Responses to Public Comments on the Draft Reference Exposure Levels for Chromium, Trivalent (Inorganic Water-Soluble Compounds)

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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On January 8, 2021, the Office of Environmental Health Hazard Assessment (OEHHA) released the draft document (Document, hereafter), *Chromium (Trivalent) and Inorganic Water-Soluble Trivalent Chromium Compounds Reference Exposure Levels: Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* to solicit public comment. The document is available online at https://oehha.ca.gov/media/downloads/air/document/criiirelpubliccommentreviewdraft010821.pdf. Comments on the draft RELs for Cr(III) and Inorganic Water-Soluble Cr(III) Compounds were received from the Specialty Steel Industry of North America (SSINA). Responses to comments received on the draft Reference Exposure Levels (RELs) are provided below. The pages referenced in OEHHA's responses are from the aforementioned Document unless stated otherwise.

Background

The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360 (b) (2)). OEHHA developed a Technical Support Document (TSD; 2008) in response to this statutory requirement that describes methodology for deriving acute, chronic, and 8-hour RELs. RELs are airborne concentrations of a chemical that are not anticipated to result in adverse noncancer health effects for specified exposure durations in the general population and sensitive subpopulations thereof. In particular, the methodology explicitly considers possible differential effects on the health of infants, children, and other sensitive subpopulations in accordance with the mandate of the Children's Environmental Health Protection Act (Senate Bill 25, Escutia, Chapter 731, Statutes of 1999, Health and Safety Code Sections 39669.5 et seq.).

The methods described in the TSD were used to develop acute, chronic, and 8-hour RELs for inorganic water-soluble trivalent chromium [Cr(III)] compounds presented in the draft document. Insolubility of a Cr(III) compound in water was defined in the

Document as having a water solubility of ≤100 mg/L at 20˚C (USP, 2015). Cr(III) compounds that have a water solubility of >100 mg/L at 20˚C were considered water-soluble. This definition of solubility is not binding on other OEHHA documents and programs.

Because of the level of scientific information contained below, those using reading-assistive software should consider enabling pronunciation of punctuation and symbols, and listen for links to footnoted text.

SSINA Comment 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:

> 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.'

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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

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."

Response to SSINA Comment 1

OEHHA agrees that Cr(III) compounds are often insoluble in water, and cites the 2012 ATSDR *Toxicological Profile* in support of this statement. OEHHA has changed the REL chemical listing from "Chromium (Trivalent) and Inorganic Water-Soluble Trivalent Chromium Compounds" to "Chromium, Trivalent (Inorganic Water-Soluble Trivalent Chromium Compounds) and added to the Document an explicit statement that the RELs are not applicable to water-insoluble Cr(III) compounds or elemental (metallic) chromium, i.e., Cr(0). OEHHA further states, the "Cr(III)" abbreviation used in the draft "is meant to represent bound and unbound forms of trivalent chromium." When possible, distinctions have been made to specify Cr(III) compounds, and the Cr(III) ion." The revised Document contains minor edits throughout the text that reflect these distinctions.

However, the RELs are based on the toxic effects produced by the Cr(III) ion. This because its formation, from the dissolution of water-soluble Cr(III) compounds, has been linked to toxic responses. As stated in the Document (page 21), "Free intracellular Cr(III) cations are able to produce intracellular ROS through direct reactions with cellular molecules or indirect reactions through cellular stimulation (Wise *et al*, 2019). Hydroxyl radicals ($^{*}OH$) and hydroxide ions (OH^{-}), for example, can be produced by Cr(III) through interactions with H_2O_2 and superoxide radicals ($^{*}O_2^{-}$) in Haber-Weiss reactions…Cr(III) and ROS can complex with ligands and attack cell membrane lipids and proteins to decrease the antioxidant capabilities of the cell and/or produce toxic responses related to oxidative stress (ATSDR, 2011; Długosz *et al.*, 2012). Such responses could include health effects like chronic inflammation and cytotoxicity (Balamurugan *et al.*, 2002; Wise *et al.*, 2019)" as indicated by the critical effects

[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

observed in the Derelanko *et al.* (1999) and Henderson *et al.* (1979) studies and used to derive the chronic/8-hour and acute RELs, respectively.

SSINA Comment 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 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.'"

Response to SSINA Comment 2

As noted in the comment above, and in the Document, the volunteers in the early studies by Fregert and Rohrsman (1964) and Samitz and Shrager (1966) were known to be exposed and sensitive to potassium dichromate ($K_2Cr_2O_7$), a Cr(VI) compound, prior to exhibiting cross-reactivity reactions to the tested Cr(III) compounds.

However, the same cannot be said for subjects in the later studies by Novey *et al.* (1983) and Park *et al.* (1994). In these studies, it is not at all clear which Cr species caused their initial sensitization. With regard to nickel exposure, multiple studies performed in humans and guinea pigs failed to find cross-reactivity reactions between chromium and nickel (Bregnbak *et al.,* 2015). Rather than cross-reactivity, concomitant allergies to chromium and nickel could be explained by their co-occurrence during the sensitizing exposures. These latter two statements have been added to the revised Document.

OEHHA recognizes that the number of Cr-sensitized individuals is low, and the number of potentially confounding variables (e.g., exposure to other allergenic metals) in the chromium industry is high. However, the controlled and comprehensive guinea pig studies by Gross *et al.* (1968) clearly show, in at least five different experiments, that allergic sensitization to a water-soluble Cr(III) compound can occur independent of prior exposure to Cr(VI) species. This is especially true if skin permeability is increased by physical or chemical means prior to contact.

SSINA Comment 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."

Response to SSINA Comment 3

The 2012 ATSDR *Toxicological Profile for Chromium* that was referenced in Comment 1 by the SSINA provides an estimate of 0.08%-7% for chromium sensitivity in the general US population. This was the most recent prevalence estimate found by OEHHA. Because the ATSDR did not cite the source of this information, OEHHA summarized studies which may have been used to derive the prevalence estimate of 0.08%-7%. Given Cr(VI)-to-Cr(III) cross-reactivity, which was acknowledged by SSINA (Comment 2), this range was used by OEHHA to calculate a worst-case estimate of the Cr(III) allergy prevalence in California.

We thank the SSINA for the math correction. The Document has been updated to reflect the correct lower-bound prevalence estimate of approximately 30,000 Californians.

SSINA Comment 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 $^{51}CrCl_3 \times 6H_2O$ 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 $CrCl_3 \times 6H_2O$.
- (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 [$Cr_2(OH)x(SO_4)y\ NaSO_4\ 2H_2O$). 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.'"

Response to SSINA Comment 4

The RELs do not apply to insoluble Cr(III) compounds as mentioned in OEHHA's response to Comment 1.

Though the concentrations used in the Henderson *et al.* (1979) study may be characterized as large step increments, there are no other data available indicating that the 2.8 mg/m^3 concentration should not be considered the NOAEL for that study. However, OEHHA has revised the Document to address this issue by including an acute REL calculation using the 15 mg Cr(III)/m^3 LOAEL as the Point of Departure (POD), the same time-adjusted exposure and HEC adjustments, and all of the same UFs except the UF_L. In the acute REL derivation, the UF_L is 1, since a NOAEL is used

as the POD. In the alternative derivation, a default UF_L of 6 was used to account for use of a LOAEL for mild effects versus the NOAEL (OEHHA, 2008).

These calculations resulted in an alternative acute REL approximately 4.5-times higher than the REL derived using the NOAEL, and they have been added to the revised Document as a point of comparison. Given OEHHA's 2008 noncancer TSD indicates use of a NOAEL over a LOAEL is preferred to derive a REL, and calculations performed with the 0.55 mg Cr(III)/m^3 NOAEL, versus the 15 mg Cr(III)/m^3 LOAEL, would result in a more health-protective draft acute REL value, the NOAEL was retained as the POD used to derive the acute REL.

It should be noted that OEHHA has revised its calculation of the acute REL to account for the percentage of Cr(III) in the aerosol. The $^{51}CrCl_3 \times 6H_2O$ concentrations of 0, 2.8, or 77 mg/m^3 were converted by OEHHA to Cr(III)-equivalent concentrations of approximately 0, 0.55, or 15 mg/m^3, which accounted for the 19% fraction of chromium. Use of metal equivalent concentrations is supported by OEHHA's 2012 REL for nickel and 2020 cancer evaluation for cobalt. Use of the 0.55 mg Cr(III)/m^3 concentration as the NOAEL along with all of the adjustments entailed in the Document yielded an acute REL of 0.48 µg/m^3 (0.0005 mg/m^3).

With regard to the Derelanko *et al.* (1999) study used to derive the draft 8-hour and chronic RELs, the true impact of the aerosol pH is unknown to OEHHA and the study authors due to factors, such as the relative concentrations of acidic sulfate and ammonia, which were mentioned in Section 6.3 of the Document but not measured in the study.

Notwithstanding those limitations, OEHHA does not believe use of basic chromium sulfate by Derelanko *et al.* (1999) represents a methodological problem. Rather, the observed responses to basic chromium sulfate are representative of some of the more severe health impacts possible with repeated exposure to inorganic water-soluble Cr(III) compounds. As stated in the Document, basic chromium sulfate has been found in chrome-plating bath solutions. It is also produced by leather-tanning (US EPA, 1984) and khaki clothes-dying operations, and used to produce other chromic compounds. Resulting air emissions of basic chromium sulfate from such operations are relevant to the Hot Spots program, especially since Cr(III) has already been identified as a Toxic Air Contaminant through the listing of chromium and chromium compounds as Hazardous Air Pollutants.

It should be noted that the chronic and 8-hour draft RELs have been recalculated based upon new BMDS modeling using the Cr(III) concentration equivalents (0, 3, 10 and 30 mg/m^3) from the Derelanko *et al.* (1999) study.

SSINA Comment 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 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)."

Response to SSINA Comment 5

Most of this comment was addressed in OEHHA's responses to the comments 1 and 4, above.

The uncertainty factors assessed in the draft RELs were based upon guidance from OEHHA's 2008 TSD and are in alignment with previously published RELs and data available at this time. With regard to the Acute REL,

1. a UF_L of 1 was chosen due to the mild effect, which produced no statistically significant changes in enzyme levels at 0.55 mg Cr(III)/m^3 (Henderson *et al*., 1979), and was consistent with a severity level of 0-1 (OEHHA, 2008). This is the lowest UF_L that can be assigned.
2. a toxicokinetic interspecies UF (UF_{A-k}) of 2 was used to account for any residual toxicokinetic differences between the non-primate animal model and humans that were not addressed by the human equivalent concentration (HEC) approach. According to OEHHA's TSD (2008), the HEC accounts for only a portion of the UF_{A-k}, leaving a residual value of 2 that should be assessed. At least one study (Menache *et al*., 1997) found that due to different allometric scaling techniques/equations, the estimated upper respiratory tract surface areas for animals and humans, and thus the resulting HECs, could vary by a factor of 2. A UF_{A-k} of 2 is the lowest value that can be assigned.
3. a toxicodynamic interspecies UF (UF_{A-d}) value of $\sqrt{10}$ was assigned to account for the lack of data on toxicodynamic interspecies differences between the hamster model and humans. A UF_{A-d} of $\sqrt{10}$ is the default when using the HEC approach (OEHHA, 2008) and is the lowest value that can be assigned.
4. a toxicokinetic intraspecies UF (UF_{H-k}) of $\sqrt{10}$ was included to account for variability that may occur due to lower protein binding; hepatic and renal clearance; and metabolic enzyme (e.g., cytochrome P450) activity, abundance, and expression in infants versus adults (Lindeman et al., 2000; Louro et al., 2000; Lu and Rosenbaum, 2014; Sadler et al., 2016). The toxicokinetics of Cr(III) is such that it does not appear to accumulate more in fetuses, infants, and children versus adults, in a manner similar to lead, for example. Therefore, use of a higher UF_{H-k} was unsupported.
5. a toxicodynamic intraspecies UF (UF_{H-d}) of 10 was added in consideration of potentially increased sensitivity of children relative to adults during critical developmental windows. In the study by Henderson *et al*., lung cell death and tissue damage were observed. Alveolar number, size, and complexity change,

exponentially at times, between infancy and adulthood. Insults to the lungs during critical time-frames can produce irrecoverable damage and stunted lung development. Potential for sensitization (Fregert and Rorsman, 1964; Samitz and Shrager, 1966) and exacerbation of asthma (Novey *et al*., 1983; Park *et al*., 1994) were also considered in designation of the $UF_{H\text{-}d}$.

The UFs were mostly the same in the acute, chronic, and 8-hour REL derivations apart from the inclusion of a subchronic UF (UF_S) of $\sqrt{10}$ which was assessed in the chronic and 8-hr RELs according to OEHHA's guidelines (2008) to account for the 13-week study duration, approximately 12% of the estimated lifetime of a rat.

The additional clarifications provided in this response were added to the revised Document.

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