October 31, 2022

Attention: Esther Barajas-Ochoa
Office of Environmental Health Hazard Assessment
P. O. Box 4010
Sacramento, California 95812-4010

(Submitted Online Via Portal at: https://oehha.ca.gov/comments)

Re: *Notice of Intent to List Antimony (Trivalent Compounds)*

Dear Ms. Barajas-Ochoa:

The California Chamber of Commerce, Consumer Brands Association and American Chemistry Council ("Coalition") thank you for the opportunity to submit comments regarding the "Notice of Intent to List Chemical by the Labor Code Mechanism: Antimony (Trivalent Compounds)" dated September 30, 2022 (the Notice). OEHHA has proposed listing "antimony (trivalent compounds)" based on the Lancet Oncology summary of the outcome of the International Agency for Research on Cancer (IARC) Working Group meeting on March 2-18, 2022.[1]

The Lancet Oncology's brief summary of IARC's action, published on April 7, 2022, does not provide sufficient information to allow OEHHA to accurately determine whether all or certain trivalent antimony compounds should be listed or to evaluate whether any such listing should be limited to the inhalation route of exposure or other relevant limitation. OEHHA should and must analyze the IARC Monograph before proposing any listing of antimony (trivalent compounds).

The IARC Monograph for certain antimony compounds (Volume 131) is currently identified on the IARC website as "in preparation."[1] Historically, OEHHA has, in at least several highly analogous cases, waited

[1] IARC (2022) List of Classifications – IARC Monographs on the Identification of Carcinogenic Hazards to Humans (who.int)

until after the publication of the IARC Monograph before proposing to list (or not list) chemicals classified by IARC, especially when the classification raises complex issues, as in the case of antimony compounds. In certain of these cases, the detailed information in the IARC Monograph has allowed OEHHA to more accurately identify how a substance should be listed under Proposition 65.

OEHHA should withdraw its proposal to list antimony (trivalent compounds) and propose an appropriate listing, if warranted, after OEHHA has analyzed the IARC Monograph (Volume 131). Without access to the IARC Monograph, OEHHA and the interested public lack sufficient information to fully understand IARC's judgment in evaluating and classifying trivalent antimony.

I. The Lancet Oncology summary, which is cited as the basis for the proposed listing, is only a brief summation of IARC's classifications, and it does not provide sufficient information to allow OEHHA to list antimony (trivalent compounds).

On April 7, 2022, the journal The Lancet Oncology published a summary of the IARC Working Group's virtual meeting on March 2-18, 2022 titled, "Carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy" (hereafter, "Lancet Summary").[2] The Lancet Summary does not elaborate on which antimony compounds were discussed.[3] The substance of the Lancet Summary concerning antimony appears below:

> "Trivalent antimony was classified as 'probably carcinogenic to humans' (Group 2A), based on 'limited' evidence for cancer in humans, 'sufficient' evidence for cancer in experimental animals, and 'strong' mechanistic evidence in human primary cells and in experimental systems."
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> "Antimony is used mainly in flame retardants, lead-acid batteries, lead alloys, plastics, brake pads, clutch discs, glass and ceramics, and as an ammunition primer in explosives. Some pentavalent antimony compounds are used in the treatment of leishmaniasis. Industrial workers can be exposed to multiple antimony compounds, mainly by inhalation, during smelting, production of antimony compounds, manufacture of glass, textiles, and batteries, and electronic processing and electrical waste processing. Non-occupational exposures, which occur via contaminated water, air, and soil, and use of consumer products and tobacco, are typically lower than occupational exposures."

[2] Karagas MR, Wang A, Dorman DC, Hall AL, Pi J, Sergi CM, et al. (2022) Carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy. The Lancet Oncology 23(5):577-578. May 1, 2022. Published April 7, 2022.
[3] Id.

"Four occupational studies and ten general-population studies investigated the association between antimony exposure and cancer risk. For cancer in humans, the Working Group concluded that there was 'limited' evidence for lung cancer. Evidence of positive associations with trivalent antimony exposure was observed in three cohort studies among antimony and tin smelter workers. One study of antimony smelter workers found elevated standardised mortality ratios (SMRs) for lung cancer by job group of antimony workers, early period of hire, and latency from first exposure. Another found elevated SMRs using ethnicity-specific reference rates and a positive trend in lung cancer risk with increasing duration of exposure (SMR 2·73 [95% CI 1·33–5·01] for >10 years employment). A study of tin smelter workers found positive trends in risk with increasing cumulative antimony exposure. Overall, the Working Group concluded that a causal association between exposure to trivalent antimony and lung cancer was plausible; however, in view of potential confounding due to co-exposure to arsenic and other lung carcinogens in smelting processes, bias could not be ruled out with reasonable confidence. Evidence for other cancer types was found to be "inadequate": studies were considered only minimally informative, too few in number, or without consistent evidence to contribute to the evaluation."

"The evidence for cancer in experimental animals was 'sufficient' for **antimony trioxide**. In two GLP studies in rodents, **inhalation exposure** caused bronchioloalveolar carcinoma in male and female mice; fibrous histiocytoma and fibrosarcoma of the skin in male mice; lymphoma in female mice; and lung and adrenal medulla tumours in female rats."

"The mechanistic evidence for trivalent antimony was 'strong' in human primary cells for genotoxicity, and in experimental systems for oxidative stress, chronic inflammation, and alterations in cell proliferation, cell death, or nutrient supply. Multiple studies in human primary cells showed that trivalent antimony increased DNA damage, chromosomal aberrations, micronucleus formation, or sister-chromatid exchanges."

"For pentavalent antimony, evidence regarding cancer in humans and cancer in experimental animals was 'inadequate', since no data were available to the Working Group. The mechanistic evidence for pentavalent antimony was 'limited'."[4]

While the Lancet Summary may be adequate for the purpose of communicating the general outcome of the IARC Working Group meeting, it is inadequate for the purpose of placing "antimony (trivalent compounds)" on the Proposition 65 list. The Lancet Summary does not identify the particular "substance"

[4] Id. (emphasis added).

to be listed pursuant to section 25249.8(a) of the Health and Safety Code or the particular "chemical or substance" to be listed pursuant to 27 C.C.R. § 25904. Moreover, the phrase "antimony (trivalent compounds)" does not appear in the Lancet Summary, which is additional evidence that the Lancet Summary should not be utilized as the basis for OEHHA's proposed Prop 65 listing.

II. The Lancet Summary leaves unclear which substance(s) have received a "sufficient evidence" assessment.

A. Overview

The Lancet Summary did not state whether the Working Group had classified all antimony trivalent compounds, or a subset thereof, as Group 2A. There are many trivalent antimony compounds, including but not limited to: antimony trioxide, antimony trisulfide, antimony trichloride, antimony trihydride, and potassium antimony tartrate dihydrate, to name a few. These substances are all identified by different CAS numbers. It is unclear from the Lancet Summary whether IARC used CAS numbers to identify which substances have been classified as Group 2A. While most substances on the Proposition 65 list are identified by CAS numbers, the Lancet Summary does not mention CAS numbers. The IARC Monograph would be expected to identify which trivalent antimony compounds and possibly which CAS numbers are included in its evaluation.

The very basis for IARC's classification is ambiguous in the Lancet Summary, particularly since the Lancet Summary focuses on antimony trioxide to establish sufficiency of evidence in experimental animals.

> "Trivalent antimony was classified as 'probably carcinogenic to humans' (Group 2A), based on 'limited' evidence for cancer in humans, ***'sufficient' evidence for cancer in experimental animals***, and 'strong' mechanistic evidence in human primary cells and in experimental systems."[5]

And:

> "The evidence for cancer in experimental animals was 'sufficient' for antimony trioxide."[6]

There is no basis provided in the Lancet Summary that would allow one to know which antimony compounds, if any, other than antimony trioxide had been judged to have "sufficient evidence" to cause cancer in animals, as opposed to classification in Group 2A based on mechanistic considerations. Nor does the Lancet Summary make clear what compounds were included in the Group 2A classification. The Lancet

[5] Id.
[6] Id. (emphasis added).

Summary's characterization of the mechanistic evidence as strong suggests that compounds other than antimony trioxide may well have been classified based on mechanistic considerations, which is not appropriate for a Labor Code listing.[7] *See Styrene Information & Research Center v. Office of Environmental Health Hazard Assessment*, 210 Cal. App. 4th 1082 (2012); 27 CCR § 25904(b).

Further, the Lancet Summary only notes that the "limited" epidemiologic data describes a positive association between cancer and trivalent antimony, and fails to indicate the specific antimony compound(s) evaluated. For example, the Lancet Summary describes a specific epidemiological study with positive trends in risk with increasing cumulative antimony exposure, without even describing which antimony compound contributed to the exposure.

> "A study of tin smelter workers found positive trends in risk with increasing cumulative antimony exposure."[8]

In summary, in order to properly identify which trivalent antimony compounds should be listed based on IARC's classification, OEHHA must understand how IARC defined the scope of antimony compounds in its classification. OEHHA cannot determine this based on the Lancet Summary alone without analyzing the IARC Monograph. As we have seen in the past, IARC sometimes defines substances in unconventional ways when it classifies them, as discussed in the next section.

B. Appropriately, OEHHA chose to wait for the IARC Monograph before considering a Proposition 65 listing of processed meat; OEHHA should do the same here.

When IARC classified "processed meat" as "carcinogenic to humans" (Group 1), OEHHA chose to wait for the IARC Monograph (Volume 114) to be published before deciding whether to list processed meat under Proposition 65. This was an appropriate decision.

Processed meat was evaluated by an IARC Working Group on October 6-13, 2015. Thirteen days later, a brief summary of the meeting was published in The Lancet Oncology. Although a definition of processed meat was provided (unlike for the case of antimony compounds),[9] OEHHA was able to fully evaluate how

[7] We do not concur in IARC's assessment of the mechanistic information, but this is not the occasion to engage in that discussion.
[8] Id.
[9] Bouvard V, Loomis D, Guyton KZ, Grosse Y, El Ghassassi F, Benbrahim-Tallaa L, et al. (2015) Carcinogenicity of consumption of red and processed meat. The Lancet Oncology 16(16):1599-1600. December 2015. Published Oct. 26, 2015. Carcinogenicity of consumption of red and processed meat - The Lancet Oncology

the Working Group ultimately defined processed meat *only after* the IARC Monograph (Volume 114) was published in 2018.[10]

This example demonstrates why it is important to have a clear understanding of what specific chemicals or products are covered by an IARC classification. In IARC classifications of more complex substances, such as processed meat (and now antimony compounds), it is critical to be able to review the full IARC Monograph to properly identify the substance to be considered for Proposition 65 listing.

III. The Lancet Summary of antimony, which is cited as the basis for listing antimony (trivalent compounds), does not adequately identify whether a listing of trivalent antimony should be qualified in any manner.

A. Overview

In certain cases, it is appropriate to qualify the Proposition 65 listing of a substance classified by IARC depending on how IARC describes its carcinogenicity findings. For example, some classifications made by IARC are qualified by various factors, such as route of exposure, particle size, or the matrix in which the substance is found. There is no way to know from the Lancet Summary whether IARC qualified its classification of trivalent antimony. A review of the IARC Monograph is necessary to evaluate whether IARC qualified its classification.

For example, it is possible that IARC intended to limit its Group 2A classification of antimony compounds to the inhalation route of exposure since there appears to be little or no evidence to suggest that oral exposure is carcinogenic. The Lancet Summary bases its "sufficient evidence" statement on inhalation studies in animals. Thus, it is reasonable to expect that the IARC Monograph will be limited to inhalation.

As another example, IARC has qualified its classification of certain substances (e.g., carbon black, titanium dioxide) when they are bound in a matrix. One of the most common uses of antimony is as a component in metal alloys where it may be bound in a matrix. Again, it is crucial to know how IARC considered bound-in-a-matrix or unbound particles of respirable size as part of its Group 2A classification. While this question is not addressed in the Lancet Summary, it is more likely to be addressed in the IARC Monograph. These are important reasons to wait for the publication of the IARC Monograph before proposing to list 'antimony (trivalent compounds)'.

[10] IARC (2018) IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Red Meat and Processed Meat. Volume 114. mono114.pdf

B. As with titanium dioxide, OEHHA should wait for the publication of the IARC Monograph for evaluating the possible listing of trivalent antimony compounds.

On September 2, 2011, OEHHA listed titanium dioxide based on the Labor Code mechanism by qualifying the listing as "titanium dioxide (airborne, unbound particles of respirable size)." According to OEHHA:

> "The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is adding *titanium dioxide (airborne, unbound particles of respirable size)* to the list of chemicals known to the State of California to cause cancer for purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). The listing does not cover titanium dioxide when it remains bound within a product matrix. The listing of *titanium dioxide (airborne, unbound particles of respirable size)* is effective September 2, 2011."[11] [emphasis in original]

Five years prior to the listing, IARC summarized its evaluation of titanium dioxide in The Lancet Oncology.[12] IARC announced, "The working group classified titanium dioxide as possibly carcinogenic to human beings (ie, group 2B)."[13] However, The Lancet Oncology summary did not provide sufficient information to have allowed OEHHA to qualify the listing of titanium dioxide, as it did in 2011 after the IARC Monograph was published. For example, the summary in The Lancet Oncology provided limited basis for OEHHA to conclude that "The listing does not cover titanium dioxide when it remains bound within a product matrix."[14] In fact, there was nothing mentioned to justify qualifying the listing with the word "unbound." While there was some mention of inhalation as a route of exposure and particle size in The Lancet Oncology summary, it was insufficient to allow OEHHA to make the definitive conclusion to qualify the listing with the phrase "airborne, unbound particles of respirable size."

The entirety of The Lancet Oncology 2006 summary of titanium dioxide appears below:

> "Titanium dioxide accounts for 70% of the total production volume of pigments worldwide. The primary particles are typically 200–300 nm in diameter, but larger aggregates and agglomerates are formed readily. Ultrafine grades of titanium dioxide (ie, 10–50 nm) are used in sunscreens and

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[11] OEHHA (2011) Chemical Listed Effective September 2, 2011 as Known to the State of California to Cause Cancer: titanium dioxide (airborne, unbound particles of respirable size) - OEHHA

[12] Baan, R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Cogliano,V et al. (2006) Carcinogenicity of carbon black, titanium dioxide, and talc. The Lancet Oncology 7(4):295-6, April 1, 2006. Carcinogenicity of carbon black, titanium dioxide, and talc - The Lancet Oncology

[13] Id.

[14] OEHHA (2011) Chemical Listed Effective September 2, 2011 as Known to the State of California to Cause Cancer: titanium dioxide (airborne, unbound particles of respirable size) - OEHHA

plastics to block ultraviolet light, and in catalysts. Highest exposures occur in titanium-dioxide production during packing, milling, site cleaning, and maintenance. Exposure data for industries that use titanium dioxide are scarce.

The largest epidemiological cohort study considered included workers in the titanium dioxide production industry in six European countries, and showed a small but significant increase in risk of lung cancer compared with that for the general population; however, the data did not suggest an exposure-response relation. Two cohort studies undertaken in the USA did not report excess risks of lung cancer, neither did a Canadian population-based case-control study. Overall, the working group concluded that the epidemiological studies on titanium dioxide provide inadequate evidence of carcinogenicity.

Pigment-grade titanium dioxide and ultrafine titanium dioxide have been tested in rats, mice, and hamsters by various routes of administration. Overall, results from studies of inhalation and intratracheal instillation provided sufficient evidence in animals for the carcinogenicity of titanium dioxide. The working group classified titanium dioxide as possibly carcinogenic to human beings (ie, group 2B)."[15]

OEHHA identified how titanium dioxide should be listed under Proposition 65 *only after* the IARC Monograph (Volume 93) was published in 2010.[16] OEHHA's Notice of Intent to List titanium dioxide was published on May 27, 2011.[17] By waiting to read the details of the IARC's evaluation in the IARC Monograph, OEHHA made an appropriate determination that IARC had classified titanium dioxide in Group 2B only when it was "airborne, unbound particles of respirable size." If OEHHA had relied upon the 2006 summary in The Lancet Oncology, the listing of titanium dioxide could have been overly broad and would not have included all the qualifiers that accurately reflected IARC's classification. OEHHA should follow the same practice here with antimony compounds.[18]

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[15] Baan, R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Cogliano,V et al. (2006) Carcinogenicity of carbon black, titanium dioxide, and talc. The Lancet Oncology 7(4):295-6, April 1, 2006. Carcinogenicity of carbon black, titanium dioxide, and talc - The Lancet Oncology.

[16] IARC (2010) IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Carbon black, titanium dioxide, and talc. Volume 93. mono93.pdf

[17] OEHHA (2011) Notice of Intent to List Titanium Dioxide (Airborne, Unbound Particles of Respirable Size) by The Labor Code Mechanism - OEHHA (ca.gov) May 27, 2011 Notice

[18] Carbon black is another example of a substance that received a qualified listing because OEHHA waited until after the IARC Monograph was published. OEHHA listed "carbon black (airborne, unbound particles of respirable size)" on February 21, 2003 based on the IARC Monograph, Volume 65, which was published in 1996. In the Notice to List, OEHHA described the unique aspects of the listing of carbon black : "The listing only pertains to

IV. Other reviews of antimony exposure and the underlying data demonstrate OEHHA should wait for and evaluate the IARC Monograph.

All the epidemiologic studies of antimony cited in the Lancet Summary appear to be inhalation studies, not ingestion studies. The 2019 ATSDR Toxicological Profile of Antimony reviewed four animal carcinogenicity studies of antimony, and all are inhalation studies of antimony trioxide. The ATSDR Toxicological Profile provided no evidence of carcinogenicity by the oral route of exposure, and ATSDR noted the existence of two older oral studies of another trivalent antimony compound (i.e., antimony potassium tartrate) in drinking water:

> "No alterations in neoplastic lesion incidence were observed in rats (Schroeder et al. 1970) or mice (Kanisawa and Schroeder 1969) orally exposed 0.63 or 0.35 mg Sb/kg/day, respectively, as antimony potassium tartrate in drinking water for a lifetime. The use of these studies to assess carcinogenicity is limited because only one exposure level was used, which was below the maximum tolerated dose."[19]

In its 2016 Public Health Goal document for antimony, OEHHA opined that the possibility cannot be ruled out that oral exposure to antimony trioxide is carcinogenic, but that assessment is quite different from the "known to cause" language of Proposition 65.[20]

US EPA based its Maximum Contaminant Level (MCL) for antimony (not antimony trioxide) in water based on a non-cancer endpoint.[21] The fact that both OEHHA and US EPA did not assume antimony trioxide is carcinogenic by the oral route when they developed drinking water guidance, adds substantial

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airborne, unbound carbon black particles of respirable size. As noted by IARC, the respirable fraction is 'that fraction of an aerosol with an aerodynamic diameter suitable for penetration into the alveoli/gas exchange region of the lung (typically <10 μm)' (pp. 171-172, Volume 65, IARC Monographs on the Evaluation of Carcinogenic Risks to Human, 1996). OEHHA and the California Air Resources Board have also noted that, 'In general, particles 10 μm or less in diameter are considered respirable by humans' (California Environmental Protection Agency, Air Resources Board, Staff Report: Public Hearing to Consider Amendments to the Ambient Air Quality Standards for Particulate Matter and Sulfates, prepared by staff of the Air Resources Board and OEHHA, 2002). Thus, for the purposes of Proposition 65, carbon black particles 10 μm or less shall be considered respirable. Exposure to carbon black, per se, does not occur when it remains bound within a product matrix, such as rubber, ink or paint." Chemical Listed Effective February 21, 2003 as Known to the State of California to Cause Cancer: Carbon Black (airborne, unbound particles of respirable size) - OEHHA

[19] ATSDR (2019) ATSDR Toxicological Profile for Antimony. Antimony | Toxicological Profile | ATSDR (cdc.gov)

[20] OEHHA (2016) Public Health Goal for Antimony in Drinking Water. September, 2016. Public Health Goal for Antimony in Drinking Water (ca.gov)

[21] US EPA (2009) npwdr_complete_table.pdf (epa.gov)

weight to the requirement that and the wisdom of OEHHA waiting for and then carefully reviewing the IARC Monograph in order to reach an informed and properly supported outcome.

V. Conclusion

The Lancet Summary does not provide sufficient information to allow OEHHA to accurately determine whether all or certain trivalent antimony compounds should be listed and whether IARC's determination supports a qualified listing of any kind. OEHHA should withdraw its current proposal to list antimony (trivalent compounds), evaluate the IARC Monograph, and then take appropriate action based upon the IARC Monograph. Without access to the IARC Monograph, OEHHA and interested members of the public are not in a position to fully understand what IARC means by the phrase "trivalent antimony", what specific "sufficient evidence" findings were made by the IARC Working Group, and whether IARC's conclusion is limited to a particular route of administration or other characteristic.

Respectfully,

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cc:
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