Comment Submissions - Public Comment Period and Workshops on the Draft Reference Exposure Levels for Chromium (Trivalent) and Inorganic Water-Soluble Trivalent Chromium Compounds

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Comment:
On behalf of the Specialty Steel Industry of North America (SSINA), attached please find comments regarding the proposed RELs for Trivalent Chromium.

Comments of the Specialty Steel Industry of North America

to

California Office of Environmental Health Hazard Assessment

regarding

Draft Reference Exposure Levels for Chromium (Trivalent) and Inorganic Water-Soluble Trivalent Chromium Compounds

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Comments of the Specialty Steel Industry of North America

On behalf of the Specialty Steel Industry of North America (SSINA), we appreciate the opportunity to submit the following comments on the draft reference exposure levels (RELs) for chromium (trivalent) and inorganic water-soluble trivalent chromium compounds proposed by the California Office of Environmental Health Hazard Assessment (OEHHA). As detailed below, the proposed draft RELs are not scientifically justified for application to elemental trivalent chromium (Cr(III)), which is well-known to be insoluble. SSINA urges OEHHA to limit the scope of the proposed RELs to water-soluble Cr(III) compounds upon which the analysis is largely based. Moreover, the risk evaluation, particularly with respect to allergic sensitization and asthma, is of questionable validity due to reliance on studies in which individuals already were sensitized by exposure to hexavalent chromium (Cr(VI)) before being exposed to Cr(III).

SSINA is the primary national trade association of producers of specialty steel products, including stainless, electric, tool, magnetic, and other alloy steels. SSINA members account for over 90 percent of the specialty steel manufactured in the United States. As major producers of chromium-containing steel alloys, SSINA is interested in ensuring that regulation of chromium is based in sound and accurate science. Accordingly, we are deeply concerned by the proposed RELs and, if adopted, their inappropriate application to insoluble elemental Cr(III).

(1) It is Fundamentally Inappropriate to Group Insoluble Elemental Trivalent Chromium with Water-Soluble Trivalent Chromium Compounds for Toxicological Evaluations

Toxicologically, there is a fundamental difference between insoluble elemental Cr(III) and water-soluble Cr(III) compounds. Due to essential differences in solubility, the respective bioavailability and resulting potential toxicity of these two different forms of Cr(III) are dramatically different, and thus not comparable. Unfortunately, the proposed draft RELs are based on toxicological findings relevant only to water-soluble Cr(III) compounds and that analysis should not be extended to insoluble elemental Cr(III).

Table 1a (page 1 of the *Technical Support Document*[1]) states that the water solubility of Cr(III) is "Not Available." This is misleading. While there apparently is not a published numeric value for the water solubility of elemental Cr(III), OEHHA should recognize that the practical insolubility of Cr(III) is widely accepted. Numerous authoritative publications document the insolubility of the large majority of forms of Cr(III) found in the environment. For example, the Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Chromium*[2] plainly states:

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1 Page references, unless otherwise noted are to *OEHHA, Chromium (Trivalent) and Inorganic Water-Soluble Trivalent Chromium Compounds Reference Exposure Levels: Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* (January 2021).

2 https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=62&tid=17

> Chromium compounds are most stable in the trivalent state under environmental conditions . . . . The solubility of chromium compounds varies, depending primarily on the oxidation state. Trivalent chromium compounds, with the exception of acetate, hexahydrate of chloride, and nitrate salts, are generally insoluble in water….

The ATSDR *Toxicological Profile* further specifies (in Table 4-2) that of Cr(III) compounds, including chromium oxide and ferrochromite, among others, are "insoluble." The World Health Organization[3], National Library of Medicine[4], U.S. Environmental Protection Agency[5], and many other resources similarly recognize that most forms of Cr(III) are insoluble.

The failure to account for this fundamental difference in solubility, and therefore bioavailability and toxicity, renders the proposed draft RELs inapplicable to *insoluble* elemental Cr(III). OEHHA must revise the scope of the draft RELs accordingly.

(2) The Allergic Sensitization and Asthma Risk Evaluation is Based on Studies of Individuals First Sensitized by Exposure to Cr(VI) Before Being Exposed to Cr(III)

The risk evaluation for allergic sensitization and asthma is of questionable validity because it relies on studies of individuals previously sensitized by exposure to Cr(VI) prior to exposure to Cr(III). Extending the findings from those studies to a broader risk evaluation is improper, particularly given that population exposure to Cr(VI) is substantially lower today (as detailed in the next section).

Moreover, as noted on page 41, most of the studies cited with respect to allergic sensitization and asthma risk were performed several decades ago, when study methodologies were significantly less rigorous and there was much more widespread environmental exposure to Cr(VI). Notably, as stated on page 44, "[a]ccording to the National Institutes of Health (2018), Cr(III)-related dermatitis is usually seen only with prior sensitization to Cr(VI)." The relevance of these studies to a current risk evaluation for Cr(III) is questionable.

- (Page 41) Fregert and Rohrsman (1964) "primarily involved 22 test subjects who developed eczematous inflammation after topical exposure hexavalent $K_2Cr_2O_7$ (0.1 M), and had reactions to intracutaneous injections of $K_2Cr_2O_7$ (0.001 M)."

- (Page 42) Samitz and Shrager (1966) "reported the results of patch test results in five chromate [Cr(VI)]-sensitive subjects challenged with $K_2Cr_2O_7$ (0.1% - 0.25%) and various Cr(III) compounds including 0.1% - 5% $CrCl_3$, 0.5% - 5% $Cr(NO_3)_3$, and 0.5 - 1% $Cr_2(SO_4)_3$."

- (Page 45) Novey *et al*. (1983) "According to their case report, a 32-year old white male patient, with no pets, personal/family history of allergies, or previous episodes

[3] https://www.who.int/water_sanitation_health/dwq/chemicals/chromium.pdf

[4] https://www.ncbi.nlm.nih.gov/books/NBK158859/table/T18/

[5] https://www.epa.gov/sites/production/files/2016-09/documents/chromium-compounds.pdf

of asthma, lung disease, or tuberculosis exposure, developed a productive cough with clear sputum, wheezing, and dyspnea (difficult, labored breathing) less than 2 weeks after starting a new job electroplating with Cr and Nickel (Ni)." The plating process employed Cr(III) sulfate solutions. As noted on page 46: "These processes take place in large bath tanks and result in aerosolization of water and Cr(III) and/or Cr(VI) in a mist." Nickel also is a known sensitizer: (page 47) "The tests with Ni compounds are mostly not discussed herein, but the patient did exhibit an acute drop in spirometric values and exacerbation of symptoms (chest tightness, wheezing) upon inhaling fumes from a nickel sulfate solution versus a control solution."

- (Page 48) Park *et al*. (1994) evaluated "4 males with occupational asthma resulting from work-place exposure to Cr…. The subjects were ex-smokers ranging in age from 26-54 years and working in metal plating, cement, or construction industries. It is unknown to OEHHA whether the Cr(III) or Cr(VI) species caused the subjects' occupational asthma, but Cr(VI) sensitization is known to occur in these occupations."

(3) The Estimated Prevalence of Cr(VI) Allergy in the California Population is Based on Studies that are Outdated, Involve Small Cohorts, and/or Reflect Unfounded Assumptions

- (Page 52) Proctor *et al.* (1998) "reviewed skin patch studies from 1950-1996" and "used data from the North American Contact Dermatitis Group (NACDG) to determine the prevalence of Cr(VI) allergy in a clinical cohort from the US and two studies from the Netherlands (Lantinga *et al.*, 1984; van Ketel, 1984)." Given substantial reductions in Cr(VI) exposure in the population over the last several decades, the continued viability of the conclusions of this study are questionable.

- (Page 53) Weston *et al*. (1986) "examined 314 'healthy' children (166 boys, 148 girls), age ≤18 years, for skin patch test responses to 20 different substances including hexavalent $K_2Cr_2O_7$ (0.5% in petrolatum)." "The source of chromium sensitization was assumed by the authors to be leather athletic shoes, consistent with previous studies on foot dermatitis and suspected contact dermatitis in children <12 years of age."

- (Page 54) "OEHHA found three other patch test studies performed in children; however, these studies were conducted in Europe with individuals suspected of having contact dermatitis. The prevalence of Cr(VI) allergy was approximately 5% for all three studies: 6 of 125 Scottish children <12 years of age (Rademaker and Forsyth, 1989), 9 of 168 Danish children ≤14 years of age (Veien *et al*., 1982), 17 of 349 Polish children age 3 - 14 years and 34 of 626 Polish children age 3 - 16 years (Rudzki and Rebandel;1996)."

- (Page 54) OEHHA incorrectly states: "A prevalence of 0.08% - 7% would account for approximately 316,456 – 2,768,993 Californians based upon the most recent California population estimate of 39,557,045 from the US Census Bureau (USCB,

2018)." The math is incorrect. A prevalence of 0.08% equates to approximately 31,646 Californians.

(4) The Rodent Toxicity Studies Have Significant Methodological Problems and OEHHA Conflates Insoluble Elemental Cr(III) Results with Findings Relevant to Water-Soluble Cr(III) Compounds Only

- (Page 58) OEHHA acknowledges "Acute exposure studies in rodents indicated that inhalation of water-soluble Cr(III) compounds at concentrations ≥2.8 mg/m^3 (2800 μg/m^3) may produce inflammation and cell membrane damage in the lungs and initiate edematous buildup in alveolar capillaries. However, some of these effects may have been related to the acidity of the tested Cr(III) salt."

- (Page 59) Henderson *et al*. (1979) describes a dosing of nebulized trivalent $^{51}CrCl_3$ x $6H_2O$ aerosol at concentrations of 0, 2.8, or 77 mg/m^3 (0, 2,800, or 77,000 μg/m^3) for 30 minutes. Such dramatically large steps in dosing result in an inability to accurately identify the NOAEL. On page 82: OEHHA identifies the LOAEL at 77 mg/m^3 , then uses the next lowest dose (2.8 mg/m^3) as the NOAEL. In fact, the NOAEL may be substantially higher given the significant differences in dose. Further, again on page 82, OEHHA applies the results of this study to insoluble Cr(III), though the study was conducted on soluble $CrCl_3$ x $6H_2O$.

- (Page 60) Johansson and Cramner (1986) studied water-soluble Cr(III) nitrate, findings for which are not relevant to insoluble Cr(III) compounds.

- (Page 61) Derelanko *et al*. (1999) studied Cr(III) oxide (Cr_2O_3; CAS 1308-38-9) and basic Cr(III) sulfate [$Cr2(OH)_x(SO4)_y$ $NaSO_4$ $2H_2O$). Though OEHHA acknowledged (on page 62) that "Derelanko et al. (1999) suggested that the differential toxicities of basic Cr(III) sulfate and Cr_2O_3 were likely due to differences in physicochemical characteristics (e.g. acidity and water solubility) that influence deposition, tissue responses, and clearance," they did not acknowledge the different toxicities elsewhere in the document, including in the conclusions. (Page 69) OEHHA also acknowledges that "No notable clinical observations or significant ($p \leq 0.05$) changes in BW, hematology, serum biochemistry, or urinalysis parameters were reported in Cr_2O_3-exposed rats relative to controls."

(5) The Derived RELs are Based on Inaccurate Selection of a LOAEL, Erroneous Application of Results from Water-Soluble Cr(III) Compounds to Insoluble Elemental Cr(III) and Inappropriate Uncertainty Factors

Regarding development of RELs for insoluble elemental Cr(III), even if sensitization is accepted as an endpoint of concern, it makes no sense to establish the standard based on endpoints relevant to water-soluble Cr(III) compounds: (1) for the Acute REL, the finding is based on based upon enzyme release consistent with cell membrane damage and tissue injury, and increased AP, ALP, and β-glucuronidase activity in lung tissue and/or BALF endpoints; and (2) for the Chronic and Acute 8-hour RELs, the finding is based on increased relative lung weights in males due to

granulomatous inflammation, Type II cell hyperplasia, and histiocytosis in lymphoid tissue endpoints. In both cases, the relevant endpoints are applicable only to water-soluble Cr(III) compounds. In addition, the derived RELs are based on inaccurate selection of a LOAEL and the application of inappropriate uncertainty factors.

- Acute REL (page 82)
  - Based on results from Henderson *et al.* (1979) on water-soluble Cr(III) compounds, and improperly applied to insoluble elemental Cr(III).
  - Used a NOAEL of 2.8 mg/m^3, based on an identified LOAEL of 77 mg/m^3 (see above).
  - Applied a significantly over-conservative cumulative uncertainty factor of 200, based upon interspecies uncertainty factors of 2 for toxicokinetic differences and √10 for toxicodynamic differences, and intraspecies uncertainty factors of √10 for toxicokinetic differences and 10 for toxicodynamic differences.
- Chronic REL (page 86)
  - Inappropriately applied results from Derelanko *et al.* (1979) on water-soluble Cr(III) compounds to insoluble elemental Cr(III). This was done despite OEHHA's acknowledgment (on page 62) that "Derelanko et al. (1999) suggested that the differential toxicities of basic Cr(III) sulfate and Cr_2O_3 were likely due to differences in physicochemical characteristics (e.g. acidity and water solubility) that influence deposition, tissue responses, and clearance." Similarly, OEHHA acknowledges (on page 91) that "[i]n attempting to derive a chronic REL for inorganic water-insoluble Cr(III) compounds, OEHHA was limited by a lack of appropriate studies. … *This prevented development of a REL for inorganic water-insoluble Cr(III) compounds*." (emphasis added) This latter statement dramatically underscores the key concern raised in our comments, and makes clear that the proposed RELs are not properly applied to insoluble elemental Cr(III), which also has significant physicochemical differences that are directly relevant to toxicity.
  - Applied a significantly over-conservative cumulative uncertainty factor of 600, based upon a subchronic uncertainty factor of 3, interspecies uncertainty factors of 2 for toxicokinetic differences and √10 for toxicodynamic differences, and intraspecies uncertainty factors of √10 for toxicokinetic differences and 10 for toxicodynamic differences.
- Acute 8-hour REL (page 92)
  - As with the chronic REL, the acute 8-hour REL was derived by applying results from Derelanko *et al.* (1979) on water-soluble Cr(III) compounds to insoluble elemental Cr(III). This was done despite OEHHA's

acknowledgment (on page 62) that "Derelanko et al. (1999) suggested that the differential toxicities of basic Cr(III) sulfate and Cr_2O_3 were likely due to differences in physicochemical characteristics (e.g. acidity and water solubility) that influence deposition, tissue responses, and clearance." Similarly, OEHHA acknowledges (on page 91) that "[i]n attempting to derive a chronic REL for inorganic water-insoluble Cr(III) compounds, OEHHA was limited by a lack of appropriate studies. … *This prevented development of a REL for inorganic water-insoluble Cr(III) compounds.*" As noted above, these same factors (*i.e.*, physicochemical differences) that prevent development of a REL for insoluble Cr(III) compounds are also applicable to insoluble elemental Cr(III).

- Applied a significantly over-conservative cumulative uncertainty factor of 600, based upon a subchronic uncertainty factor of 3, interspecies uncertainty factors of 2 for toxicokinetic differences and √10 for toxicodynamic differences, and intraspecies uncertainty factors of √10 for toxicokinetic differences and 10 for toxicodynamic differences.

* * * * *

For the foregoing reasons, OEHHA must reframe the proposed draft RELs as applicable only to water-soluble Cr(III) compounds. As highlighted above, the agency's own analysis makes clear that the studies and analysis prevent development of RELs for *insoluble* forms of Cr(III), including elemental Cr(III) which is widely recognized as practically insoluble. Extending findings relevant to soluble compounds to insoluble forms of chromium that have fundamentally different bioavailability and potential toxicity is scientifically unjustified and inappropriate from a policy perspective. SSINA urges OEHHA to correct the scientific record and make clear that the proposed RELs do not apply to insoluble elemental Cr(III).

Respectfully submitted,

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