Air Toxics Hot Spots Program

Noncancer Reference Exposure Levels

Chromium, Trivalent
(Inorganic Water-Soluble Compounds)

Office of Environmental Health Hazard Assessment

Scientific Review Panel Workshop
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Trivalent Chromium, Cr(III), and Inorganic Water-Soluble Cr(III) Compounds

- **Solubility:** Cr(III) compounds that have a water solubility of >100 mg/L at 20˚C are considered water-soluble.

- **Examples:**

  - **Chromic chloride hexahydrate ($CrCl_3 \times 6H_2O$):** used in colorants, and chrome-plating solutions

  - **Basic chromium sulfate:** used in leather tanning and chrome-plating solutions

Selected Examples of Inorganic Cr(III) Compounds

Molecular Formula	Name	Molecular Weight (g/mol)	Chemical Abstracts Service #	Water Solubility
$CrCl_3 \times 6\ H_2O$	Cr(III) chloride hexahydrate	266.44	10060-12-5	Soluble
$CrCl_3$	Cr(III) chloride	158.35	10025-73-7	Insoluble
$Cr_2(OH)_x(SO_4)_y$ $NaSO_4\ 2H_2O$	Basic Cr(III) sulfate	Variable	Variable	Soluble
$Cr_4(SO_4)5(OH)_2$	As above	722.31	39380-78-4	Soluble
$Cr(HO_4S)_3$	As above	343.21	As above	Soluble
$Cr(SO_4)(OH)$	As above	165.07	12336-95-7	Soluble

Why Develop Cr(III) RELs?

- Replacement for hexavalent chromium in chrome plating processes.
- Potential for inhalation exposure to airborne Cr(III) in community and off-site workers.
- No previously developed Cr(III) RELs.
- Cr(III) inhalation toxicity data available for REL development.

Toxicokinetics

- **Toxicokinetics of inhaled Cr(III):** variable and influenced in part by physicochemical aerosol characteristics (e.g. size, surface area, and water-solubility), and exposure routes, doses, and dose rates.

- **Potential absorption pathways for water-soluble Cr(III) species**

  1) Deposition in the upper respiratory tract. Dissolution and translocation to blood through the mucus. (particle size > 5 μm)
  2) Deposition in gas exchange region. Rapid absorption into blood and extra-pulmonary translocation, or binding to proteins in lungs with retention and slower absorption into blood. (particle size < 5 μm).

Toxicokinetics (continued)

- **Distribution**
  1) Approximately 2-fold greater partitioning into plasma vs whole blood.
  2) Wide distribution to gastrointestinal tract, bone, kidney, and liver within the first 24 hours.

- **Metabolism**
  1) Binding to biomolecules generally excludes Cr(III) from the intracellular space.
  2) Cellular entry occurs via phagocytic or non-specific diffusion mechanisms.
  3) Free intracellular Cr(III) can produce reactive oxygen species which may decrease antioxidant capabilities and/or produce toxic responses.

Toxicokinetics (continued)

- **Excretion of absorbed chromium**

  1) Approximately 50% is excreted via urine, 5% is excreted via feces, and the rest is deposited in deep body compartments, e.g. bone and soft tissue.

  2) Eliminated from the body in a rapid phase representing clearance from the blood, and a slower phase representing clearance from tissues.

  3) Occupational exposure studies suggest renal excretion of approximately half of the absorbed dose took <12 hours.

Acute REL: Key Study

- **Acute RELs:** levels at or below which infrequent one-hour exposures are not expected to result in adverse non-cancer health effects.
- **Study:** Henderson *et al.*, 1979
- **Study population:** Syrian hamsters; n = 96 (4/sex/group/time-point)
- **Exposure:** Nose-only inhalation of unstated carrier solvent (control) or Cr(III) at 0, 0.55, or 15 mg/m^3 as nebulized $^{51}CrCl_3 \times 6H_2O$ (isotope of chromium chloride hexahydrate) aerosol at 0, 2.8, or 77 mg/m^3 for 30 minutes.

Acute REL: Key Study (continued)

- **Sacrifice:** 2 hours or 1, 7, or 21 days post exposure (PE). Lung tissue and bronchoalveolar lavage fluid (BALF) collected.

- **No Observable Adverse Effect Level (NOAEL):** 0.55 mg Cr(III)/m^3

- **Critical Effects at 15 mg Cr(III)/m^3 relative to control:**

  1) a sharp 75% increase ($p < 0.05$) in tissue acid phosphatase (AP) activity at 1 day PE with resolution to near-control levels on days 7 and 21 PE;

Acute REL: Key Study (continued)

- **Critical Effects (cont'd):**

  2) an increase of unstated magnitude in tissue β-glucuronidase activity at day 1 PE;

  3) a doubling of tissue alkaline phosphatase (ALP) activity at day 21 PE; and

  4) an increase in BALF AP activity at days 1, 7, and 21 PE, with variable levels of BALF ALP activity at days 1 and 21 PE ($p < 0.05$ for all stated endpoints).

Acute REL Derivation

Key Study	Henderson *et al*., 1979
LOAEL	15 mg Cr(III)/m³
NOAEL (Point of Departure)	0.55 mg Cr(III)/m³
Exposure continuity and duration	once for 0.5 hours (h)
Time-adjusted exposure (K), using Haber's Law	$= C^n \times t$, where n = 1 $= (0.55\ mg/m^3)^1 \times (0.5\ h/1\ h)$ $= 0.27\ mg/m^3$

Acute REL Derivation (continued)

Regional Deposited Dose Ratio (RDDR)	0.35 (from Jarabek, 1995)
Human Equivalent Concentration (HEC)	= RDDR × K = (0.35) × (0.27 mg/m³) = 0.10 mg/m³
LOAEL uncertainty factor (UF_L)	1 (the point of departure (POD) is a NOAEL)

Acute REL Derivation (continued)

Inter-species uncertainty factors

Toxicokinetic (UF_{A-k})	= 2 (for residual toxicokinetic differences not addressed by the HEC approach).
Toxicodynamic (UF_{A-d})	= √10 (lack of toxicodynamic data).

Acute REL Derivation (continued)

Intra-species uncertainty factors

Toxicokinetic (UF_{H-k})	√10 (for variability that may occur between human infants and adults).
Toxicodynamic (UF_{H-d})	10 (potential increased sensitivity of children relative to adults).

Acute REL Derivation Summary

Point of Departure (NOAEL)	0.55 mg/m^3
Time-adjusted Exposure	0.27 mg/m^3
Regional Deposited Dose Ratio (RDDR)	0.35
Human Equivalent Concentration (HEC)	0.10 mg/m^3
LOAEL uncertainty factor (UF_L)	1
Inter-species uncertainty factors	
Toxicokinetic ($UF_{A\text{-}k}$)	2
Toxicodynamic ($UF_{A\text{-}d}$)	√10
Intra-species uncertainty factors	
Toxicokinetic ($UF_{H\text{-}k}$)	√10
Toxicodynamic ($UF_{H\text{-}d}$)	10
Cumulative uncertainty factor	200
Acute REL	0.48 µg/m³ (0.0005 mg/m^3)

Chronic and 8-hour RELs: Key Study

- **Chronic RELs:** levels at or below which adverse non-cancer health effects are not likely to occur in the general human population exposed continuously over a lifetime.
- **8-hour RELs:** designed to protect against daily work week exposures in off-site workers.
- **Study:** Derelanko *et al*., 1999
- **Study population:** CDF® (Fischer 344)/Crl BR VAF/Plus® rats; n = 4-5/sex/group
- **Exposure:** Nose-only inhalation of air or Cr(III) at 0, 3, 10, or 30 mg/m^3 as basic Cr(III) sulfate (pH ≈ 2.8) at 17, 54, or 168 mg/m^3 for 13 weeks (6 hr/day, 5 days/wk).

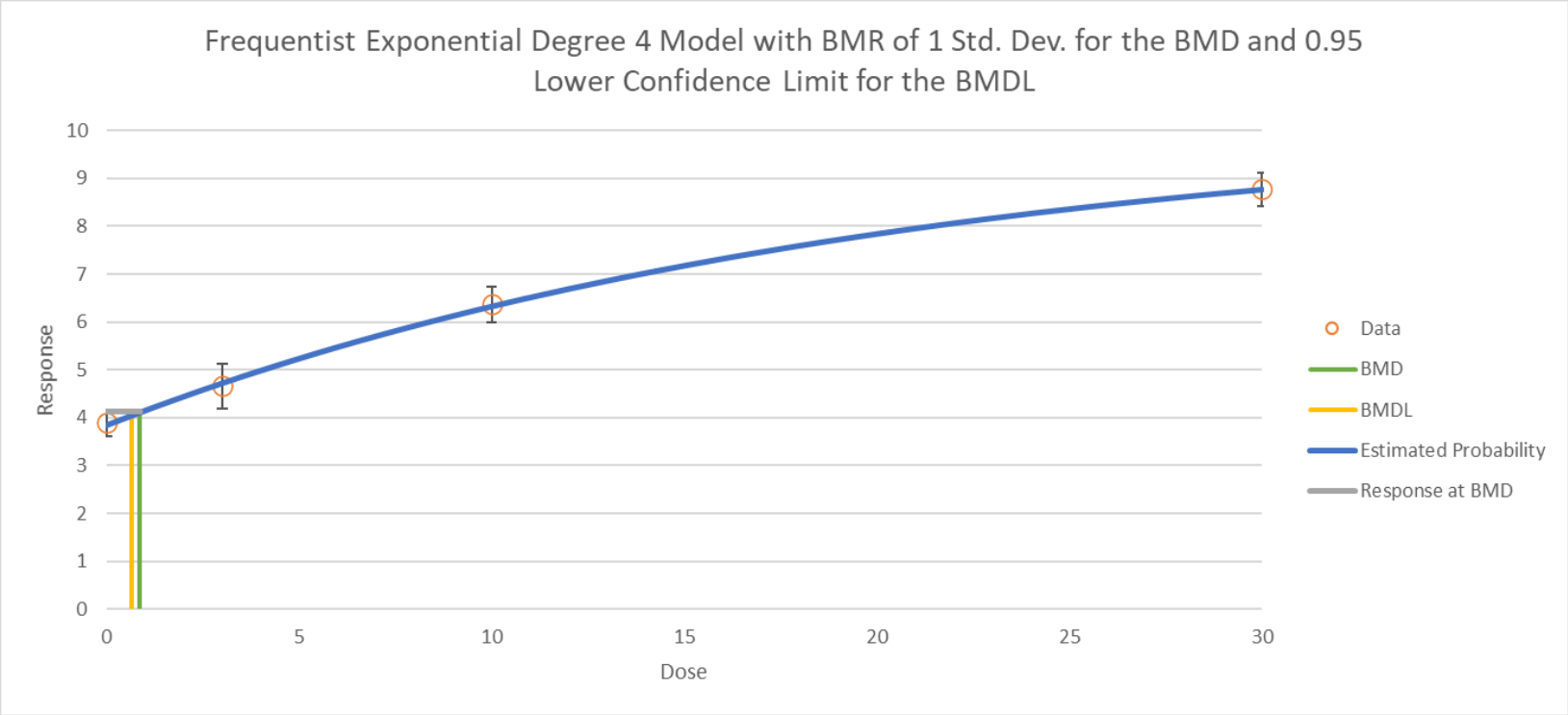
Chronic REL: Key Study (continued)

- **Sacrifice:** Immediately after the last exposure or 13 weeks PE. Blood, BALF, urine, sperm, and various organ tissues collected.
- **LOAEL:** 3 mg Cr(III)/m^3
- **Critical effect:** Increased lung weight relative to bodyweight in males due to granulomatous inflammation, Type II cell hyperplasia, and histiocytosis in lymphoid tissue.

Chronic REL: BMD Analysis of Relative Lung Weights in Rats

Biological Endpoint	Model Type	BMR (mg/m^3)	$BMCL_{SD}$ (mg/m^3)	AIC	p-value
Males (13 weeks PE)	Exponential (4); Homoscedastic; Restricted	0.869	0.656	12.0	0.466
Females (1 day PE)	Hill; Heteroscedastic; Restricted	0.923	0.622	96.8	0.937
Females (13 weeks PE)	Exponential (4); Heteroscedastic; Restricted	0.993	0.646	40.0	0.860
Same as above	Exponential (4); Homoscedastic; Restricted	1.40	0.104	36.0	0.932

BMD Analysis (continued)



The model assumes constant variance among the treatment groups. It uses a benchmark response (BMR) of one standard deviation from the control mean, and the 95% lower confidence limit of the BMR for the benchmark confidence level ($BMCL_{1SD}$). The BMR and $BMCL_{1SD}$ are shown as BMD and BMDL, respectively, in the figure above.

Chronic REL Derivation

Key Study	Derelanko *et al*., 1999
Exposure continuity and duration	13 weeks (6 h/d, 5 d/wk)
Benchmark Concentration ($BMCL_{SD}$)	0.656 mg Cr(III)/m³
Time-adjusted exposure (C_{AVG})	= $BMCL_{SD}$ × (H h/24 h) × (D d/7 d) = (0.656 mg/m³) × (6/24) x (5/7) = 0.117 mg/m³

Chronic REL Derivation (continued)

Regional Deposited Dose Ratio (RDDR)	0.3
Human Equivalent Concentration (HEC)	= RDDR × C_{AVG} = (0.3) × (0.117 mg/m³) = 0.04 mg/m³
LOAEL uncertainty factor (UF_L)	1 ($BMCL_{SD}$ used)
Subchronic uncertainty factor (UF_S)	3 (13-week study duration)

Chronic REL Derivation (continued)

Inter-species uncertainty factors

Toxicokinetic (UF_{A-k})	= 2 (for residual toxicokinetic differences not addressed by the HEC approach).
Toxicodynamic (UF_{A-d})	= √10 (lack of toxicodynamic data).

Chronic REL Derivation (continued)

Intra-species uncertainty factors

Toxicokinetic (UF_{H-k})	√10 (for variability that may occur between human infants and adults).
Toxicodynamic (UF_{H-d})	10 (potential increased sensitivity of children relative to adults).

Chronic REL Derivation Summary

Benchmark Concentration	0.656 mg/m^3
Time-adjusted Exposure	0.117 mg/m^3
Regional Deposited Dose Ratio (RDDR)	0.3
Human Equivalent Concentration (HEC)	0.04 mg/m^3
LOAEL uncertainty factor (UF_L)	1
Subchronic uncertainty factor (UF_S)	3
Inter-species uncertainty factors	
Toxicokinetic (UF_{A-k})	2
Toxicodynamic (UF_{A-d})	√10
Intra-species uncertainty factors	
Toxicokinetic (UF_{H-k})	√10
Toxicodynamic (UF_{H-d})	10
Cumulative uncertainty factor	600
Chronic REL	0.06 µg/m^3

Differences between the Chronic and 8-hour REL Derivations

Parameter	Chronic REL	8-hour REL
Protected Exposure Duration and Continuity	Continuously over a lifetime	Long-term periodic exposure, as often as daily
Time-adjusted Exposure (C_{AVG})	= (0.656 mg/m^3) × (6/24 hours) × (5/7 days) = 0.117 mg/m^3	= (0.656 mg/m^3) × (6/24 hours) × (5/7 days) × (20 m^3/10 m^3) = 0.234 mg/m^3
Human Equivalent Concentration	0.035 mg/m^3	0.070 mg/m^3
Proposed REL	0.06 µg/m^3	0.12 µg/m^3

8-hour REL Derivation Summary

Benchmark Concentration	0.656 mg/m^3
Time-adjusted Exposure	0.234 mg/m^3
Regional Deposited Dose Ratio (RDDR)	0.3
Human Equivalent Concentration (HEC)	0.07 mg/m^3
LOAEL uncertainty factor (UF_L)	1
Subchronic uncertainty factor (UF_S)	3
Inter-species uncertainty factors	
Toxicokinetic ($UF_{A\text{-}k}$)	2
Toxicodynamic ($UF_{A\text{-}d}$)	$\sqrt{10}$
Intra-species uncertainty factors	
Toxicokinetic ($UF_{H\text{-}k}$)	$\sqrt{10}$
Toxicodynamic ($UF_{H\text{-}d}$)	10
Cumulative uncertainty factor	600
8-hour REL	0.12 µg/m^3

Differential Sensitivity of Children

OEHHA found no studies concerning the effects of Cr(III) exposure in children. However, it is likely children would experience similar health effects as adults, possibly to greater severity. In view of:

1) the potential of Cr(III) to produce immune sensitization and allergic asthma; and

2) the higher susceptibility of children to these impacts, especially during critical windows of development

OEHHA considers Cr(III) to be a Toxic Air Contaminant that may disproportionately impact children.

Summary of Proposed RELs

Acute: 0.48 µg/m^3 (4.8 × 10^{-4} mg/m^3)

8-hour: 0.12 µg/m^3 (1.2 × 10^{-4} mg/m^3)

Chronic: 0.06 µg/m^3 (5.9 × 10^{-5} mg/m^3)

Questions?

Public Comments and Responses

During the public comment period, OEHHA received comments from the Specialty Steel Industry of North America (SSINA) regarding the draft REL document (Document, hereafter) released on January 08, 2021. Those comments are addressed below.

Public Comments and Responses

Comment 1: The proposed draft RELs are inapplicable to insoluble elemental Cr(III). OEHHA must revise the scope of the draft RELs accordingly.

Response 1: OEHHA has 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” as the RELs are applicable to the Cr(III) ion.

Public Comments and Responses

Comment 2: The allergic sensitization and asthma risk evaluation is based on studies that

1. involved individuals first sensitized by exposure to Cr(VI) before being exposed to Cr(III); and

2. were performed several decades ago, when study methodologies were significantly less rigorous and there was much more widespread environmental exposure to Cr(VI).

The relevance of these studies to a current risk evaluation for Cr(III) is questionable.

Additionally, nickel is a known sensitizer mostly not discussed in the Document. The patient in the study by Novey et al. (1983) exhibited an acute drop in spirometric values and exacerbation of symptoms upon inhaling fumes from a nickel sulfate versus control solution.

Public Comments and Responses

Response 2: In the later studies by Novey et al. (1983) and Park et al. (1994), it is not clear which Cr species caused the initial sensitization in the human subjects.

With regard to nickel exposure,

- human and guinea pig studies failed to find cross-reactivity reactions between chromium and nickel.
- concomitant allergies to chromium and nickel could be explained by their co-occurrence during the sensitizing exposures.
- 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.

Public Comments and Responses

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.

OEHHA incorrectly states a prevalence of 0.08% would account for approximately 316,456 Californians based upon the most recent California population estimate of 39,557,045 from the US Census Bureau. The math is incorrect. A prevalence of 0.08% equates to approximately 31,646 Californians.

Public Comments and Responses

Response 3: The 2012 ATSDR Toxicological Profile for Chromium

- provided the estimate of 0.08%-7% for chromium sensitivity in the general US population;
- is the most recent prevalence estimate found by OEHHA; and
- did not cite the source of this information.

OEHHA summarized studies which may have been used to derive the prevalence estimate.

Given Cr(VI)-to-Cr(III) cross-reactivity, the 0.08%-7% 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 revised Document reflects the corrected lower-bound prevalence estimate of 31,646 Californians.

Public Comments and Responses

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.

In the 1979 study by Henderson et al., nebulized $^{51}CrCl_3$ x $6H_2O$ aerosol concentrations of 0, 2.8, or 77 mg/m^3 were used. OEHHA identifies the LOAEL at 77 mg/m^3, then uses the next lowest dose (2.8 mg/m^3) as the NOAEL. However, the NOAEL may be substantially higher given the significant differences in dose. Further, OEHHA applies the results of this study to insoluble Cr(III), though the study was conducted on soluble $CrCl_3$ x $6H_2O$.

In the 1999 study by Derelanko et al., some of the effects may have been related to the acidity of the tested Cr(III) salt.

Public Comments and Responses

Response 4: The RELs do not apply to insoluble Cr(III) compounds as mentioned in OEHHA's response to Comment 1.

With regard to the Henderson et al. (1979) study,

- there are no data indicating the 2.8 mg/m^3 concentration should not be considered as a NOAEL.
- use of a NOAEL is preferable to use of a LOAEL when deriving a REL.
- the 2.8 mg/m^3 NOAEL is an appropriate POD for derivation of the acute Cr(III) REL.
- calculations performed with the 2.8 mg/m^3 NOAEL resulted in a more health-protective draft acute REL value of 2.5 µg/m^3 (0.0025 mg/m^3).
- calculations performed with the 77 mg/m^3 LOAEL, the same time-adjusted exposure and HEC adjustments, and all of the same uncertainty factors (UFs) except for the LOAEL uncertainty factor (UF_L) would yield an acute REL of 11 µg/m^3 (0.0112 mg/m^3).

Differences between the Public Comment and SRP Draft Acute REL Derivations

OEHHA has revised its original (public comment) 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 20% 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 a revised acute REL of 0.48 µg/m^3 (0.0005 mg/m^3).

Public Comments and Responses

Response 4 (continued): With regard to the Derelanko et al. (1999) study used to derive the draft chronic and 8-hour 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 not measured in the study.
- OEHHA does not believe the use of basic chromium sulfate by Derelanko et al. (1999) represents a methodological problem.
- the 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.
- basic chromium sulfate has been found in chrome-plating bath solutions. It is also used by leather-tanning and khaki clothes-dyeing operations, and used to produce other chromic compounds.

Public Comments and Responses

Response 4 (continued): 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.

Public Comments and Responses

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.

Response 5: Most of this comment was addressed in OEHHA's responses to 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 LOAEL UF (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.

Public Comments and Responses

Response 5 (continued):

2. a toxicokinetic interspecies UF ($UF_{A\text{-}k}$) 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 HEC approach.

3. a toxicodynamic interspecies UF ($UF_{A\text{-}d}$) value of $\sqrt{10}$ was assigned to account for the lack of data on toxicodynamic interspecies differences between the hamster model and humans. A $UF_{A\text{-}d}$ of $\sqrt{10}$ is the default when using the HEC approach.

Public Comments and Responses

Response 5 (continued):

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.

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. Potential for sensitization and exacerbation of asthma were also considered in designation of the UF_{H-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 $\sqrt{10}$ in the latter two. The UF_S of $\sqrt{10}$ was assessed according to OEHHA's guidelines (2008) to account for the 13-week study duration, approximately 12% of the estimated lifetime of a rat.

Questions?