INTERNATIONAL MOLYBDENUM ASSOCIATION
THE VOICE OF THE MOLYBDENUM INDUSTRY

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Re: Molybdenum Trioxide (CAS NO. 1313-27-5) and Proposition 65

This letter is submitted by the International Molybdenum Association (IMOA) in relation to molybdenum trioxide and Proposition 65. The proposal to list molybdenum trioxide is based on Volume 118 of the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans ("the IARC Monograph").

Based on the IARC Monograph, we submit that the listing of molybdenum trioxide under Proposition 65 should be considered a qualified listing under the 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).

It is recommended and requested that molybdenum trioxide be placed on the Proposition 65 list as a qualified listing. We submit that the listing should be *"molybdenum trioxide (airborne particles of respirable size)."*

Airborne

Molybdenum trioxide is one of a number of substances that have been demonstrated to produce lung tumors in mice, but not rats, when inhaled as *airborne particles of respirable size*. As OEHHA notes, the IARC Monograph concluded: "There is ***sufficient evidence*** in experimental animals for the carcinogenicity of molybdenum trioxide." According to the IARC Monograph, the *sufficient evidence* conclusion is based on increased lung tumors in male and female mice:

> "In the inhalation study in mice, molybdenum trioxide significantly increased the incidence of carcinoma of the bronchioloalveolar in male mice (with a significant positive trend), the incidence of adenoma of the bronchioloalveolar in female mice (with a significant positive trend), and the incidence of adenoma or carcinoma (combined) of the bronchioloalveolar in female (with a significant positive trend) and male mice. There

> was also a positive trend in the incidence of carcinoma of the bronchioloalveolar in female mice."[1]

In comparison, there was limited evidence of an increase in lung tumors among rats inhaling molybdenum trioxide. The IARC Monograph states:

> "In the inhalation study in rats, there was no statistically significant increase in tumor incidence in male and female rats. In male rats, however, there was a significant positive trend in the incidence of adenoma and adenoma or carcinoma (combined) of the bronchioloalveolar; the incidences were within historical control ranges."[2]

When 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. The IARC Monograph states:

> "Four groups of 20 A/J mice (equal numbers of male and female mice; age, 6–8 weeks) were given intraperitoneal injections of 0 (vehicle control), 950, 2735, or 4750 mg/kg bw (total doses) reagent-grade molybdenum trioxide (purity > 97%; impurities unspecified) in saline three times per week for a total of 19 injections (except saline controls: 24 injections). After 30 weeks, 13, 19, and 15 animals were still alive in the three treated groups. At that time, these animals and 19 surviving vehicle controls were killed and their lungs examined macroscopically for tumour induction; a few of the grossly visible nodules were examined microscopically to confirm the typical appearance of adenomas of the lung. The incidences of mice with lung tumours were 7 out of 19, 4 out of 13, 7 out of 19, and 10 out of 15 [no statistically significant differences], and the average number of lung tumours per mouse (multiplicity) was 0.42 ± 0.10, 0.30 ± 0.08, 0.50 ± 0.13, and 1.13 ± 0.20 (average ± standard error) for the 0, 950, 2735, or 4750 mg/kg bw groups, respectively. Lung tumour multiplicity in the 4750 mg/kg bw group was significantly (P < 0.05) higher than the vehicle control group (Stoner et al., 1976). [The Working Group noted the limitations of the study: the non-physiological route of exposure, the limited histopathological examination, and the combination of tumour incidences for male and female mice.]"[3]

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 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.

[1] IARC Monograph (2018) Vol. 118, p. 278.
[2] Id.
[3] Id., p. 275.

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Particles of Respirable Size

The IARC Monograph describes the test material that caused cancer in mice as "molybdenum trioxide (purity, ~99%; mass median aerodynamic diameter, 1.3–1.8 μm)." Particles in this size range meet the definition of particles of *respirable size* according to the OECD definition and the NTP guidelines. The OECD Guidelines[4] state:

> 108. Although the standard for acute studies (MMAD of ≤4 μm with a σg of 1-3) remains unchanged at this time, the standard for repeated-exposure studies has been changed to accommodate the testing of nano-range aerosols and to enhance deposition in the pulmonary region. The new recommended standard for repeated exposure studies is: MMAD of ≤2 μm with a σ_g of 1-3. Justification should be provided in the study report if this standard cannot be met, including a description of efforts taken to meet it, such as milling. Although a reasonable effort should be made to meet the acute and repeated-exposure MMAD standards, expert judgment should be provided if they cannot be achieved. For example, electrostatically charged particles, fibrous particles, and

The NTP Guidelines[5] state:

> 13. If the test atmosphere is an aerosol, the particle size distribution shall be controlled and monitored. The measurement method must provide the mass median aerodynamic diameter (MMAD) and the geometric standard deviation for the distribution. Particle size distribution of the aerosol shall be determined as part of the development of test atmosphere generation techniques during the first week of exposures and checked monthly during the in-life study and with each new batch. The initial particle size distribution determination shall be done by impactor and shall have a MMAD of less than 3 microns with a sigma g of less than 3.

The above citations confirm that the molybdenum trioxide particle sizes 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 of respirable size)'.

We look forward to your response in due course.

Yours sincerely

Sandra Carey, HSE Executive Please respond to: sandracarey@imoa.info

[4] OECD Guidance document on inhalation toxicity studies, Series on Testing & Assessment, No. 39, Second edition, 6 July 2018. Page 41, paragraph 108

[5] Specifications for the conduct of studies to evaluate the toxic and carcinogenic potential of chemicals, biological and physical agents in laboratory animals for the National Toxicology Program (NTP). Section IV Chemistry, page 10 paragraph 13.