Response to Comments Concerning the Notice of Intent to List Molybdenum Trioxide as Causing Cancer under Proposition 65

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
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Background

On October 9, 2020, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Intent to List[1] molybdenum trioxide and indium tin oxide under Proposition 65[2] as chemicals known to the state to cause cancer. The October 9 notice initiated a 45-day public comment period that closed on November 23, 2020. Comments were received on molybdenum trioxide; none were received on indium tin oxide. This document responds to comments received on the Notice of Intent to List molybdenum trioxide.

The process by which OEHHA lists chemicals and substances via the Labor Code listing mechanism is covered in regulation at Title 27, Cal. Code of Regs., section 25904[3]. The regulations cover the requirements for listing as causing cancer pursuant to Health and Safety Code section 25249.8(a) and Labor Code section 6382(b)(1).

Both molybdenum trioxide and indium tin oxide are identified by the International Agency for Research on Cancer (IARC) as having sufficient evidence of carcinogenicity in animals, and are classified as possibly carcinogenic to humans (Group 2B)[4]. Pursuant to Health and Safety Code section 25249.8(a) and Title 27, Cal. Code of Regs., section 25904(c), a chemical must be included on the Proposition 65 list if it is identified by IARC in its Monographs series on the Evaluation of Carcinogenic Risks to Humans (most recent edition), based on sufficient human or animal evidence, as carcinogenic to humans (Group 1), probably carcinogenic to humans (Group 2A) or possibly carcinogenic to humans (Group 2B). Molybdenum trioxide and indium tin oxide meet this criterion for listing.

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[1] Notice of Intent to List Chemicals by the Labor Code mechanism: Molybdenum Trioxide and Indium Tin Oxide, available at: https://oehha.ca.gov/proposition-65/crnr/notice-intent-list-chemicals-labor-code-mechanism-molybdenum-trioxide-and-indium

[2] The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq.*) hereinafter referred to as Proposition 65 or the Act.

[3] All further references are to sections of Title 27, Cal. Code of Regs unless otherwise stated.

[4] International Agency for Research on Cancer (IARC 2018). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 118. Welding, Molybdenum Trioxide, and Indium Tin Oxide. IARC, World Health Organization, Lyon, France. Available at: https://publications.iarc.fr/569

OEHHA received one set of comments addressing molybdenum trioxide during the comment period from the International Molybdenum Association (IMOA). No comments were received on indium tin oxide.

Response to Comments

After careful consideration of the public comments received, OEHHA has determined that molybdenum trioxide meets the requirements for listing as known to the state to cause cancer.

The public comments by IMOA and responses by OEHHA are summarized below.

Overall, IMOA requests that "molybdenum trioxide be placed on the Proposition 65 list as a qualified listing", with the name "molybdenum trioxide (airborne particles of respirable size)". IMOA provided several reasons for this request, and they are discussed here as separate comments, each followed by OEHHA's response.

Comment 1: IMOA makes the following statement regarding this request, and gives "titanium dioxide (airborne, unbound particles of respirable size)" as a precedent for such a qualified listing.

> "Based on the IARC Monograph, we submit that the listing of molybdenum trioxide under Proposition 65 should be considered a qualified listing under that Labor Code listing mechanism, and there is precedent for qualified Proposition 65 listings under that listing mechanism. For example, titanium dioxide was placed on the Proposition 65 list as a qualified listing via the Labor Code mechanism based on an IARC monograph; the listing of titanium dioxide appears as "titanium dioxide (airborne, unbound particles of respirable size)."

Response 1: OEHHA disagrees that the 2018 IARC monograph[5] provides a basis under the Labor Code listing mechanism for qualifying the Proposition 65 listing of molybdenum trioxide as causing cancer. Section 25904 provides in relevant part as follows:

> b) A chemical or substance shall be included on the list if it is classified by the International Agency for Research on Cancer (IARC) in its IARC Monographs series on the Evaluation of Carcinogenic Risks to Humans (most recent edition), or in its list of Agents Classified by the IARC Monographs, as:

[5] IARC (2018), full citation provided in footnote 4.

> …(3) Possibly carcinogenic to humans (Group 2B) with sufficient evidence of carcinogenicity in experimental animals, …

The IARC (2018)[6] monograph clearly states the following in section "6.2 Cancer in experimental animals":

> "There is sufficient evidence in experimental animals for the carcinogenicity of molybdenum trioxide".

In summarizing the evidence in experimental animals, IARC noted that increases in tumor incidence were observed in multiple inhalation studies and increases in tumor multiplicity were observed in the one available intraperitoneal injection study.

IARC (2018) also states the following in "6.3 Overall evaluation":

> "Molybdenum trioxide is possibly carcinogenic to humans (Group 2B)".

Thus, IARC did not qualify its classification of molybdenum trioxide.

OEHHA disagrees that the listing of "titanium dioxide (airborne, unbound particles of respirable size)" via the Labor Code listing mechanism provides an appropriate precedent to support the listing of molybdenum trioxide with the qualifier "(airborne particles of respirable size)". There are important differences in the chemical properties of molybdenum trioxide and titanium dioxide, and the lung responses to these chemicals following inhalation exposures, including the following:

- Molybdenum trioxide is soluble in water[7,8], while titanium dioxide is insoluble in water[9].
- Molybdenum trioxide is rapidly absorbed following inhalation exposures, readily distributed to tissues throughout the body, and completely excreted[10], while titanium dioxide is a poorly soluble particle that can accumulate in the lungs following inhalation exposures[11].

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[6] IARC (2018), full citation provided in footnote 4.
[7] *Ibid*.
[8] National Toxicology Program (NTP, 1997). NTP toxicology and carcinogenesis studies of molybdenum trioxide (CAS No. 1313-27-5) in F344/N rats and B6C3F1 mice (inhalation studies). Technical Report Series No. 462, Research Triangle Park, NC: US Department of Health and Human Services. Available at: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr462.pdf
[9] IARC (2010). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 93. Carbon Black, Titanium Dioxide, and Talc. IARC, World Health Organization, Lyon, France. Available at: https://publications.iarc.fr/111
[10] NTP (1997), full citation provided in footnote 8.
[11] IARC (2010), full citation provided in footnote 9.

- Molybdenum trioxide induces lung tumors, but not lung inflammation in male and female mice in long-term inhalation cancer bioassays[12,13], while titanium dioxide induces lung inflammation, but not lung tumors in mice in long-term inhalation cancer bioassays[14].
- Molybdenum trioxide induces lung inflammation, but not lung tumors in rats in long-term inhalation cancer bioassays[15,16], while titanium dioxide induces lung inflammation and lung tumors in rats in long-term inhalation cancer bioassays[17].

There are important differences in the extent to which molybdenum trioxide and titanium dioxide have been tested for carcinogenicity. Specifically, the carcinogenicity of molybdenum trioxide has not been studied in experimental animals by routes other than inhalation and intraperitoneal injection. The carcinogenicity of titanium dioxide has been studied in experimental animals by the inhalation, oral, intratracheal instillation, intraperitoneal injection, and subcutaneous injection routes, including multiple well-conducted long-term oral and inhalation studies.

IARC (2010) found that in studies conducted by the oral route, or by intraperitoneal or subcutaneous injection titanium dioxide did not induce tumors. Importantly, the carcinogenicity of titanium dioxide has been tested by the oral route in several well-conducted long-term studies that showed no treatment-related effects (i.e., 103-week dietary studies in male and female B6C3F1 mice, 103-week dietary studies in male and female Fischer rats, and 130-week dietary studies in male and female Fischer 344 rats).

Thus, a more extensive database that included several well-conducted oral studies supported the qualified listing of titanium dioxide.

Comment 2: IMOA states that "there was limited evidence of an increase in lung tumors among rats inhaling molybdenum trioxide", and that "[w]hen molybdenum trioxide was given to mice by intraperitoneal injection, there was no clear evidence of carcinogenicity in contrast to the results of the mouse inhalation study." IMOA also stated the following:

> "The only data that formed the basis of IARC's conclusion of "sufficient evidence in animals" were the NTP inhalation studies of molybdenum trioxide in

[12] IARC (2018), full citation provided in footnote 4.
[13] NTP (1997), full citation provided in footnote 8.
[14] IARC (2010), full citation provided in footnote 9.
[15] IARC (2018), full citation provided in footnote 4.
[16] NTP (1997), full citation provided in footnote 8.
[17] IARC (2010), full citation provided in footnote 9.

male and female mice. No form of molybdenum trioxide is "known to cause cancer" other than airborne molybdenum trioxide. The effects observed in the NTP inhalation studies were from respiratory exposure to *micronised particles* of molybdenum trioxide, and findings were limited to the respiratory tract." (emphasis in original)

Response 2:

In summarizing the animal carcinogenicity evidence for molybdenum trioxide, IARC (2018) noted the increased incidences of malignant bronchioloalveolar neoplasms and of combined benign and malignant bronchioloalveolar neoplasms observed in the NTP studies conducted in male and female mice.

OEHHA acknowledges that there were no robust findings of lung tumors among exposed rats in the NTP studies, but does note that there was an intraperitoneal study in strain A/J mice, which was summarized by IARC (2018)[18]. With respect to the intraperitoneal injection study in strain A/J mice, a tumorigenic response was observed in the lungs even though the chemical was not administered directly to the lungs. The following information is provided on the strain A/J mouse carcinogenicity assay, to put in context the findings from the molybdenum trioxide intraperitoneal injection study in that mouse strain. The strain A/J mouse carcinogenicity assay was designed as a short-term (up to six months) assay to detect carcinogens administered by various routes of exposure, using a specific mouse strain that is particularly susceptible to the development of lung tumors[19]. Histopathological examination of tissues is routinely limited to the lungs in this assay. Interpretation of results from studies using this model is explained as follows by Maronpot et al. (1983)[20]:

> "The pulmonary tumor bioassay is traditionally considered positive when there is a statistically significant increase in the incidence of tumor-bearing mice as well as statistically significant increase in tumor multiplicity, with the latter carrying more weight."

While strain A/J mouse studies often examine only the lungs for tumors, the chemicals that test positive in this assay can induce tumors at sites other than the lungs when tested in long-term carcinogenesis studies in rats and other strains of mice. For

[18] IARC (2018), see p. 275, full citation provided in footnote 4.
[19] Stoner GD and Shimkin MB (1982). Strain A Mouse Lung Tumor Bioassay. Journal of the American College of Toxicology. 1(1):145-169.
[20] Maronpot RR, Witschi HP, Smith LH, McCoy JL (1983). Recent Experience with the Strain a Mouse Pulmonary Tumor Bioassay Model. In: Waters MD, Sandhu SS, Lewtas J, Claxton L, Chernoff N, Nesnow S. (eds) Short-Term Bioassays in the Analysis of Complex Environmental Mixtures III. Environmental Science Research, vol 27. Springer, Boston, MA.

example, the carcinogen aflatoxin B1 tests positive (i.e., increases lung tumor incidence or multiplicity) in strain A mice via intraperitoneal injection and induces liver tumors—but not lung tumors—in (C57Bl x C3H)F1 mice and Fischer rats via intraperitoneal injection[21]. Aflatoxin B1 is also well established as a cause of liver cancer in humans[22]. In another example, the carcinogen 2-acetylaminofluorene (2-AAF) tests positive in strain A mice via intraperitoneal injection[23,24], and in dietary studies induces mammary and urinary bladder tumors in BALB/c mice and liver and urinary bladder tumors in mice (strain not specified)[25], but not lung tumors in these strains.

Comment 3: IMOA states that "the molybdenum trioxide particle size in the NTP inhalation study do comply with the definition of respirable particles, and thereby support the rationale of this request for the qualified listing 'molybdenum trioxide (airborne particles or respirable size)'". IMOA also presented NTP and Organisation for Economic Co-operation and Development (OECD) guidelines regarding particle size.

Response 3: OEHHA agrees that the molybdenum trioxide particles administered by inhalation in each of the long-term carcinogenicity studies of molybdenum trioxide conducted to date, i.e., the NTP studies, were of respirable size, with a mass median aerodynamic diameter of 1.3-1.8 µm. However, the observation that respirable particles were administered in these inhalation studies does not provide a sufficient basis to limit the listing of molybdenum trioxide to particles of respirable size.

Conclusion

Thus, for the reasons discussed above, OEHHA has determined that "molybdenum trioxide" will be added to the Proposition 65 list as causing cancer without the requested parenthetical qualifier.

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[21] IARC (1993). IARC Monographs on the Carcinogenic Risks to Humans, Volume 56. Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins. IARC, World Health Organization, Lyon, France. Available at: https://publications.iarc.fr/74

[22] IARC (2012). IARC Monographs on the Carcinogenic Risks to Humans, Volume 100F. Chemical Agents and Related Occupations. IARC, World Health Organization, Lyon, France. Available at: https://publications.iarc.fr/123

[23] Stoner and Shimkin (1982), full citation provided in footnote 19.

[24] Stoner GD (1991). Lung Tumors in Strain A Mice as a Bioassay for Carcinogenicity of Environmental Chemicals, Experimental Lung Research, 17:2, 405-423.

[25] NTP (National Toxicology Program). 2016. Report on Carcinogens, Fourteenth Edition. 2-Acetylaminofluorene. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. Available at: https://ntp.niehs.nih.gov/ntp/roc/content/profiles/acetylaminofluorene.pdf