organization designated as an "authoritative body" (AB) by the CIC or DART Identification Committee[1]. This decision is supported by a more recent study. According to the National Toxicology Program (NTP 2018) [2] Antimony(III) trioxide is "*reasonably anticipated to be a human carcinogen"* and draws its conclusion using "*sufficient evidence of carcinogenicity from studies in experimental animals and supporting data from mechanistic studies.*" NTP is also an authoritative source to trigger a cancer listing in the State of California[3].

Basis of Cancer Slope Factor used by OEHHA is appropriate

The proposal correctly notes that "*The NSRL for antimony trioxide is based upon the results of the most sensitive scientific study deemed to be of sufficient quality.*" We find this to be an appropriate characterization.

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1 Antimony Oxide (Antimony trioxide) Proposition 65 warnings. Date Unknown. Accessed October 3rd, 2022. https://www.p65warnings.ca.gov/chemicals/antimony-oxide-antimony-trioxide

2 National Toxicology Program (NTP 2018). Report on Carcinogens Monograph on Antimony Trioxide. RoC Monograph 13. US Department of Health and Human Services, NTP, Research Triangle Park, NC. Available from https://ntp.niehs.nih.gov/ntp/roc/monographs/antimony_final20181019_508.pdf.

3 OEHHA 2003. The National Toxicology Program Processes in Relation to the Authoritative Bodies Mechanism in Proposition 65. Accessed October 3, 2022, https://oehha.ca.gov/proposition-65/general-info-background-policy-procedure/national-toxicology-program-processes

The sources used to develop the NSRL are appropriate. OEHHA developed the proposed NSRL for antimony trioxide based on two key sources: The 2017 National Toxicology Program (NTP) technical report entitled "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)";[4] and The NTP Report on Carcinogens "Monograph on Antimony Trioxide".[2]

The NTP technical report and the NTP Report on Carcinogens monograph summarize the available data from rodent carcinogenicity studies, as well as other information relevant to the carcinogenic activity of antimony trioxide. The NTP is an authoritative body as designated by the Carcinogen Identification Committee, and therefore the NTP sources are scientifically appropriate and deemed to be sufficiently rigorous for deriving the cancer slope factor. The above studies follow the best available scientific methodologies in terms of study design, exposure, and outcome assessments; they also take into consideration confounding variables.

Therefore the use of these studies to develop the dose response curve is appropriate for the derivation of the antimony trioxide NSRL.

The use of a multistage linear model for low-dose response estimation is appropriate

The NTP 2018 Report on Carcinogens establishes carcinogenicity of antimony trioxide in animal subjects. In terms of specific pathways of carcinogenicity, decades of studies cited in the NTP 2018 Report demonstrate that antimony trioxide exhibits carcinogenicity through multiple pathways that have been established in animal subjects and that are relevant to human systems. Both genotoxic and non-genotoxic pathways are cited as mechanisms of action.

NTP uses a standard time-to-tumor extension of the multistage model used to derive a cancer potency estimate drawing on the male mouse NTP study. We agree with OEHHA that this is the most appropriate dose-response estimation given current data and methods.

It is appropriate that the proposed NSRL does not delineate a limited exposure pathway

The studies summarized in the NTP 2018 Report on Carcinogens suggest that antimony trioxide shows clear *systemic evidence* of carcinogenicity. Antimony trioxide exposure increased the incidence of lung and adrenal tumors in rat test subjects, and lung, skin, and lymphoid tumor occurrence in mice.

While the focus of previous studies (drawing on animal test subjects, as well as assessments of workers in environments with chronic and/or elevated antimony trioxide exposure[1]), has been on

4 National Toxicology Program (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. US Department of Health and Human Services, NTP, Research Triangle Park, NC. Available from https://ntp.niehs.nih.gov/go/tr590.

inhalation as a carcinogenicity pathway, it is currently standard and best practice to assume the NSRL applies to all pathways of entry into human systems when dealing with a systemic carcinogen[5] such as antimony trioxide.

This is also consistent with the way previously proposed Proposition 65 NSRL values have been treated. Out of 971 chemicals and chemical classes listed for cancer under "type of toxicity", 318 of these have NSRLs listed. Of these, the vast majority (296) do not specify a route of exposure, while only 14 carcinogens have NSRLs that are listed as being limited to either an inhalation and oral exposure pathway [6].

For all of the above reasons, the proposed NSRL is appropriate and should be finalized in Title 27, California Code of Regulations, section 25705(b).

All trivalent antimony compounds should be listed under Proposition 65 as known to the State of California to cause cancer

We also appreciate and agree with OEHHA's recently proposed Prop 65 listing of all trivalent antimony compounds, given IARC's most recent report concerning the meeting for IARC Monographs Volume 131: Cobalt, Antimony Compounds, and Weapons-Grade Tungsten Alloy, convened by the International Agency for Research on Cancer (IARC)[7]. This report finds that all antimony(III) compounds are classified as "*probably carcinogenic to humans (Group 2A) on the basis of limited evidence for cancer in humans (for cancer of the lung), sufficient evidence for cancer in experimental animals, and strong mechanistic evidence (related to key characteristics of carcinogens in human primary cells and in experimental systems)*."

Thank you for considering these comments.

Signed,

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5 Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF et al. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect. 124(6):713-721. http://dx.doi.org/10.1289/ehp.1509912

6 February 25, 2022 Proposition 65 List (Excel). Downloaded September 27, 2022, https://oehha.ca.gov/proposition-65/proposition-65-list

7 Karagas, M.R., Wang, A., Dorman, D.C., Hall, A.L., Pi, J., Sergi, C.M., Symanski, E., Ward, E.M., Arrandale, V.H., Azuma, K. and Brambila, E., 2022. Carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy. The Lancet Oncology, 23(5), pp.577-578. https://doi.org/10.1016/S1470-2045(22)00219-4

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