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Chromium

All Compounds except Hexavalent Chromium

CAS Registry Numbers:

Trivalent Chromium (16065-83-1)

Elemental Chromium (7440-47-3)

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Chapter 1 Summary Tables

A summary of health- and welfare-based values from an acute and chronic evaluation for inhalation exposures to trivalent chromium can be found in Table 1. The values for trivalent chromium are also applicable to elemental chromium and most other valence states of chromium compounds (II, IV and V), although these other states are highly unstable and are unlikely to exist in ambient air. Hexavalent forms of chromium are addressed in a separate development support document (DSD).

Table 1 Health- and Welfare-Based Values

Short-Term Values	**Concentrations as Cr3+**	**Notes**
^{acute}ESL [1 h] (HQ = 0.3)	3.6 µg/m^3 * **Short-Term ESL for Air Permit Reviews**	**Critical Effects:** Increased precursor enzymes that are early indicators of lung damage. Specifically, increased acid phosphotase activity in bronchoalveolar lavage fluid, and increased acid phosphotase and β-glucuronidase activity in lung tissue in Syrian hamsters
acute ReV (HQ = 1.0)	12 µg/m^3 **	**Critical Effects:** Same as above
^{acute}ESL$_{odor}$	---	Odorless
^{acute}ESL$_{veg}$	---	No data found
Long-Term Values	**Concentrations as Cr3+**	**Notes**
^{chronic}ESL$_{nonlinear(nc)}$ (HQ = 0.3)	0.041 µg/m^3 **Long-Term ESL for Air Permit Reviews**	**Critical Effects**: Increased relative lung and trachea weight in male and female rats; widespread inflammatory effects in the nasal cavity, larynx, and lungs; and mediastinal lymph node enlargement
chronic ReV (HQ = 1.0)	0.14 µg/m^3 **	**Critical Effects:** Same as above
^{chronic}ESL$_{linear(c)}$ ^{chronic}ESL$_{nonlinear(c)}$	---	Elemental, trivalent, and divalent chromium compounds are not likely to be carcinogenic to humans
^{chronic}ESL$_{veg}$	---	No data found

* Exceedences of this value for air permits should be minimized since chromium has been identified as a sensitizer

** Values that may be used for evaluation of ambient air monitoring data

Abbreviations used: **HQ**, hazard quotient; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ReV**, Reference Value; **ESL**, Effects Screening Level; ^{acute}**ESL**, acute health-based ESL; ^{acute}**ESL$_{odor}$**, acute odor-based ESL; ^{acute}**ESL$_{veg}$**, acute vegetation-based ESL; ^{chronic}**ESL$_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; ^{chronic}**ESL$_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effect; ^{chronic}**ESL$_{nonlinear(c)}$**, chronic health-based ESL for nonlinear dose-response cancer effect; and ^{chronic}**ESL$_{veg}$**, chronic vegetation-based ESL.

Summary information on the physical/chemical parameters of elemental chromium can be found in Table 2, while similar information on several common compounds of trivalent chromium *(i.e.*, chromium acetate, chromium carbonate, chromium chloride, chromium nitrate, chromium oxide, chromium phosphate, chromium picolinate, and chromium sulfate) can be found in Appendix A (Tables 6 through 13). Some other chromium compounds and their chemical abstract service registry numbers (CAS No's) can be found in Appendix A (Table 14).

Table 2 Chemical and Physical Data – Elemental Chromium

Parameter	**Value**	**Reference**
Molecular Formula	Cr	ATSDR 2009, Chemfinder 2004a
Molecular Weight	51.996 (g/mole)	Chemfinder 2004a
Physical State	Very hard metal, cubic steel, solid crystals	Chemfinder 2004a
Color	Gray, steel gray, silver-gray	ATSDR 2009, Chemfinder 2004a, Fisher 2001
Odor	Odorless	Fisher 2001
CAS Registry Number	7440-47-3	Science Lab 2005a
Synonyms/Trade Names	Chrome; chrom; chromium(0)	ATSDR 2009
Solubility in water	Insoluble, insoluble in common organic solvents	ATSDR 2009
Log K_{ow}	Not applicable	ATSDR 2009
Vapor Pressure	1 mm Hg at 1616 ^{o}C	Science Lab 2005a
Vapor Density (air = 1)	Not available	ATSDR 2009, Chemfinder 2004a
Density (water = 1)	7.20 at 28 ^{o}C	ATSDR 2009, Fisher 2001
Melting Point	1857 ^{o}C, 3375 ^{o}F	ATSDR 2009, Fisher 2001
Boiling Point	2672 ^{o}C, 4784 ^{o}F	ATSDR 2009, Fisher 2001
Conversion Factors	Not applicable	Not applicable

* Summary information for some common trivalent chromium compounds can be found in Appendix A

Chapter 2 Valence States, Major Sources and Uses, Exposure, and Ambient Levels

2.1 Common Valence States of Chromium

According to the World Health Organization (WHO 1988) and the Agency for Toxic Substances and Disease Registry (ATSDR 2009), chromium can occur in each of the oxidation states from -2 to +6; however, only the +2 (divalent), +3 (trivalent), and +6 (hexavalent) states occur naturally. Although stable once produced, the elemental (0) form of chromium does not occur naturally. Chromium compounds in the divalent state are relatively unstable and are easily oxidized to trivalent compounds in air (WHO 1988); although, anhydrous divalent chromium salts can be somewhat stable (OSHA 2006). Compounds in valence states such as +4 (tetravalent) and +5 (pentavalent) usually require special handling procedures as a result of their instability. However, chromium (+4) dioxide (CrO_2) is used in magnetic storage devices. There is evidence that tetravalent and pentavalent chromium compounds are formed as transient intermediates in the reduction of hexavalent chromium to trivalent chromium in the body (OSHA 2006). Hexavalent chromium is typically produced from anthropogenic sources (ATSDR 2009).

Chromium compounds are most stable in the trivalent state and occur in nature in this state, with hexavalent compounds being the second-most stable (ATSDR 2009). According to the United States Environmental Protection Agency (USEPA 1998), trivalent chromium forms stable complexes with both organic and inorganic ligands, while hexavalent chromium exists primarily as oxo-species that are strongly oxidizing. Only the trivalent and hexavalent oxidation states are particularly environmentally relevant for human health, and each of these oxidation states has very different properties and effects on living organisms. Therefore, they must always be examined separately, and valid generalizations of the biological effects of chromium as an element cannot be made (WHO 1988). However, it is common to group elemental, divalent and trivalent species together when considering toxicity (ACGIH 2001, NIOSH 2005). In this DSD, all forms of chromium other than hexavalent forms will be considered together to evaluate the inhalation exposure pathway.

2.2 Sources, Uses, and Routes of Exposure

Chromium occurs primarily in trivalent compounds in animals, plants, rocks, soil, and in volcanic dust and gases (ATSDR 2009). Trivalent chromium is an essential nutrient that is required in small amounts to promote the action of insulin, which allows the body to use sugar, protein, and fat (ATSDR 2009). One trivalent form is chromium picolinate, which is used as a dietary supplement. Chromium is used in the metallurgical industry (to produce stainless steel alloys, alloy cast irons, nonferrous alloys and other miscellaneous materials), in the refractory industry (in various linings for high temperature bricks), and in the chemical industry (in pigments and wood preservatives and for metal finishing and leather tanning) (ATSDR 2009). Lesser amounts are used in drilling muds, as rust and corrosion inhibitors, in textiles, and in toner for copiers.

The most probable route of human exposure to trivalent chromium is through ingestion by eating foods that contain chromium, including many fresh vegetables, fruits, meat, yeast, and grain (ATSDR 2009). People may also be exposed to chromium from using consumer products like household utensils, wood preservatives, cement, cleaning products, textiles, and tanned leather, or in occupational settings. Specific industries that may involve exposure to trivalent chromium include the ferrochromium industry, production of chrome pigments, and leather tanning, while specific occupations where one may be exposed to trivalent chromium compounds include painters, candle makers, dye makers, printers, rubber makers, and cement workers (ATSDR 2009). Dermal exposure to chromium compounds, including trivalent compounds, can cause contact dermatitis in sensitive individuals (ATSDR 2009). Inhalation exposure is discussed in Section 2.3. See WHO (1988), ATSDR (2009), USEPA (1990) and USEPA (1998) for additional source and use information.

2.3 Inhalation Exposure and Ambient Levels of Chromium in Air

Although ingestion is the most common route of exposure to chromium, chromium exposure can also occur via inhalation. Information on ambient levels of total chromium and hexavalent chromium are available from a number of sources. Together they provide a fairly comprehensive picture of the relationship between total chromium and hexavalent chromium. This is important because the toxicity of hexavalent chromium compounds is so different than the toxicity of other chromium compounds.

2.3.1 National Scale Air Toxics Assessment

The USEPA 2001 National-Scale Air Toxics Assessment (NATA) of emissions from the 1996 National Toxics Inventory (NTI) indicates that chromium emissions from major facilities and area/other sources (e.g., smaller facilities) accounted for approximately 89% of the NTI chromium emissions in Texas, while on-road mobile and non-road mobile sources comprised the remaining 11% (USEPA 2001). USEPA made the conservative assumption in their 1996 NATA evaluation that 34% of all atmospheric chromium is hexavalent. Speciated chromium data from sites in Texas indicate that assuming hexavalent chromium is 34% of total atmospheric chromium is extremely conservative.

2.3.2 Annual Monitoring for Total Chromium in PM2.5 in Texas

When chromium has been quantified in ambient monitoring of particulate matter (PM) in Texas, the focus has typically been on total chromium. Annual averages of total chromium monitored in PM less than or equal to 2.5 micrometers (µm) in aerodynamic diameter ($PM_{2.5}$), also known as fine particulates, at 22 sites monitored in Texas in 2004 ranged from 0.59 to 3.9 nanograms per cubic meter (ng/m^3). The 2005 annual averages at 26 sites monitored in Texas ranged from 0.39 to 1.3 ng/m^3. Fewer locations were sampled for total chromium in 2006, 2007, and 2008. At twelve sites monitored in Texas in 2006 the annual average range was from 0.42 to 1.12 ng/m^3 and in 2007 was from 0.33 to 1.38 ng/m^3. At thirteen sites monitored in Texas in 2008 the annual average range was from 0.36 to 1.14 ng/m^3. These reported ranges of total chromium in $PM_{2.5}$ in

Texas are typical of ambient concentrations reported in other urban and suburban regions of the US (between 2 – 20 ng/m^3) (Werner *et al*. 2007).

2.3.3 Ambient Monitoring for Total and Hexavalent Chromium in PM_{10} in Texas and California

2.3.3.1 Midlothian Study

The first and second quarter of data collected for a 2008/2009 study near Midlothian, Texas measured total chromium and hexavalent chromium in PM less than or equal to 10 µm in diameter (PM_{10}) at five TCEQ sites. Total chromium ranged from <2 to 10 ng/m^3, while hexavalent chromium ranged from <0.001 to 0.4 ng/m^3. The average hexavalent chromium percentage at these five TCEQ monitored sites in Midlothian in December 2008 ranged from 0.84 to 2.70% with an overall average of 1.55%. In February/March 2009 the average hexavalent chromium percentage ranged from 0.12 to 2.07% with an overall average of 0.99%. Looking at paired total and hexavalent chromium for individual days during the first and second quarter of data collected for the Midlothian study shows ambient levels of hexavalent chromium ranging from <0.1% to as high as 8.0% of total chromium.

2.3.3.2 Deer Park and Karnack

Annual averages of total chromium monitored in PM_{10} at four sites in Texas in 2004 ranged from 2.1 to 7.3 ng/m^3. Annual averages at three sites in Texas from 2005 through 2008 ranged from 2.0 to 5.5 ng/m^3. Hexavalent chromium data has also been collected in PM_{10} samples at two of these locations (Deer Park and Karnack) from three monitors. Two monitors are co-located in Deer Park and one is located in Karnack. Data from these three monitors collected in 2007 and 2008 show annual average hexavalent chromium concentrations that range from 0.1 to 0.2 ng/m^3. These data were paired with annual average total chromium levels from the same locations to evaluate the percentage of hexavalent chromium. At these two sites, the annual average hexavalent chromium percentages ranged from 6.4 to 9.2%.

2.3.3.3 California

The California Air Resources Board (CARB) has summary information available on total chromium and hexavalent chromium for several years on their website. CARB shows annual mean total chromium from all of their monitoring sites from 1989 to 2002 ranging from 3.9 to 5.5 ng/m^3 (CARB 2008a). Similar data for hexavalent chromium from 1992 to 2007 shows a range of annual mean concentrations from 0.069 to 0.29 ng/m^3 (CARB 2008b).

2.3.4 Urban Air Toxics Monitoring Program

Additional information on ambient levels of hexavalent chromium is available from the 2005 Urban Air Toxics Monitoring Program (UATMP). The UATMP and the National Air Toxics Trends Station (NATTS) networks are sponsored by USEPA to characterize the composition and magnitude of urban air pollution through ambient air monitoring. Hexavalent chromium

monitoring is a part of this effort. The final report on hexavalent chromium (USEPA 2007) includes up to 12 months of 1-in-6 or 1-in-12 day measurements of ambient air quality at 22 monitoring sites in or near 19 urban/rural locations, including 14 metropolitan statistical areas (MSAs). Some monitors were placed near the centers of heavily populated cities (*e.g.*, Chicago, IL and Seattle, WA), while others were place in more rural areas (*e.g.*, Chesterfield, SC and Hazard, KY).

A total of 1,153 hexavalent chromium concentrations were collected at the 22 sites in 2005. Details on data collection, statistical characterization, data distribution, and risk characterization are available in USEPA (2007). The maximum measured daily hexavalent chromium concentration was 2.97 ng/m^3 but was deemed an outlier, while the next highest daily concentration at any site was 0.269 ng/m^3. The highest annual average was 0.057 ng/m^3, and the highest seasonal 3-month average was 0.069 ng/m^3. Only four 24-hour concentrations exceeded 0.25 ng/m^3, and over 96 percent of the concentrations measured were less than 0.10 ng/m^3. The UATMP monitored hexavalent chromium data is very similar to the CARB reported data on hexavalent chromium.

USEPA used the annual average at each site and the most recent USEPA (1998b) integrated risk information system (IRIS) unit risk factor (URF) to calculate cancer risk (which ranged from 0.17 to 0.69) and reference concentration (RfC) to calculate noncancer hazard (which ranged from 1.45E-04 to 5.73E-04). In addition, the monitored levels were compared to the 1999 NATA-modeled concentrations and their calculated theroretical risk and hazard estimates. “All of the NATA-modeled concentrations and risks were within an order of magnitude of each other suggesting very good agreement between the modeled and measured concentration values.” (USEPA 2007).

2.3.5 Conclusions on Ambient Levels of Chromium

Overall, the data reviewed on speciated chromium indicate that hexavalent chromium measured in ambient air makes up less than 10% of the total chromium, and the USEPA assumption (34% of total atmospheric chromium is hexavalent) is very conservative. Monitored data, while variable, is fairly consistent across data-sets. In other words, forms of chromium other than hexavalent typically make up more than 90% of measured ambient chromium levels.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

Acute toxicity values were developed by the Toxicology Division (TD) for trivalent chromium compounds but toxicity studies were not available for other common valence states. The only other valence states of chromium that are stable or even remotely stable in the environment, other than trivalent or hexavalent (which is discussed in a separate DSD), are elemental chromium and its compounds and divalent chromium compounds. Based on what is known about

absorption of chromium in the human body, its potential mechanism of action in cells, and occupational data indicating that valence states other than hexavalent exhibit a relative lack of toxicity as compared to hexavalent chromium, the toxicity of elemental and divalent chromium compounds is expected to be similar to or less than common trivalent forms. Therefore, the acute Reference Value (acute ReV) and acute Effects Screening Level (^{acute}ESL) for trivalent chromium are expected to be protective for these forms of chromium as well. As a science policy decision the acute ReV and ^{acute}ESL derived for trivalent chromium will be used for all compounds of chromium, except for hexavalent compounds. As stated previously, this approach is consistent with the typical evaluation of all chromium compounds other than hexavalent as having similar toxicity (ACGIH 2001, NIOSH 2005).

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

Trivalent chromium compounds are generally insoluble in water, with the exception of chromium acetate, hexahydrate of chromium chloride, chromium carbonate, chromium nitrate salts, and basic chromium sulfate (CAS No. 12336-95-7). Common insoluble forms of trivalent chromium include chromium oxide, chromium chloride, chromium sulfate (CAS No. 10101-53-8), chromium phosphate, and chromium picolinate (ATSDR 2009). Each of these trivalent chromium compounds has a unique molecular weight and physical/chemical properties, although all exist in the solid state at standard temperature and pressure. Elemental and all valence states of chromium considered in this DSD exist in the solid state at standard temperature and pressure. For inhalation exposure, all trivalent and other chromium compounds are treated as particulates, not gases (USEPA 1994). For additional information on the chemical and physical properties of elemental chromium, please refer to Table 2. Chemical and physical properties of some of the common forms of trivalent chromium compounds can be found in Tables 6 to 13 in Appendix A.

3.1.1.2 Essential Data and Key Studies

Few studies that directly address the toxicity of trivalent chromium compounds are available in the literature, especially studies that evaluate the inhalation route of exposure (USEPA 1998). Even fewer studies exist that evaluate elemental chromium exposure or exposure to other (typically unstable) valence states. The general inability of trivalent chromium to traverse membranes and thus be absorbed or reach peripheral tissue in significant amounts is generally accepted as a probable explanation for the overall absence of systemic trivalent chromium toxicity (O'Flaherty 1996). Elemental and divalent forms of chromium are not able to traverse membranes readily either. This is not to say that elemental, divalent, or trivalent chromium compounds cannot traverse membranes and reach peripheral tissue, the mechanism of absorption is simply less efficient in comparison to absorption of hexavalent chromium compounds. Obviously, some trivalent chromium is absorbed by the human body, as chromium is an essential nutrient. Investigators have examined potential portal of entry effects, systemic effects, and other endpoints, but nearly all of the occupational evidence of effects are from mixed exposures to both trivalent and hexavalent chromium (USEPA 1998).

Human inhalation studies on the short-term (i.e., acute, subacute) effects of elemental, trivalent, or other valence states of chromium were not identified. Chromium can be a potent sensitizer in a small minority of humans, both from dermal and inhalation exposures (ATSDR 2009). A discussion of reproductive and developmental occupational exposure studies and potential immunological effects to chromium can be found in ATSDR (2009). The occupational studies were either of insufficient quality or had too many confounding factors (i.e., co-exposure to other compounds) to be used to derive toxicity factors. Overall, human data are not available on which to base the calculation of an acute ReV or an ^{acute}ESL.

The most sensitive endpoint identified in animal studies of acute exposure to trivalent chromium appears to involve the respiratory system. Specifically, acute exposure to trivalent chromium is linked to increased acid phosphatase activity in lung tissue and bronoalveolar lavage fluid (BALF) of hamsters. These endpoints have been identified as early indicators of impaired lung function and lung damage (Henderson 2005). Subchronic studies in rats (Derelanko *et al*. 1999) and rabbits (Johannson *et al*. 1986a, 1986b, 1987) have identified similar and other respiratory endpoints (decreased macrophage activity, respiratory tract inflammation, microscopic cellular alterations, and potentially impaired lung function).

3.1.1.2.1 Key Animal Study – Henderson *et al*. (1979)

The key acute inhalation study conducted by Henderson *et al.* (1979) is the only acute inhalation study highlighted by ATSDR (2009) for any chromium compound other than hexavalent forms. Additional acute inhalation studies since 2000 were not identified in the scientific literature. The Henderson *et al*. (1979) study was not designed specifically to evaluate the adverse effects of inhalation exposure to trivalent chromium, but attempted to examine the validity of using the enzymatic and cytological profile of airway fluids to indicate lung damage by testing animals exposed by inhalation to either cadmium chloride or to chromium chloride. Cadmium chloride ($CdCl_2$) is a known toxic metallic salt, while chromium chloride ($CrCl_3$) is a relatively innocuous, less toxic salt (Henderson *et al*. 1979).

Thirty-two Syrian hamsters per concentration group, 12-16 weeks old, were exposed for 30 minutes (min) at the following air concentrations: 0.0 milligrams per cubic meter (mg/m^3) (controls); 2.8 mg/m^3 $CrCl_3$ (0.9 mg Cr^{3+}/m^3); or 77 mg/m^3 $CrCl_3$ (25 mg Cr^{3+}/m^3). Eight animals (equally divided by sex) were sacrificed in each exposure group at 2 h, 1 day, 1 week, and 3 weeks after exposure. At each sacrifice time, four animals from each dose level were sacrificed for histopathologic evaluation, including a histopathologic section from each lung lobe. The other four animals from each dose group were sacrificed for biochemical and cytologic studies. Biochemical variables were measured in lavage fluid and tissue homogenate supernatant on the basis of their ability to indicate cell injury. The measured variables included two cytoplasmic enzymes (lactate dehydrogenase [LDH] and glucose-6-phosphate-dehydrogenase [glu-6P-DH]), two lysosomal enzymes (β-glucuronidase and acid phosphotase), and lavage fluid alkaline phosphotase. In addition, Henderson *et al.* (1979) measured total protein, trypsin inhibitory capacity (TIC), sialic acid, and soluble collagen. All of the endpoints were selected to

represent potential early indication of impaired lung function or lung damage. Although these endpoints are measurable effects levels, it is questionable as to whether they are truly "adverse effects" according to the TD guidance (TCEQ 2006) or precursors to adverse effects. Statistically significant biochemical changes in these enzymes are best described as lowest observed effects levels (LOELs).

No animals died prior to their sacrifice time in either of the trivalent chromium exposure groups. BALF from $CrCl_3$-exposed animals showed a statistically significant increase in acid phosphotase activity one day after exposure in the higher (77 mg/m^3) dose group. Lung tissue showed a statistically significant increase in acid phosphotase activity and β-glucuronidase activity at one day after exposure in the higher dose group, but not at days seven or 21. These biochemical responses are indicative of increased activation of macrophages and cell injury, with the potential to impact the functioning of the respiratory system. These measures are early indicators of biochemical changes leading to later morphological changes in a disease or process (Henderson 2005). Although statistically significant effects, they are only precursors to actual adverse outcomes, and as such are not in themselves adverse effects. No cytological responses in BALF and no significant histopathological alterations were noted in any of the trivalent chromium exposure animals. The lungs of all animals exposed to $CrCl_3$ were essentially normal, although after 1 day of exposure there were focal accumulations of macrophages and polymorphonuclear leukocytes in alveoli surrounding occasional respiratory and terminal bronchioles, and alveolar wall capillaries were diffusely congested. There was no evidence of bronchiolar or parenchymatous necrosis, and the minor histopathologic effects that were noted were considered to be "representative of a mild, probably nonspecific, irritation" (Henderson *et al.* 1979).

The mild biochemical effects of increased acid phosphotase activity in BALF and increased acid phosphotase and β-glucuronidase activity in lung tissue in the 77 mg/m^3 $CrCl_3$ exposure group were chosen as the critical acute precursor effects for trivalent chromium inhalation exposure. Because the noted precursor effects are minor and potentially reversible at the 77 mg/m^3 exposure group, this exposure concentration is considered a no-observed-adverse-effect level (NOAEL). An acute NOAEL of 77 mg/m^3 was determined for both male and female Syrian hamsters from this study.

3.1.1.2.2 Supporting Animal Studies

A poor quality, repeated dose inhalation study of a trivalent chromium compound (chromium carbonate dust [$Cr_2(CO_3)_3$]) was identified, although it is dated and of extremely limited value (Akatsuka and Fairhall 1934 in USEPA 1998). Two cats were exposed to chromium carbonate dust at an average level of 58.3 mg Cr^{3+}/m^3 for 86 sessions, with each session lasting from 10 to 60 minutes. No effects in gross or microscopic pathology were observed upon termination of the experiment, and, no examination of control animals was reported (Akatsuka and Fairhall 1934, in USEPA 1998). This study was not appropriate for selection as a key study.

One subchronic study of two trivalent chromium compounds was conducted by Derelanko *et al*. (1999) and is discussed in greater detail in the chronic section of this DSD. Several subchronic studies for trivalent chromium toxicity were conducted by Johansson *et al.* (1986a, 1986b, 1987) and are discussed in greater detail in the chronic section and in Appendix D of this DSD. Data from the series of papers by Johansson *et al.* (1986a, 1986b, 1987) and Derelanko *et al*. (1999) support the position that the respiratory tract is the primary target of trivalent chromium toxicity following inhalation (USEPA 1998).

3.1.2 Mode-of-Action (MOA) Analysis and Pharmacokinetics

The toxicokinetics of chromium are dependent on the valence state of the particular compound and the nature of its ligands. Of all toxicokinetic parameters, absorption may be the key factor in determining chromium toxicity (O'Flaherty 1996). The lesser potency of trivalent chromium relative to hexavalent chromium is likely related to the higher redox potential of hexavalent chromium and its greater ability to enter cells (ATSDR 2009). Naturally occurring compounds of chromium, which are poorly absorbed, are generally in a trivalent state (ATSDR 2009). The majority of chromium-induced effects following inhalation exposures are seen in the respiratory tract, with some systemic effects seen at extremely high concentrations (ATSDR 2009). The specific respiratory effects following inhalation are those identified as key precursor effects, as well as changes in lung and trachea weight, changes in microscopic pathology, and widespread inflammation of respiratory tract tissues. The specific mode-of-action, or how trivalent chromium exposure causes respiratory tract effects, is not understood, although consistent effects are seen across studies and exposure durations. As would be expected, soluble forms of trivalent chromium tend to deposit throughout the respiratory tract, including in the upper respiratory regions, while insoluble forms of trivalent chromium that are respirable primarily tend to deposit in the lower reaches of the lungs and result in lower respiratory effects.

3.1.2.1 Absorption

In general, trivalent chromium compounds are poorly absorbed, compared to hexavalent chromium compounds. The molecular structure of hexavalent chromium compounds facilitates their absorption. Hevalent chromium compounds exist as tetrahedral chromate anions, resembling the forms of other natural anions like sulfate and phosphate which are permeable across nonselective membranes. Trivalent chromium forms octahedral complexes which cannot easily enter though these channels, instead being absorbed via passive diffusion and phagocytosis (ATSDR 2009). Absorption of inhaled chromium depends on the physical and chemical properties of the particles (oxidation state, size, solubility), the activity of alveolar macrophages, and the interaction of chromium with biomolecules following deposition in the lung (ATSDR 2009). Absorption of inhaled chromium is typically estimated to be about 3%, but as high as 12% for trivalent forms (CEPA 1994) and has been well documented in occupational settings. Although trivalent chromium is less well absorbed than hexavalent chromium, workers exposed to trivalent compounds have had detectable levels of chromium in the urine at the end of a workday (USEPA 1998).

3.1.2.2 Distribution

Absorbed chromium is widely distributed throughout the body via the bloodstream, and can reach the fetus (CEPA 1994). Although there is ample *in vivo* evidence that hexavalent chromium is efficiently reduced to trivalent chromium in the gastrointestinal tract and can be reduced to the trivalent form by ascorbate and glutathione in the lungs, there is no evidence that trivalent chromium is converted to hexavalent chromium in biological systems (Amdur *et al.* 1993, cited in USEPA 1998). In general, trivalent chromium compounds are cleared rapidly from the blood and more slowly from the tissues.

3.1.2.3 Metabolism

Although not fully characterized, the biologically active trivalent chromium molecule appears to be chromodulin, also referred to as (GTF) (Jacquamet et al. 2003 as cited in ATSDR 2009). Chromodulin is an oligopeptide complex containing four chromic ions. Chromodulin may facilitate interactions of insulin with its receptor site, influencing protein, glucose, and lipid metabolism (ATSDR 2009). Chromodulin may operate through activation of membrane phosphotyrosine phosphatase in mammals (USEPA 1998). Inorganic trivalent chromium compounds, which do not appear to have insulin-potentiating properties, are capable of being converted into biologically active forms by humans and animals (Anderson 1986). Trivalent chromium compounds are essential for normal glucose, protein, and fat metabolism in animals and humans. A deficiency of chromium can cause changes in the metabolism of glucose and lipids and may be associated with maturity-onset diabetes, cardiovascular diseases, and nervous system disorders (Anderson 1993 & 1995, cited in USEPA [1998]). Thorough discussions of the metabolism of chromium are available in USEPA (1984) and ATSDR (2009), including information on elimination and excretion.

3.1.2.4 Physiologically Based Pharmacokinetic (PBPK) Model

PBPK models for chromium have been published, one in rats (O'Flaherty 1996) and one in humans (O'Flaherty *et al*. 2001), which incorporate absorption and disposition schemes for hexavalent and trivalent chromium throughout the body. The O'Flaherty (1996) model accounts for most of the major features of chromium kinetics in the rat and was calibrated using published oral and intratracheal kinetics studies using soluble trivalent and hexavalent chromium. It accounts for reduction from hexavalent chromium to trivalent chromium. Model parameters are available in ATSDR (2009) or directly from O'Flaherty (1996). The model performs reasonably well in simulations of rat inhalation exposure and can also predict tissue concentrations after chronic exposure (O'Flaherty 1996). The O'Flaherty (1996) model was validated using inhalation and drinking water studies, and the model appears to accurately predict tissue levels of both trivalent and hexavalent chromium in the rat lung, erythrocyte, liver, and kidney. The model is based solely on rat kinetic studies, and no species extrapolation was attempted (ATSDR 2009), so it is of limited use for other species. The O'Flaherty *et al*. (2001) model also includes parameters for simulating inhalation and ingestion, but was calibrated and evaluated against data from ingestion studies only. Determining the robustness of the human model for predicting

chromium kinetics following inhalation exposure in humans has not been reported (ATSDR 2009). Therefore, this PBPK model was not used.

3.1.2.5 Mechanisms of Toxicity

The mechanisms of chromium toxicity are very complex, and although many studies on chromium are available, there is a great deal of uncertainty about how chromium exerts its toxic influence. Much more is known about the mechanisms of hexavalent chromium toxicity than trivalent chromium toxicity. Available information is discussed in detail in ATSDR (2009).

3.1.3 Dose Metric

In the key study using Syrian hamsters (Henderson *et al.* 1979), data on exposure concentration of the parent chemical are available. Since the selected precursor adverse effect, or LOEL, for the key study is related to effects in the lung from exposure to the parent chemical, exposure concentration of the parent chemical is the appropriate dose metric (TCEQ 2006).

3.1.4 Point of Departure (POD) for the Key Study

The selected precursor adverse effect, which occurred at 77 mg/m^3 ($CrCl_3$) from a 30-min exposure in Syrian hamsters identified in the key study (Henderson *et al.* 1979) was considered a NOAEL and was used as the POD. Adequate information was not available in the key study to perform benchmark-dose modeling for trivalent chromium compounds.

3.1.5 Dosimetric Adjustments

3.1.5.1 Exposure Duration Adjustments

According to the ESL guidance (TCEQ 2006), an adjustment from an exposure duration of less than 1 h to 1 h is appropriate if concentration and duration both play a role in toxicity or if MOA information is not available. Information for trivalent chromium compounds is limited, and because similar mild adverse effects noted in the supporting subchronic exposure studies (Derelanko *et al*. 1999 and Johansson *et al.* 1986a, 1986b, 1987) appear to have occurred at lower doses than the LOAEL noted in the key study, there is evidence that toxicity is related to concentration and duration of exposure.

According to the ESL guidance (TCEQ 2006), Haber's rule as modified by ten Berge (1986) with n = 1 is used to adjust from a 30-min exposure to a 60-min exposure to derive an adjusted POD (POD_{ADJ}).

$$C_2 = (C_1) \times (T_1 / T_2)]$$
$$= [(77 \text{ mg/m}^3) \times (30 \text{ min}/60 \text{ min})]$$
$$= 38.5 \text{ mg/m}^3$$

where : C_1 = exposure concentration in key study (POD)

C_2 = POD_{ADJ} – exposure concentration adjusted to 1 h exposure
T_1 = exposure duration in key study
T_2 = desired exposure duration

3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

The USEPA regional deposition dose ratio (RDDR) model version 2.3 was used to calculate the depositional fraction for trivalent chromium in the target respiratory region for the key study (USEPA 1994). The RDDR model allows the adjustment of a hamster concentration to a human equivalent concentration for PM and aerosolized compounds.

In order to use the RDDR model, information on particle size and standard deviation from the pertinent toxicity study must be available, in addition to dose. The Henderson *et al.* (1979) study reported a count median diameter (CMD) of the $CrCl_3$ aerosol of 1.2 µm with a geometric standard deviation (σ_g) of 1.5. In order to use the RDDR model, the CMD was converted to a mass median aerodynamic diameter (MMAD) using the particle density (ρ). The particle density was calculated using the density of water (1.00 gram/milliliter [g/mL]), the density of $CrCl_3$ (2.87 g/mL), and the amount of $CrCl_3$ aerosolized in water (30 mg/mL). A ratio of the densities was calculated according to the following equation (Whitten and Gailey 1984):

$$\rho = (C_w \times D_w) + (C_c \times D_c)$$
$$= (0.97 \text{ g/mL} \times 1.00 \text{ g/mL}) + (0.03 \text{ g/mL} \times 2.87 \text{ g/mL})$$
$$= 1.06 \text{ g/mL}$$

where: C_w = concentration of water in solution (g/mL)
C_c = concentration of compound in solution (g/mL)
D_w = density of water (g/mL)
D_c = density of compound (g/mL)
ρ = particle density (g/mL)

Particle density (ρ) can be reported in units of g/mL or g/cm^3, which are equivalent units of measure (Whitten and Gailey 1984). The ρ was then used to convert the CMD to a MMAD for input into the RDDR model using the following equation:

$$MMAD = \rho^{0.5} \text{ CMD } e(3[\ln \sigma_g]^2)$$
$$= 1.06^{0.5} \times 1.2 \text{ µm} \times e(3[\ln 1.5]^2)$$
$$= 1.03 \times 1.2 \text{ µm} \times e(0.49)$$
$$= 2.02$$

where: CMD = count median diameter (µm)
e = irrational constant, base of ln
ln = natural logarithm

MMAD = mass median aerodynamic diameter (μm)
σ_g = geometric standard deviation
ρ = particle density (g/cm^3)

The MMAD and the σ_g were then used in the RDDR model (version 2.3) (USEPA 1994), along with species-specific information on the Syrian hamster, to convert the hamster concentration to a human equivalent concentration (HEC). The input terms and the output from the RDDR model run using the Henderson *et al.* (1979) study are presented in Figure 1.

The particle diameter in the toxicity study was small enough that one would expect particle deposition throughout the respiratory tract, including in the lower alveolar regions of the human lung. In addition, the mild adverse effect noted in the key study and in the supporting studies was observed in BALF flushed from the alveolar region and lung tissue in this respiratory region. Although one could use the RDDR for the tracheobronchial and pulmonary regions combined, as represented by BALF, it is conservative to use the RDDR of just the pulmonary region. Thererfore, the RDDR of the pulmonary region was selected as the appropriate output to use to develop a human equivalent concentration (POD_{HEC}). The RDDR for the pulmonary region was multiplied by the POD_{ADJ} for the Henderson *et al.* (1979) study to derive a POD_{HEC}.

$$POD_{HEC} = POD_{ADJ} \times RDDR$$
$$= 38.5 \text{ mg/m}^3 \times 0.281$$
$$= 10.82 \text{ mg/m}^3$$

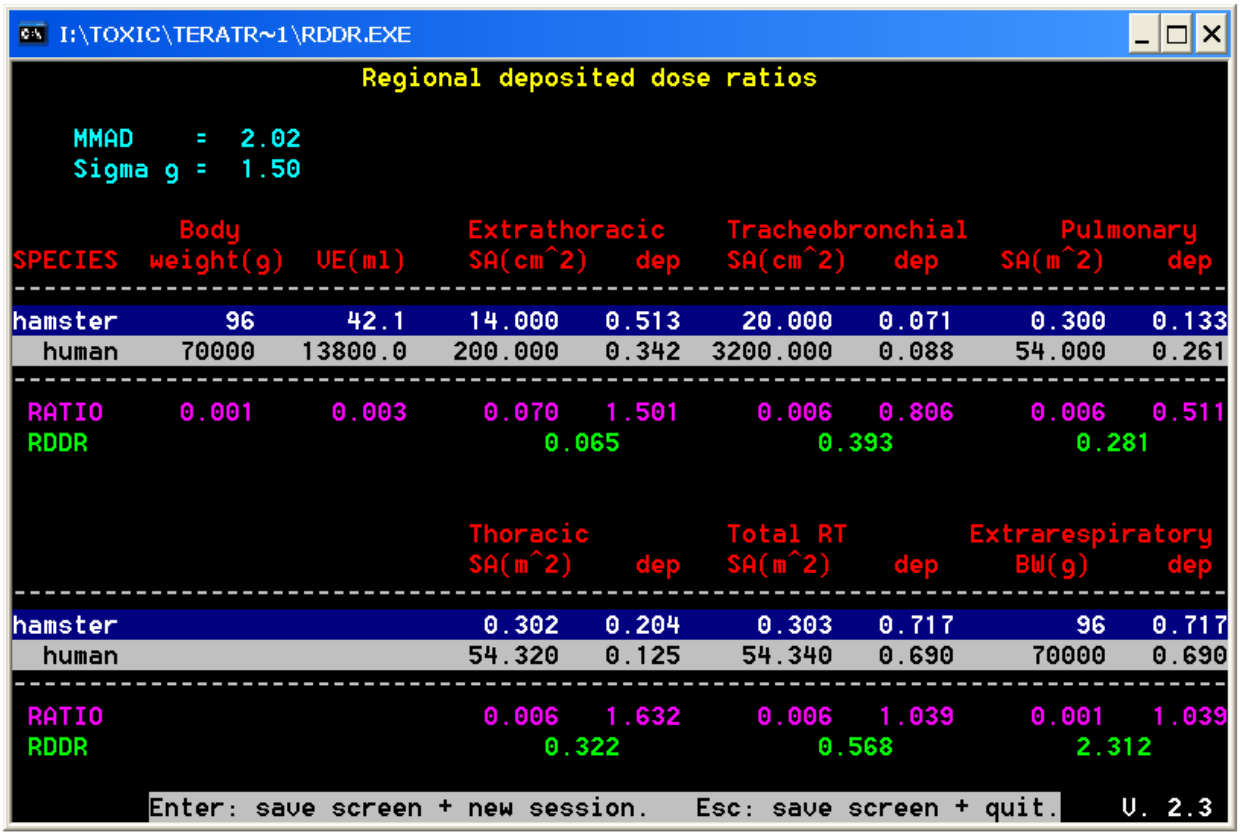

Figure 1 RDDR Model Run for $CrCl_3$ data from Henderson *et al.* (1979)

3.1.6 Critical Effect and Adjustments of the POD_{HEC}

The MOA by which trivalent chromium produces respiratory system toxicity is not understood (Section 3.1.2), so appropriate uncertainty factors (UFs) were applied to the POD to derive a ReV. The ReV was calculated by applying the following UFs to the POD_{HEC} of 10.82 mg/m^3 based on Henderson *et al.* (1979): an interspecies UF (UF_A) of 3 for extrapolation from animals to humans; an intraspecies UF (UF_H) of 10 to account for variability within the human population; a LOAEL-to-NOAEL UF (UF_L) of 1; and a database UF (UF_D) of 10 (total UFs = 300).

An UF_A of 3 was used because the RDDR program accounts for toxicokinetic differences and limits uncertainty for extrapolation from hamsters to humans but does not account for toxicodynamic differences. A full UF_H of 10 was applied because no information on variability in the human population to effects from trivalent chromium inhalation exposure was available and because chromium and its compounds cause sensitization that can result in asthma and dermatitis (ATSDR 2009). According to the ESL Guidance (Table 18, TCEQ 2006), an additional UF_L was not applied since the noted effects are mild cytological, enzymatic, and

physiological effects in lung tissue, all precursor effects to actual adverse outcomes. The noted effects were treated as NOAELs. A full UF_D of 10 was applied because the database on acute inhalation toxicity of trivalent chromium compounds is limited.

3.1.7 Health-Based Acute ReV and ^{acute}ESL

As discussed in the previous section, UFs are applied to the POD_{HEC} from the key study (Henderson *et al.* 1979) to derive the acute ReV.

$$\text{acute ReV} = [POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D)] \times CF$$
$$= [10.82 \text{ mg/m}^3 / (10 \times 3 \times 1 \times 10)] \times 1000 \text{ µg/mg}$$
$$= (0.03616 \text{ mg/m}^3) \times 1000 \text{ µg/mg}$$
$$= 36.16 \text{ µg/m}^3$$

where: CF = conversion factor from mg to µg

The acute ReV value was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then used to calculate the ^{acute}ESL. Rounding to two significant figures, the 1-h acute ReV for $CrCl_3$ is 36 µg/m^3. At the target hazard quotient of 0.3, the ^{acute}ESL for $CrCl_3$ is 11 µg/m^3 (Table 3).

Table 3 Derivation of the Acute ReV and ^{acute}ESL

Parameter	**Summary**
Study	Henderson et al. (1979)
Study Population	16 male; 16 female Syrian hamsters per dose group
Study Quality	Medium
Exposure Methods	Inhalation of metal salt aerosol (0.0, 2.8, 77 mg/m^3 as $CrCl_3$) = (0.0, 0.9, 25 mg/m^3 Cr^{3+})
NOAEL	77 mg/m^3 as $CrCl_3$
Critical Effects	Increased acid phosphotase activity in lavage fluid and increased acid phosphotase and β-glucuronidase activity in lung tissue (precursors to adverse effects)
POD	77 mg/m^3 as $CrCl_3$ (mild precursor effects)
Exposure Duration	30 min
Extrapolation to 1 h	Haber's Rule, n = 1
POD_{ADJ} (extrapolated 1-h concentration)	38.5 mg/m^3
POD_{HEC}	10.82 mg/m^3 (RDDR = 0.281 for pulmonary region)
Total UFs	300
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL UF	*1*
Incomplete Database UF	*10*
Database Quality	*Low*
acute ReV [1 h] (HQ = 1)	**36 µg/m^3 as $CrCl_3$** **12 µg/m^3 as Cr^{3+}**
^{acute}ESL [1 h] (HQ = 0.3)	**11 µg/m^3 as $CrCl_3$** **3.6 µg/m^3 as Cr^{3+} ***

* To protect against sensitization, exceedences of the ^{acute}ESL should be minimized during the permit review process

The acute ReV and ^{acute}ESL are for the trivalent chromium compound $CrCl_3$. The molecular weight (MW) of chromium is 51.996 daltons (Da) and the MW of $CrCl_3$ is 158.35 Da (Table 8). Dividing the MW of Cr by the MW of $CrCl_3$ (51.996 / 158.35) gives the fraction of Cr in the compound $CrCl_3$ (0.32835). The acute ReV and ^{acute}ESL for trivalent chromium can then be calculated by multiplying the acute ReV and ^{acute}ESL for $CrCl_3$ respectively, by 0.32835. Rounding to two significant figures, the 1-h acute ReV for trivalent chromium is 12 µg/m^3. At the target hazard quotient of 0.3, the ^{acute}ESL for trivalent chromium is 3.6 µg/m^3 (Table 3).

Subchronic toxicity studies which are discussed in Chapter 4 of this DSD indicate that soluble forms of trivalent chromium exert toxicity at lower concentrations than insoluble forms of trivalent chromium. This relationship likely holds true for acute toxicity as well. Since CrCl3 is a soluble trivalent chromium compound, using the Johansson et al. (1979) study to develop a ReV and acuteESL for trivalent chromium is expected to be protective of both soluble and insoluble compounds.

As already discussed, the only other valence states of chromium that are stable or even remotely stable in the environment, other than trivalent or hexavalent (which is discussed in a separate DSD), are elemental chromium and its compounds and divalent chromium compounds. The toxicity of elemental and divalent chromium compounds is expected to be similar to or less than common trivalent forms; therefore, the acute ReV and ^{acute}ESL for trivalent chromium is expected to be protective for these forms of chromium as well. As a science policy decision the acute ReV and ^{acute}ESL derived for trivalent chromium will be used for all compounds of chromium, except for hexavalent compounds.

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Elemental chromium and several trivalent chromium compounds (chromium chloride, chromium nitrate, chromium oxide, chromium picolinate and chromium sulfate) are odorless (Fisher 2001; JT Baker 2007a; Fisher 2007; JT Baker 2005; Science Lab 2005d; and JT Baker 2007b). For other trivalent and divalent chromium compounds information on odor was not available. Therefore, an odor-based acute ESL ($^{acute}ESL_{odor}$) cannot be developed for elemental, trivalent, or divalent chromium compounds.

3.2.2 Vegetation Effects

Total chromium is present in plants but has not been shown to be an essential element to plants (WHO 1988). Limited information on absorption and toxicity of chromium to plants from soil and water is available. At high tissue concentrations chromium can be toxic to plants, with the main feature of chromium intoxication being chlorosis, which is similar to iron deficiency (Hewitt 1953 cited in WHO 1988). No data were found on the toxicity of air concentrations of chromium to plants. Therefore, a vegetation-based acute ESL ($^{acute}ESL_{veg}$) was not developed.

3.3. Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation of elemental, divalent, and trivalent chromium compounds resulted in the derivation of the following values:

acute ReV = 12 µg/m^3 as Cr^{3+}
^{acute}ESL = 3.6 µg/m^3 as Cr^{3+}

The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 3.6 µg/m^3 (Table 1). As a science policy decision, this value will be used for elemental, divalent, and trivalent chromium compounds. Exceedences of this value for air permits should be minimized since chromium has been identified as a sensitizer. The acute ReV of 12 µg/m^3 will be used for the evaluation of air monitoring data (Table 1). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

This section is based on the USEPA (1998) toxicological review in support of the summary information in the Integrated Risk Information System (IRIS) and the ATSDR (2009) toxicological profile for chromium. Both human and animal data show that inhalation exposure to chromium has adverse effects on the airways and that these effects occur at lower exposure concentrations than the occurrence of systemic effects. This phenomenon may be particularly relevant for inhalation exposures to elemental, trivalent, and divalent chromium compounds, since they are much less readily absorbed than hexavalent chromium compounds. However, the majority of exposures in humans and animals that have been studied are to mixtures of chromium compounds (primarily trivalent and hexavalent forms). These mixed exposure studies make it difficult to elucidate which effects are related to a particular valence state of chromium. The USEPA (1998) toxicological review of trivalent chromium has a thorough discussion of available studies through 1998 and ATSDR has a thorough discussion of studies through 2008. In addition to the USEPA (1998) and ATSDR (2009) reviews, the scientific literature since 1998 was reviewed to identify any additional subchronic or chronic studies that could be used to derive a chronic ReV for trivalent chromium.

Chronic toxicity values were developed by the TD for trivalent chromium compounds since toxicity studies were not specifically available for other common valence states (elemental and divalent). The only other valence states of chromium that are stable in the environment, other than trivalent or hexavalent (which is discussed in a separate DSD), are elemental chromium and its compounds and divalent chromium compounds. As mentioned in the acute section, the toxicity of elemental and divalent chromium compounds is expected to be similar or less than that of common trivalent forms. Therefore, the chronic ReV and ^{chronic}ESL for trivalent chromium is expected to be protective for these forms of chromium as well. As a science policy decision the chronic ReV and ^{chronic}ESL derived for trivalent chromium will be used for all compounds of chromium, except for hexavalent compounds.

4.1.1 Physical/Chemical Properties and Key Studies

Physical/chemical properties of trivalent chromium compounds have been previously discussed in Section 3.1.1.1. A key consideration for trivalent chromium toxicity is its role as an essential nutrient.

4.1.1.1 Human Studies

Occupational exposure to chromium by inhalation has been studied in several different industries; however, all of the studies include mixed exposures to both trivalent and hexavalent chromium. Human studies addressing exposures to elemental, trivalent, or divalent chromium alone are not available, and the specific role of any particular valence state in disease following these mixed exposures cannot be determined (USEPA 1998). Noncarcinogenic endpoints evaluated in epidemiological studies of occupational chromium exposures include upper respiratory irritation and atrophy, lower respiratory effects including biochemical and cytological changes, and systemic effects. The majority of the effects noted in the occupational settings were to the respiratory tract, and although systemic effects were also noted (particularly renal effects), the respiratory effects occurred at concentrations below which renal effects were noted (USEPA 1998). Information on reproductive and developmental effects following inhalation exposures to chromium is limited and equivocal. There is ample evidence of allergic sensitization causing dermatitis on cutaneous exposures to chromium in humans, and limited but clear evidence of asthmatic responses (Dayan and Paine 2001). ATSDR (2009) thoroughly discusses specific chronic studies that attribute at least some adverse effect to chromium species other than hexavalent forms.

4.1.1.2 Animal Studies

Many of the chronic inhalation animal studies of trivalent chromium compounds are focused on assessing its carcinogenic potential in the respiratory tract, which is discussed in Section 4.2. Similar to acute studies, the primary target for noncarcinogenic chromium toxicity following subchronic inhalation is the respiratory tract (USEPA 1998). In general, the database of trivalent chromium inhalation studies is limited, and is scarce for elemental and divalent compounds. However, the minimum database requirements as described in Section 4.3 of the ESL Guidelines (TCEQ 2006) for development of a chronic ReV are satisfied. The available data were used to develop a chronic ReV and it is presented below. The confidence in the derived chronic ReV is discussed at the end of the chronic section.

4.1.1.2.1 Key Animal Study (Derelanko *et al.* 1999)

One subchronic study that evaluated inhalation exposures to two forms of trivalent chromium was conducted by Derelanko *et al.* (1999). This study was selected as the key study for the evaluation of chronic noncarcinogenic toxicity of trivalent chromium compounds. This study was also selected by ATSDR (2009) to derive intermediate duration inhalation MRLs for soluble and insoluble trivalent chromium compounds. The Derelanko *et al.* (1999) study identified a LOAEL of 17 mg/m^3 as basic chromium sulfate ($Cr_2[OH]_x[SO_4]_y$ $NaSO_4$ $2H_2O$) (equivalent to 3.0 mg Cr^{3+}/m^3), and a NOAEL of 4.4 mg/m^3 as chromic oxide (Cr_2O_3) (equivalent to 3.0 mg Cr^{3+}/m^3). The specific endpoints varied for each chromium compound, but both caused point-of-entry effects in the respiratory tract. The authors selected these two forms of trivalent chromium (one soluble and the other insoluble) for their study, since solubility appears to play a role in chromium toxicity.

Exposure

Male and female CDF (Fischer 344)/Crl BR VAF/Plus rats were exposed in stainless steel and acrylic nose-only inhalation chambers. Chromic oxide particles were generated with a modified low-output dust generator using spinning glass beads over a packed cake of test material, while basic chromium sulfate particles were generated using an auger dust feeder and an air micronizer. Seven groups of 30 rats (15 of each sex) were randomly assigned to the following groups: a control group, chromic oxide (4.4, 15, or 44 mg/m^3), or basic chromium sulfate (17, 54, 168 mg/m^3). "The desired exposure levels were selected to be multiples of the threshold limit value (TLV) for trivalent chromium and set at equivalents of 3, 10 and 30 mg/m^3 for each test article" (Derelanko *et al*. 1999). Animals were exposed for 6 h/day, 5 days/week, for 13 consecutive weeks (total of 65 exposures). Mean particle sizes (in microns ± geometric standard deviation) in the 4.4, 15, and 44 mg/m^3 chromic oxide exposure groups were 1.8±1.93, 1.9±1.84, and 1.9±1.78, respectively. Mean particle sizes in the 17, 54, and 168 mg/m^3 basic chromium sulfate exposure groups were 4.2±2.48, 4.2±2.37, and 4.5±2.50, respectively. The chromic oxide and basic chromium sulfate test materials were analyzed for hexavalent chromium, and none was detected. Ten males and ten females from each group were sacrificed after 13 weeks, while 5 males and 5 females from each group were maintained for an additional 13-week recovery period with no additional exposures. In addition to the main study groups, 10 additional rats (5/sex) were exposed to the same exposure conditions for 5 consecutive days then sacrificed for evaluation of BALF parameters.

Endpoints Evaluated

Clinical observations included signs of toxicity, morbidity, mortality, body weights, and ophthalmoscopic examination. Clinical pathology included hematology, biochemistry, urinalysis (including β-microglobulin analysis), and bone marrow smears. At necropsy, heart, lungs and trachea (combined), liver, spleen, kidneys, brain, adrenal glands, thyroid and parathyroid (combined), testes, and ovaries were weighed and other tissues typically harvested for subchronic studies were removed and preserved. All hematoxylin and eosin-stained tissues from the control and high-exposure groups were evaluated microscopically. Bone marrow was examined and differential cell counts of bone marrow were conducted. The kidneys, livers, nasal tissues, trachea, lungs, larynx, mediastinal and mandibular lymph nodes, and gross lesions from all animals in the low- and mid-exposure groups were also examined. A formal peer review of the histopathologic findings was performed. At necropsy, sperm samples were evaluated for motility, count, and morphology. The BALF evaluation after just 5 days of exposure involved nucleated cell counts, cell differential counts, chemical analysis for lactate dehydrogenase (LDH), total protein, β-glucoronidase, and glutathione reductase.

Results for Basic Chromium Sulfate

Body weight was significantly decreased in males in the mid (54 mg/m^3) and high (168 mg/m^3) basic chromium sulfate exposure groups and in females in the high exposure group. Significant

organ weight changes were noted in males and females in the high exposure group, but were not considered by the authors to be adverse due to the absence of histopathological changes. Exposure to the lowest concentration of basic chromium sulfate (17 mg/m^3) resulted in widespread effects in the nasal cavity, larynx, lungs, and mediastinal lymph nodes. In addition, there were statistically significant increases in mean absolute and relative combined lung and trachea weights, statistically reduced total nucleated cell counts, and mediastinal lymph node enlargement. Microscopic evaluation of the lung revealed that exposure to the lowest concentration of basic chromium sulfate resulted in chronic inflammation in alveoli and alveolar spaces filled with macrophages, neutrophils, lymphocytes, and cellular debris; foci with intense inflammation and thickened alveolar walls; chronic interstitial inflammation with cell infiltration; hyperplasia of Type II pneumocytes; and granulomatous inflammation with infiltration of macrophages and multinucleated giant cells. In addition to the microscopic effects in the lungs, there was macrophage infiltration and granulomatous inflammation of the larynx, acute inflammation and suppurative and mucoid exudates of nasal tissues, and histiocytosis and hyperplasia of peribronchial lymphoid tissues and the mediastinal lymph node. A LOAEL of 17 mg/m^3 (3.0 mg Cr^{3+}/m^3) as basic chromium sulfate was identified from the Derelanko *et al*. (1999) study for a subchronic exposure duration. Table 4 is a summary of results that were statistically significantly different from controls at the lowest concentration after 13 weeks of exposure and after a 13-week recovery period.

Results for Chromic Oxide

Absolute and relative lung and trachea (combined) weights were significantly elevated in the high (44 mg/m^3) chromic oxide exposure group compared to controls for males, but not for females. Mediastinal lymph node enlargement was also noted in the high dose group. Exposure to the mid-level (15 mg/m^3) concentration of chromic oxide resulted in pathologic changes in the bronchial and mediastinal lymphatic tissue and lungs. The mid-level exposure group also had statistically significant increases in mean absolute and relative thyroid and parathyroid (combined) weights in females. However, the organ weight changes failed to show a clear dose-response, and the authors indicated that the biological importance could not be determined. Lymphoid hyperplasia of the mediastinal lymph node was reported in all treatment groups. Although a few microscopic effects were observed in the respiratory tracts of some animals exposed to the low level of chromic oxide, these minimal effects (trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats) were not determined to be adverse. Therefore, a subchronic NOAEL of 4.4 mg/m^3 (3.0 mg Cr^{3+}/m^3) and a subchronic LOAEL of 15 mg/m^3 (10 mg Cr^{3+}/m^3) as chromic oxide were identified from the Derelanko *et al*. (1999) study. Although the mid-level concentration group 15 mg/m^3 (10 mg Cr^{3+}/m^3) for chromic oxide was identified as a LOAEL, the remainder of this DSD focuses on basic chromium sulfate, which produced clearly significant adverse effects at a lower trivalent chromium level (3 mg Cr^{3+}/m^3).

Table 4 Significant Adverse Effects at LOAEL (17 mg/m^3) from Derelanko *et al.* (1999)

Subchronic Exposure to Basic Chromium Sulfate	**Recovery Period**	**Amenable to BMC Modeling**
6 h/day, 5 days/week, 13 weeks	**13 weeks**	
Body Weight, Organ Weights, Gross Anatomic Pathology		
Increased mean total lung and trachea weight (male & female)	No significant effects	Yes
Increased relative lung and trachea weight/body weight (male & female)	Same significant effects	Yes
Mediastinal lymph-node enlargement	Same significant effects	No
Microscopic Pathology		
Chronic inflamation of alveoli (alveolar spaces filled with macrophages, neutrophils, lymphocytes, and cellular debris, with some thickening of alveolar walls)	Similar effects, but reduced in severity	No
Chronic instersticial inflamation, multifocally distributed consisting of thickened alveolar septa caused by inflamatory cell infiltration and hyperplasia of alveolar septal cells (type II pneumocytes)	Similar effects, but reduced in severity	No
Multifocal areas of granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells (associated with foreign material presumed to be the test article)	Similar effects, but with decreased incidence	No
Trace to severe, mutifocal to diffuse pulmonary infiltration of alveolar macrophages with foamy or granular appearing acidophilic cytoplasm in the alveolar lumens	Similar effects, but reduced in severity	No
Green refractile foreign material was present in the lamina propria and submucosa of the larynx	No foreign material detected	No
Histiocytosis consisting of macrophages or histiocytes with abundant foamy cytoplasm and lymphoid hyperplasia in the peribronchial lymphoid tissue and mediastinal lymph node, correlating with lymph-node enlargement	Same effects	No
Acute inflamation, suppurative exudate, and mucoid exudate in nasal tissues, particularly in the mid-posterior portion	Effects no longer present	No

Bronchoalveolar Lavage Fluid (BALF) Evaluation

Although the BALF evaluation is not particularly relevant to chronic toxicity, since BALF parameters were evaluated after only 5 days of exposure, several compound-related effects were noted in the basic chromium sulfate exposure groups. Males and females at all exposure levels showed statistically reduced total nucleated cell counts. Although it is reasonable to assume that effects seen after 5 days of exposure could also be present over a chronic exposure period, the sub-acute exposure duration and the questionable ultimate long-term adversity of reduced total nucleated cell counts made the BALF evaluation not useful as a POD for the chronic evaluation. Other notable effects, although not statistically significant, included increased segmented neutrophils, decreased mononuclear cells, increased protein and lactate dehydrogenase, and increased amounts of cell debris and lysed cells. A yellow, intracytoplasmic, crystalline material was present within mononuclear cells from all chromic oxide exposure groups. However, no statistically significant differences were noted in BALF parameters in any of the chromic oxide exposure groups.

4.1.1.2.2 Supporting Animal Studies (Johansson *et al.* 1986a, 1986b, 1987)

Several subchronic studies that evaluated trivalent inhalation exposures were conducted by Johansson *et al.* (1986a, 1986b, 1987). These studies were selected as supporting studies for the evaluation of chronic noncarcinogenic toxicity. The Johansson *et al.* (1986a, 1986b, 1987) studies identified a mild LOAEL of 0.6 mg Cr^{3+}/m^3.

Although the Johannson *et al*. (1986a, 1986b, 1987) studies were used to derive supporting chronic toxicity values for trivalent chromium, no other regulatory agency has developed values based on these studies. There was only a control group and one (1986a, 1986b) or two (1987) exposure concentrations, limited endpoints were evaluated, and similar mild effects were noted over different exposure durations and concentrations. The key study selected in this DSD (Derelanko *et al*. 1999) was a better study that examined two different forms of trivalent chromium in rats. In addition, Derelanko *et al*. (1999) looked at a wider range of endpoints, exposed subjects to more doses, and provided more statistical information about the significant effects. Overall, the deficiencies in the Johannson *et al*. (1986a, 1986b, 1987) studies, combined with the advantages of the Derelanko *et al*. (1999) study, make the Johansson *et al*. (1986a, 1986b, 1987) data less reliable for derivation of chronic toxicity values.

Although the Derelanko *et al*. (1999) study was selected as the key study, the LOAEL from Johansson *et al*. (1986a, 1986b, 1987) was used to derive a supporting ReV for comparison purposes (Appendix D).

Johannson et al. (1986a, 1986b)

Rabbits were exposed to hexavalent chromium (0.9 mg Cr^{6+}/m^3) as an aerosol of sodium chromate (Na_2CrO_4), or to trivalent chromium (0.6 mg Cr^{3+}/m^3) as an aerosol of chromium nitrate

[$Cr(NO_3)_3$], intermittently for 5 days/week, 6 h/day for 4 to 6 weeks. Eight rabbits in each exposure group (0.9 mg Cr^{6+}/m^3, 0.6 mg Cr^{3+}/m^3 and a control group exposed to filtered air) were held in exposure chambers during the exposure period. Chromium aerosols were produced by an ultrasonic nebulizer, with a MMAD of about 1 µm. At the end of the exposure, rabbits were euthanized with sodium pentobarbital and the lungs were excised. Alveolar macrophages were collected, concentrations measured, viability tested, and size distribution determined. Thin sections of the lung were examined by electron microscopy and metal content of macrophages was determined. The oxidative metabolic activity of the macrophages and the phagocytic activity of the macrophages were measured.

Although the number of macrophages from rabbits exposed to hexavalent chromium were increased, the number of macrophages in rabbits exposed to trivalent chromium were not increased. However, trivalent chromium caused striking morphological changes, including: round dark chromium-rich inclusions in the cytoplasm, increased number of cells with a smooth inactive cell surface, enlarged Golgi apparatus, and a tendency toward elongated cell shape. Phagocytosis and oxidative metabolic activity was impaired by trivalent chromium. These effects represent a decrease in the functional and metabolic activity of the macrophage (Johansson *et al.* 1986b), and could be considered a mild subchronic effect of trivalent chromium from inhalation exposure.

Johanson et al. (1987)

Rabbits were exposed to filtered air, 0.6 or 2.3 mg Cr^{3+}/m^3 as an aerosol of $Cr(NO_3)_3$ intermittently for 5 days/week, 6 h/day for 17 to 21 weeks. Eight male rabbits in each exposure group were held in exposure chambers during the exposure period. Chromium aerosols were produced by an ultrasonic nebulizer, with a MMAD of about 1 µm. At the end of the exposure, rabbits were euthanized with sodium pentobarbital and the right lung was excised. Alveolar macrophages were collected, concentrations measured, viability tested, and cell-size distribution determined. The upper left lung was examined by light microscopy, while pieces from the lower left lung were sampled for electron microscopy. Light microscopy was used to examine inflammatory lesions and the structure of the alveolar epithelium and macrophages. The electron microscopy was used for morphometrical measurements of the volume density of alveolar type II cells. The remainder of the left lung lobe was used for analysis of phospholipid content.

The results of the Johansson *et al*. (1987) study were similar to the results of the Johansson *et al*. (1986a, 1986b) studies, with macrophages characterized by round dark, chromium rich inclusions, very large lysosomes with membranous fragments, increased numbers of lamellar inclusions, and a frequent elongation of the cell profile. Both chromium-exposed groups showed nodular accumulation of macrophages with abnormal appearance. These effects were associated with no or only minor effects on other cells, which is compatible with the effects noted by Henderson *et al*. (1979) in their acute study. Overall, mild lung effects were noted in this subchronic study (Johansson *et al*. 1987) at the same LOAEL (0.6 mg Cr^{3+}/m^3) as in the earlier

subchronic studies (Johansson *et al*. 1986a, 1986b).

The exposure dose of 0.6 mg Cr^{3+}/m^3 from the Johannson *et al*. studies (1986a, 1986b, 1987) was identified as a mild LOAEL, and this POD was used for the derivation of a supporting ReV (Appendix D). Alveolar macrophages play a central role in the defense system of the lung; however, the relevance of the mild effects to adverse outcomes is questionable. The authors themselves (Johansson *et al*. 1987) state that further studies are needed to elucidate the pathophysiological significance of their observations.

4.1.1.2.3 Other Animal Studies

Lee *et al*. (1989) treated rats with 0.31 or 15.5 mg Cr^{4+}/m^3 as chromium dioxide dust for two years. All rats treated at both exposure levels had discolored midastinal lymph nodes and lungs, and dust laden macrophages. Lung weight was increased at 12 and 24 months in the higher dose group. The authors concluded that all of the noted effects represent increased lung burden of chromium dioxide dust and normal physiological responses of macrophages to dust. No cardiovascular effects, histological evidence of kidney damage, or impairment of kidney function were noted in this study. Serum levels of blood urea nitrogen, creatinine, and bilirubin were normal (Lee *et al*. 1989). No treatment-related histopathological lesions were found in the stomach, large intestine, duodenum, jejunum, or ileum of the rats; there were no histopatholgical abnormalities in adrenals, pancreas, and thyroid glands; no adverse hepatic effects were noted; and there were no changes in hematological parameters. In addition, there was no effect on body weight gain, ocular tissue had normal morphology, and no histopathological lesions were observed in the prostate, seminal vesicle, testes, or epididymis of male rats or in the uterus, mammary gland, or ovaries of female rats (Lee *et al*. 1989). A chronic NOAEL at the highest dose of 15.5 mg/m^3 was identified for tetravalent chromium as chromium dioxide. Although this was a well-conducted chronic study, this study was not selected for development of a ReV because of the use of an uncommon tetravalent form of chromium (chromium dioxide) and because the only noted effects were dust-related, not chromium related.

A continuous, sub-chronic exposure study in rats was identified in a search of the Registry of Toxic Effects of Chemical Substances (RTECS) database, but is only published in Russian and was not obtainable. This study exposed rats to chromium sulfate continuously 24 h/day for 17 weeks and identified a threshold concentration low (TC_{Lo}) for adverse effects at 4.2 mg/m^3. Details of this study were not available, so it was not used to derive a ReV for trivalent chromium as chromium sulfate.

Glaser *et al.* (1986 and 1988) performed chronic exposure experiments in rats, which were exposed by inhalation to a 3:2 mixture of hexavalent chromium trioxide and trivalent chromium oxide for 18 months. The studies by Glaser *et al.* (1986 and 1988) examined mixed trivalent and hexavalent chromium exposures, and neither study could be used to derive a chronic ReV for trivalent chromium as chromium oxide or other chromium compounds.

4.1.2 MOA Analysis

The toxicokinetics of chromium are discussed in detail in the acute section of this DSD (Section 3.1.2). The chronic MOA for effects from trivalent chromium exposure are expected to be similar to the acute MOA, since acute and chronic exposures appear to affect primarily the respiratory tract and lungs. As stated in the acute section, the majority of chromium-induced effects following inhalation exposures are seen in the respiratory tract, with some systemic effects seen at extremely high concentrations (ATSDR 2009).

4.1.3 Dose Metric

In the key study using rats (Derelanko *et al*. 1999), data on exposure concentration of the parent chemical are available. The adverse effect for the key study is related to effects in the respiratory tract from exposure to the parent chemical and other dose metrics are not available. Therefore, exposure concentration of the parent chemical is the appropriate dose metric (TCEQ 2006).

4.1.4 POD for Key Study

Data on several of the adverse effects noted in the key study were evaluated as PODs (Table 4). The only data amenable to benchmark concentration (BMC) modeling were data on statistically significant changes in male and female organ weight (absolute and relative lung and trachea weight [combined]), which were continuous data. These data were modeled with BMD Software (BMDS) (USEPA Version 2.0) using continuous models (Section 4.1.4.2 *BMC Modeling*).

4.1.4.1 Data Not Amenable to BMC Modeling

According to guidance in USEPA (2000), if the data for an endpoint are not amenable to modeling, the POD will be the statistically derived study NOAEL, if a NOAEL is available, or the LOAEL. The LOAEL for basic chromium sulfate of 17 mg/m^3 (3.0 mg Cr^{3+}/ m^3) was used as an alternative POD. Several significant adverse endpoints were identified at this LOAEL, primarily lesions throughout the respiratory tract. However, they were not amenable to BMD modeling, since incidence data were not reported by Derelanko *et al*. (1999). This LOAEL was selected because it was the lowest effect level for adverse effects and corresponds to the same concentration used in BMC modeling for other endpoints. Table 4 lists some of the significant adverse effects noted at the LOAEL and whether the effects were any less severe after a 13-week recovery period.

The selected endpoints are from a single study (Derelanko *et al*. 1999) so the same dosimetric adjustments were applied to each endpoint. The endpoint with the lowest POD determined with BMC modeling, or the LOAEL of 17 mg/m^3 (if data were not amenable to BMC modeling), may be the critical effect. Any endpoint which is considered adverse, biologically plausible, and consistent with the proposed MOA may be identified as the critical effect.

All of the adverse effects noted in the key study at the LOAEL are correlated (subchronic lung and trachea weight changes, macroscopic and microscopic inflammatory responses in respiratory

tract tissues, and acute BALF changes) indicating that a modeled BMC would likely be representative of the entire array of endpoints. However, to be thorough, endpoints not amenable to BMC modeling were carried forward for comparison to the BMC results.

4.1.4.2 BMC Modeling

The terms benchmark concentration (BMC) and 95% upper confidence limit benchmark concentrations (BMCL) are used instead of BMD and benchmark dose low (BMDL), respectively, since the data represents an inhalation exposure concentration in air, not an oral exposure dose.

4.1.4.2.1 Critical Effect Size

If there is an acceptable level of change in the endpoint that is considered to be biologically significant, then that amount of change is chosen for evaluation (USEPA 2000). For dichotomous data, this level is typically expressed as a certain increase in the incidence of adverse outcomes and is referred to as the benchmark response (BMR). In order to distinguish continuous data from dichotomous data, Dekkers *et al*. (2001) recommended the term "critical effect size" (CES) be used instead of the term "BMR," since for continuous data, the effect measure is expressed on a continuous scale. A CES defines the demarcation between non-adverse and adverse changes in toxicological effect parameters for continuous data (Dekkers *et al*. 2001). For example, a CES of 10% or CES_{10} for continuous data (*i.e.*, a 10% change in the mean of a treated group compared to the control mean) is not the same as a BMR of 10% or BMR_{10} (*i.e.*, 10% of total animals responding [dichotomous data]).

A 10% change in organ weight relative to the mean organ weight in the control animals (*i.e.*, CES_{10}) is typically considered an adverse effect (USEPA 2000, Dekkers *et al*. 2001). The significant change seen in organ weight in the key study (Derelanko *et al*. 1999) is accompanied by other macroscopic and microscopic inflammatory responses in the respiratory tract. Although many of these microscopic and macroscopic effects were reduced or even reversible after a 13-week recovery period, they are important for potential chronic, daily exposure. The array of effects is considered to be mild per Table 18 of TCEQ (2006). Therefore, for the Derelanko *et al*. (1999) study, a BMC_{10} and $BMCL_{10}$ were calculated for the CES_{10} based on the critical effect of increased total lung and trachea weight (combined) relative to body weight in male and female rats. The BMC and BMCL with a CES of 1 standard deviation (SD) from the control mean (BMC_{1SD} and $BMCL_{1SD}$) were also calculated and are presented in Appendix B for comparison purposes, as suggested by USEPA (2000). ATSDR (2009) did BMC modeling with the same endpoint and data, but selected the $BMCL_{1SD}$ as their critical value instead of the $BMCL_{10}$.

4.1.4.2.2 BMC Modeling Results

Appendix B contains detailed information on the BMC modeling results whereas the following sections provide a summary of results.

Increased total lung and trachea weight (combined) relative to body weight in male and female

rats was identified by the TD as a potential POD from the Derelanko *et al*. (1999) study. BMC analysis was conducted using USEPA BMD software (version 2.0) based on male and female total lung and trachea weight (combined) data relative to body weight from Table 3 in Derelanko *et al*. (1999). The specific data modeled is given in Appendix B. Expressing total lung and trachea weight (combined) relative to body weight is used to normalize changes in lung and trachea weight. Therefore, BMC modeling results based on total lung and trachea weight (combined) relative to body weight were used for identification of a POD. Goodness of fit was evaluated by p-values > 0.1, visual inspection of the dose-response curves, and scaled residuals less than an absolute value of 2. Tests from BMC continuous models were examined to evaluate the hypothesis that response and variance do not differ among dose levels as well as whether a homogeneous (constant) or nonhomogeneous variance was appropriate.

The unrestricted power model with nonhomogeneous variance was the only model that had an adequate fit to the male rat data. The following models had an adequate fit to the female rat data: unrestricted power, polynomial, and linear with the high dose removed, all with nonhomogeneous variance.

For male rats the only acceptable model was the unrestricted power model which produced a $BMCL_{10}$ value of 3.451 mg/m^3. For female rats, the polynomial model had a lower AIC value than the other 4-concentration models, indicating a better fit. The linear model (no high concentration) also provided an adequate fit, but didn't include the highest dose level, so the results from the polynomial model (4-concentration) were used. The polynomial model for female rats produced a $BMCL_{10}$ value of 6.070 mg/m^3 which was higher that the $BMCL_{10}$ value for male rats. Since data from the study indicates that male rats may be more sensitive to the effects of basic chromium sulfate exposure, the $BMCL_{10}$ for male rats of 3.451 mg/m^3 was selected for use as a potential POD for the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$.

4.1.5 Dosimetric Adjustments

4.1.5.1 Exposure Duration Adjustments

According to the ESL guidance (TCEQ 2006), the PODs from Derelanko *et al*. (1999) were adjusted to a continuous exposure concentration:

$BMCL_{10}$ Approach

$$POD_{ADJ} = POD \times D/24 \times F/7$$
$$= (3.4515 \text{ mg/m}^3) \times (6 \text{ h}/24 \text{ h}) \times (5 \text{ d}/7 \text{ d})$$
$$= 0.61635 \text{ mg/m}^3$$

LOAEL Approach

$$POD_{ADJ} = POD \times D/24 \times F/7$$
$$= (17 \text{ mg/m}^3) \times (6 \text{ h}/24 \text{ h}) \times (5 \text{ d}/7 \text{ d})$$
$$= 3.0357 \text{ mg/m}^3$$

where : POD = point of departure in key study
D = h per day
F = days per week
POD_{ADJ} = point of departure adjusted for continuous duration

4.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

The MPPD model version 2.3 (CIIT and RIVM 2002) was used to calculate the depositional fraction for basic chromium sulfate in the target respiratory region. Parameters necessary for this model are particle diameter, particle density, chemical concentration, and species. Although the USEPA RDDR model is also available, the MPPD model is preferred for modeling from rats to humans (TCEQ 2006). The MPPD model allows the adjustment of a rat dose to a human equivalent dose for PM and aerosolized compounds. At the LOAEL concentration (17 mg/m^3) the key study by Derelanko *et al.* (1999) reported a MMAD and σ_g of the basic chromium sulfate of 4.2 µm and 2.48, respectively. The density of basic chromium sulfate is 1.25 g/cm^3 (ILO 2004). The MMAD, σ_g and density were then used in the CIIT and RIVM (2002) model (version 2.3), along with species specific information on the rat, to convert the rat dose to a human equivalent concentration (HEC). The input terms and the output from the MPPD model run using the Derelanko *et al*. (1999) study are presented in Appendix C.

Significant effects were noted throughout the respiratory region in the key study (Derelanko *et al*. 1999). The target region for basic chromium sulfate was considered to be the total particle distribution for the head, tracheobronchial, and pulmonary regions. Since adverse effects were noted throughout the respiratory tract, and no one effect was determined to be more critical than another, one could conservatively assume particle deposition in each respiratory tract region separately, as done in ATSDR (2009). However, since there is no proximal to distal difference seen in the effects, or any distinct pattern in severity or incidence, then looking at separate regions in the respiratory tract is overly conservative (Jarabek 2009). Once total particle dosimetery was determined, the RDDR was calculated (RDDR = 1.3135965). The RDDR was then used to dosimetrically adjust from a rat to a human POD. The RDDR was multiplied by the POD_{ADJ} for the Derelanko *et al*. (1999) study to get a POD_{HEC}.

$BMCL_{10}$ Approach

$POD_{HEC} = POD_{ADJ}$ x RDDR
= 0.61635 mg/m^3 x 1.3135965
= 0.8086 mg/m^3

LOAEL Approach

$POD_{HEC} = POD_{ADJ}$ x RDDR
= 3.03571 mg/m^3 x 1.3135965
= 3.9877 mg/m^3

4.1.6 Critical Effect and Adjustments of the POD_{HEC}

The MOA by which trivalent chromium produces respiratory system toxicity is not yet understood (Section 3.1.2). Assuming a threshold/nonlinear MOA, appropriate UFs were applied to the POD_{HEC} to derive a chronic ReV.

4.1.6.1 $BMCL_{10}$ Approach

The POD_{HEC} of 0.8086 mg/m^3 based on the $BMCL_{10}$ for increases in total lung and trachea weight relative to body weight in male rats from the Derelankno *et al.* (1999) study was used to derive a ReV. The ReV was calculated by applying the following UFs to the POD_{HEC}: an UF_A of 3 for extrapolation from animals to humans; an UF_H of 10 to account for variability within the human population; a UF_L of 1; a UF_D of 3; and a subchronic to chronic UF (UF_{Sub}) of 10 (total UFs = 1000).

An interspecies UF of 3 was used because the MPPD program accounts for toxicokinetic differences and limits uncertainty between rat and human extrapolation but does not account for toxicodynamic differences. A full UF_H of 10 was applied because little information on variability in the human population to effects from trivalent chromium inhalation exposure was available (ATSDR 2009) and because sensitive humans in the population have been identified. Per TCEQ (2006), a UF_L is not applicable as BMC modeling was performed and the $BMCL_{10}$ that was used as the POD is expected to be similar to a NOAEL. A UF_D of 3 was applied because the database on toxicity of trivalent chromium compounds is limited and lacks multigenerational reproductive and developmental studies. Available data consistently indicates that respiratory effects, the effects evaluated as critical effects, occur at lower concentrations than systemic effects. A subchronic to chronic uncertainty factor of 10 was applied because no chronic trivalent chromium studies were available, even though in general, trivalent chromium is relatively nontoxic and several subchronic studies identified similar mild LOAELs across a range of exposure durations (28 to 147 days).

4.1.6.2 LOAEL Approach

The POD_{HEC} of 3.9877 mg/m^3 based on the LOAEL for mediastinal lymph-node enlargement and multiple microscopic effects in the respiratory tract characteristic of lung inflammation from the Derelankno *et al.* (1999) study was used to derive a comparison ReV. These effects were considered early adverse effects and relevant to humans. The ReV was calculated by applying the following UFs to the POD_{HEC}: an UF_A of 3 for extrapolation from animals to humans; UF_H of 10 to account for variability within the human population; a UF_L of 3; a UF_D of 3; and a UF_{Sub} of 10 (total UFs = 3000).

The UF_A of 3, UF_H of 10, UF_D of 3 and UF_{Sub} of 10 were similar to the UFs applied to the POD_{HEC} derived using BMC modeling, and similar reasons were used for these UFs. The UF_L was the only UF that differed. According to the ESL Guidance (Table 18, TCEQ 2006), the noted effects are relatively mild and precursors to more significant impacts. Therefore, a UF_L of

3 was applied.

4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

As discussed in the previous section, UFs are applied to the POD_{HEC} from the key study (Derelanko *et al.* 1999) to derive the chronic ReV.

$BMCL_{10}$ Approach

$$\text{chronic ReV} = [POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D \times UF_{Sub})] \times CF$$
$$= [0.8086 \text{ mg/m}^3 / (10 \times 3 \times 1 \times 3 \times 10)] \times 1000 \text{ µg/mg}$$
$$= (0.0008086 \text{ mg/m}^3) \times 1000 \text{ µg/mg}$$
$$= 0.8086 \text{ µg/m}^3$$

LOAEL Approach

$$\text{chronic ReV} = [POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D \times UF_{Sub})] \times CF$$
$$= [3.9877 \text{ mg/m}^3 / (10 \times 3 \times 3 \times 3 \times 10)] \times 1000 \text{ µg/mg}$$
$$= (0.001329 \text{ mg/m}^3) \times 1000 \text{ µg/mg}$$
$$= 1.329 \text{ µg/m}^3$$

Although BMC modeling is the preferred approach to developing a ReV, the comparability of the results from the LOAEL approach, and the fact that the statistically significant effects noted at the LOAEL are all correlated, makes the information from both approaches valuable. The $BMCL_{10}$ derived chronic ReV of 0.8086 µg/m^3 was lower than the ReV based on the LOAEL approach and was selected as the preferred ReV. The ReV was rounded to two significant figures at the end of all calculations. The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{nonlinear(nc)}$. Rounding to two significant figures, the chronic ReV is 0.81 µg/m^3. At the target hazard quotient of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 0.24 µg/m^3 (Table 5).

The chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ which were derived are for basic chromium sulfate, which in the study was approximately 25% chromic oxide (Cr_2O_3). The MW of chromium is 51.996 Da and the MW of Cr_2O_3 is 151.99 Da (Appendix 10). Dividing the MW of Cr_2 by the MW of Cr_2O_3 (103.992 / 151.99) gives the fraction of Cr (0.684) in the compound Cr_2O_3. Since basic chromium sulfate used in the Derelanko *et al*. (1999) study was approximately 25% Cr_2O_3, the fraction of trivalent chromium relative to the dose of basic chromium sulfate is 0.684 x 0.25 = 0.171 (17.1 %). The chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ for trivalent chromium can then be calculated by multiplying the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ for basic chromium sulfate, respectively, by 0.171. Rounding to two significant figures, the chronic ReV for trivalent chromium is 0.14 µg/m^3. At the target hazard quotient of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ for trivalent chromium is 0.041 µg/m^3 (Table 5).

There is clear evidence in the Derelanko *et al*. (1999) study and in other studies that trivalent chromium toxicity varies substantially from compound to compound and is related to the

physical properties of the compound (*i.e*, water-solubility and acidity), not just the presence of trivalent chromium. The derivation of the chronic ReV and the $^{chronic}ESL_{nonlinear(nc)}$ for a soluble trivalent chromium compound (basic chromium sulfate) that causes adverse effects at a lower concentration than an insoluble trivalent chromium compound (chromic oxide) is likely to be protective for trivalent chromium compounds in general (both soluble and insoluble). The toxicity of elemental and divalent chromium compounds is expected to be similar or less than that of common trivalent forms. Therefore, the chronic ReV and $^{chronic}ESL$ for trivalent chromium is expected to be protective for these forms of chromium as well. As a science policy decision the chronic ReV and $^{chronic}ESL$ derived for trivalent chromium will be used for all compounds of chromium, except for hexavalent compounds.

Table 5 Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	**Summary**
Study	Derelanko *et al*. (1999) $BMCL_{10}$
Study Population	Ten rats per dose group
Study Quality	High
Exposure Methods	Inhalation of basic chromium sulfate particulate (0, 17, 54, 168 mg/m^3)
LOAEL	17 mg/kg (3 mg/m^3 Cr^{3+})
Critical Effects	Increased total lung and trachea weight relative to body weight in male and female rats
POD	3.45156 mg/m^3 ($BMCL_{10}$)
Exposure Duration	13 weeks (5 day/week, 6 h/day)
POD_{ADJ} (extrapolated to continuous exposure)	0.61635 mg/m^3
POD_{HEC}	0.8086 mg/m^3 (RDDR = 1.3135965 for entire respiratory tract)
Total UFs	1000
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL UF	*1*
Subchronic to Chronic UF	*10*
Incomplete Database UF	*3*
Database Quality	*Medium*
chronic ReV (HQ = 1)	0.81 $\mu g/m^3$
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	0.24 $\mu g/m^3$
Chronic ReV (HQ = 1)	**0.81 $\mu g/m^3$ as basic chromium sulfate** **0.14 $\mu g/m^3$ as Cr^{3+}**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**0.24 $\mu g/m^3$ as basic chromium sulfate** **0.041 $\mu g/m^3$ as Cr^{3+}**

4.1.8 Supporting Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Two supporting health-based chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ values are presented in Appendices D and E. Appendix D is an alternative chronic noncarcinogenic approach using a series of supporting studies (Johannson *et al*. 1986a, 1986b, 1987). The chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ values based on this analysis were 0.012 µg Cr^{+3}/m^3 and 0.0036 µg Cr^{+3}/m^3, respectively. As discussed previously, the Johannson *et al*. studies (1986a, 1986b, 1987) were not selected as key studies because they evaluated only a limited number of endpoints, were not as well conducted as the Derelanko *et al*. (1999) study, and the noted effects were not clearly adverse.

Appendix E is an alternative chronic noncarcinogenic approach considering total chromium (as trivalent compounds) as an essential nutrient. The chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ values based on this analysis were 0.1 µg Cr^{+3}/m^3 and 0.03 µg Cr^{+3}/m^3, respectively. These values are presented for comparison purposes only.

4.1.9 Conclusion on Selection of Key Study

Although few studies were identified in the scientific literature that could be used to develop a chronic ReV for elemental, trivalent, or divalent chromium compounds, several studies had adequate information according to TCEQ (2006). Section 4.3 of the ESL Guidelines (TCEQ 2006) indicates that if the minimum database requirements are met to derive a chronic ReV, then a chronic ReV should be derived. The subchronic study by Derelanko *et al*. (1999) was used to derive a chronic ReV. Studies by Johansson *et al*. (1986a, 1986b, 1987) were used to derive a supporting chronic ReV (Appendix D). In addition, a chronic ReV was derived using adequate intake values (AIVs) from NAS (2004), since chromium is an essential nutrient (Appendix E).

The approach in this DSD diverges from USEPA and California EPA, neither of which has developed a chronic toxicity value for elemental, divalent, or trivalent chromium compounds. ATSDR has recently developed intermediate duration inhalation MRLs for soluble and insoluble trivalent chromium compounds. No assessments of chronic elemental, divalent, or trivalent chromium toxicity were identified from international agencies or other countries that could be considered as additional sources of toxicity assessment information. In agreement with the most recent review by ATSDR (2009) the TD evaluated the available studies and determined that adequate information existed, the minimum database requirements were satisfied, and a chronic ReV was developed.

4.2 Carcinogenic Potential

There is an abundance of information available on the carcinogenic potential of chromium compounds and on the genotoxicity and mutagenicity of chromium compounds in experimental systems. The consensus from various reviews and agencies is that evidence of carcinogenicity of elemental, divalent, or trivalent chromium compounds is lacking. The American Council of Governmental and Industrial Hygienists (ACGIH 2001) determined that elemental and trivalent

chromium compounds are not classifiable as human carcinogens (A4). The International Agency for Research on Cancer (IARC 1990) has classified elemental chromium and trivalent chromium compounds as not classifiable as to their carcinogenicity to humans (Group 3). According to USEPA (1998), human data addressing exposure to trivalent chromium compounds alone are not available and animal data are inadequate for the evaluation of the carcinogenicity of trivalent chromium compounds. Two oral studies that were located for trivalent chromium reported negative results in rats and mice, and several inhalation studies have not found an increased incidence of lung tumors following exposure by natural routes, intrapleural injection, or intrabronchial implantation (USEPA 1998).

ATSDR (2009) reviewed the epidemiological studies of workers in a number of industries (chromate production, chromate pigment production and use, and chrome plating) and concluded that while occupational exposure to hexavalent chromium compounds is associated with an increased risk of respiratory system cancers (primarily bronchogenic and nasal), results from occupational exposure studies to mixtures that were mainly elemental and trivalent (ferrochromium alloy worker) were inconclusive. Studies in leather tanners, who were exposed to trivalent chromium were consistently negative. Langard (1990) reviewed 100 years of epidemiological evidence of chromium and cancer and concluded that there is no evidence indicating that human exposure to trivalent chromium is associated with increased cancer risk.

Although a few notable researches have concluded that the potential for carcinogenic risk extends to all forms of chromium and total chromium (Mancuso 1975 and 1997), the scientific consensus is that only hexavalent chromium is a known human carcinogen. A recent review by Nurminen (2006) looked at the body of evidence from international and national organizations and by individual scientists on occupational exposure to elemental chromium and trivalent chromium compounds and concluded that evidence of carcinogenicity is inadequate in humans. In summary, the evidence in regards to the carcinogenic potential of elemental and trivalent chromium compounds is lacking.

In addition to the lack of direct evidence of carcinogenicity of trivalent or elemental chromium and its compounds, the genotoxic evidence is overwhelmingly negative. Chromium and its compounds have been studied more extensively than any other metal compounds in short-term genotoxicity tests using various targets and/or genetic endpoints (DeFlora *et al.* 1990). The genotoxicity of chromium was reviewed by the World Health Organization (WHO 1988), DeFlora *et al*. (1990), and more recently by ATSDR (2009). DeFlora *et al*. (1990) summarize the relationship between mutagenicity and carcinogenicity of elemental and trivalent chromium compounds as follows:

> “The conclusions that can be drawn from the analysis of the results obtained in short-term tests are consistent with the available information on the carcinogenicity of chromium in humans and in experimental animals. In particular, the inactivity of Cr(0) and of Cr(III) compounds in short-term tests, as reported in most studies, is in agreement with the

> allocation of metallic chromium and Cr(III) compounds to Group 3, *i.e.*, compounds for which there is inadequate evidence of carcinogenicity in humans (IARC, 1980, 1987b)."

Therefore, according to the 2005 Cancer Guidelines, elemental, divalent, and trivalent chromium compounds are "not likely to be carcinogenic to humans." (USEPA 2005)

4.3. Welfare-Based Chronic ESL

No data were found regarding vegetative effects from exposures to airborne chromium (see Section 3.3).

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation of trivalent chromium compounds resulted in the derivation of the following values:

- chronic ReV = 0.14 µg/m^3 as Cr^{3+}
- $^{chronic}ESL_{nonlinear(nc)}$ = 0.041 µg/m^3 as Cr^{3+}

The long-term ESL for air permit reviews is the health-based $^{chronic}ESL_{nonlinear(nc)}$ of 0.041 µg/m^3 (Table 1). As a science policy decision, this value will be used for elemental, divalent, and trivalent chromium compounds. The chronic ReV of 0.14 µg/m^3 will be used for the evaluation of air monitoring data (Table 1). The $^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

Chapter 5 References

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Appendix A: Chemical/Physical Data and CAS Numbers for Common Trivalent Chromium Compound other than Hexavalent

Table 6 Chemical and Physical Data – Chromium Acetate

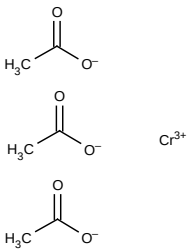
Parameter	Value	Reference
Molecular Formula	$C_6CrH_9O_6$	Chemfinder 2004b
Chemical Structure		ChemID Plus Advanced 2009
Molecular Weight	229.13 (g/mole)	Chemfinder 2004b
Physical State	Solid crystalline powder or paste-like material	Science Lab 2005a
Color	Violet, grayish green, bluish green, violet plates	Chemfinder 2004b, ATSDR 2009
Odor	Not available	ATSDR 2009
CAS Registry Numbers	1066-30-4 (chromium acetate) 25013-82-5 (chromium acetate monohydrate)	Science Lab 2005a
Synonyms/Trade Names	Chromic acetate, chromium (III) acetate, chromium triacetate, chromium(III) acetate monohydrate	Science Lab 2005a, ATSDR 2009, Chemfinder 2004b
Solubility in water	Slightly soluble in water, insoluble in alcohol	Science Lab 2005a, ATSDR 2009
Log K_{ow}	Not applicable	TD
Vapor Pressure	Not applicable	Science Lab 2005a
Vapor Density (air = 1)	Not applicable	Chemfinder 2004b
Density (water = 1)	Not available	ATSDR 2009
Melting Point	Decomposes	Science Lab 2005a
Boiling Point	Not available	Science Lab 2005a
Conversion Factors	Not applicable	Not applicable

Table 7 Chemical and Physical Data – Chromium Carbonate

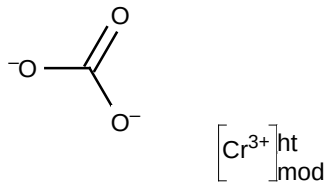
Parameter	Value	Reference
Molecular Formula	$C_3Cr_2O_9$	Chemfinder 2004c
Chemical Structure		ChemID Plus Advanced 2009
Molecular Weight	284.02 (g/mole)	Chemfinder 2004c
Physical State	Amorphous mass	Hawley's 1993
Color	Grayish-blue	Hawley's 1993
Odor	Not available	Hawley's 1993
CAS Registry Number	29689-14-3	Chemfinder 2004c
Synonyms/Trade Names	Chromium (III) carbonate basic, carbonic acid chromium salt,	Chemfinder 2004c
Solubility in water	Slightly soluble, insoluble in alcohol	Hawley's 1993
Low K_{ow}	Not applicable	TD
Vapor Pressure	Not available	Hawley's 1993
Vapor Density (air = 1)	Not available	Hawley's 1993
Density (water = 1)	2.75 (temp not specified)	Hawley's 1993
Melting Point	Not available	Hawley's 1993
Boiling Point	Not available	Hawley's 1993
Conversion Factors	Not applicable	Not applicable

Table 8 Chemical and Physical Data – Chromium Chloride

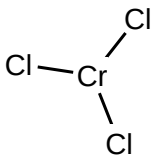
Parameter	Value	Reference
Molecular Formula	Cl_3Cr	Chemfinder 2004d
Chemical Structure		ChemID Plus Advanced 2009
Molecular Weight	158.35 (g/mole)	Chemfinder 2004d
Physical State	Crystals	J.T. Baker 2007a, OSHA 1996
Color	Greenish-black or violet	J.T. Baker 2007a, ATSDR 2009
Odor	Odorless	J.T. Baker 2007a
CAS Registry Numbers	10025-73-7 (chromium chloride) 10060-12-5 (chromium chloride hexahydrate)	J.T. Baker 2007a, Chemfinder 2004d
Synonyms/Trade Names	Chromic chloride, chromium(III) chloride, chromium chloride (3), chromium trichloride anhydrous	ATSDR 2009, J.T. Baker 2007a, OSHA 1996, Chemfinder 2004d
Solubility in water	Soluble in water, insoluble in alcohol	J.T. Baker 2007a, ATSDR 2009
Log K_{ow}	Not applicable	TD
Vapor Pressure	Not available	ATSDR 2009, J.T. Baker 2007a
Vapor Density (air = 1)	Not applicable	Chemfinder 2004d
Density (water = 1)	2.76 (temp not specified)	Chemfinder 2004d
Melting Point	1152 ^{o}C (2100 ^{o}F)	Chemfinder 2004d, J.T. Baker 2007a
Boiling Point	> 1300 ^{o}C (>2372 ^{o}F), dissociates	J.T. Baker 2007a
Conversion Factors	Not applicable	Not applicable

Table 9 Chemical and Physical Data – Chromium Nitrate

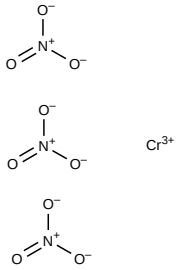
Parameter	Value	Reference
Molecular Formula & Structure	CrN_3O_9	Chemfinder 2004e
Chemical Structure		ChemID Plus Advanced 2009
Molecular Weight	238.01 (g/mole)	Chemfinder 2004e
Physical State	Solid crystalline powder or paste-like material	Science Lab 2005b, OSHA 1996
Color	Violet, grayish green, bluish green	Science Lab 2005b, ATSDR 2009
Odor	Odorless	Fisher 2007
CAS Registry Numbers	13548-38-4 (chromium nitrate) 7789-02-8 (chromium nitrate nonahydrate)	Chemfinder 2004e
Synonyms/Trade Names	Chromic nitrate, chromium (III) nitrate, chromium(III) nitrate monohydrate, chromium trinitrate, nitric acid chromium (3+)	ATSDR 2009, Science Lab 2005b, OSHA 1996, Chemfinder 2004e
Solubility in water	Soluble in water, insoluble in alcohol	Science Lab 2005b, ATSDR 2009, Chemfinder 2004e
Log K_{ow}	Not applicable	TD
Vapor Pressure	Negligible	Fisher 2007
Vapor Density (air = 1)	Not available	Chemfinder 2004e, Fisher 2007
Density (water = 1)	1.80 (temp not specified)	Fisher 2007
Melting Point	140 ^oC	Fisher 2007
Boiling Point	212 ^oF, decomposes	Fisher 2007
Conversion Factors	Not applicable	Not applicable

Table 10 Chemical and Physical Data – Chromium Oxide

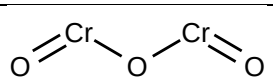
Parameter	Value	Reference
Molecular Formula & Structure	Cr_2O_3	````
Chemical Structure		ChemID Plus Advanced 2009
Molecular Weight	151.99 (g/mole)	J.T. Baker 2005
Physical State	Crystalline solid	J.T. Baker 2005
Color	Light to dark green or bright green	J.T. Baker 2005
Odor	Odorless	J.T. Baker 2005
CAS Registry Number	1308-38-9	J.T. Baker 2005
Synonyms/Trade Names	Chromic oxide, chromium (III) oxide, chrome green, chrome oxide green, green cinnabar, dichromium trioxide, chromium sesquioxide, ultramarine green	ATSDR 2009, J.T. Baker 2005, Chemfinder 2004f
Solubility in water	Negligible (<0.1%), insoluble in water, acids, alcohols, and alkalies	J.T. Baker 2005, Hawley's 1993
Log K_{ow}	Not applicable	TD
Vapor Pressure	Not applicable	J.T. Baker 2005
Vapor Density (air = 1)	Not applicable	J.T. Baker 2005
Density (water = 1)	5.21 (temp not specified) [1]	Chemfinder 2004f
Melting Point	2435 ^{o}C (4415 ^{o}F)	Science Lab 2005c
Boiling Point	4000 ^{o}C (7232 ^{o}F)	Science Lab 2005c
Conversion Factors	Not applicable	Not applicable

Table 11 Chemical and Physical Data – Chromium Phosphate

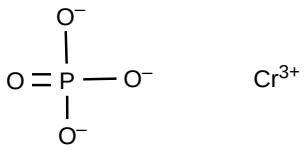
Parameter	Value	Reference
Molecular Formula	CrO_4P	Chemfinder 2004g
Chemical Structure		ChemID Plus Advanced 2009
Molecular Weight	146.97 (g/mole)	Chemfinder 2004g
Physical State	Crystals	Hawley's 1993
Color	Violet or green	Hawley's 1993
Odor	Not available	Hawley's 1993
CAS Registry Number	7789-04-0	Chemfinder 2004g
Synonyms/Trade Names	Chromium (III) phosphate, phosphoric acid chromium (3+) salt	Chemfinder 2004g
Solubility in water	Insoluble, soluble in acids	Hawley's 1993
Log K_{ow}	Not applicable	TD
Vapor Pressure	Not available	Chemfinder 2004g, Hawley's 1993
Vapor Density (air = 1)	Not available	Chemfinder 2004g, Hawley's 1993
Density (water = 1)	2.12 (14 C)	Hawley's 1993
Melting Point	Not available	Chemfinder 2004g, Hawley's 1993
Boiling Point	Not available	Chemfinder 2004g, Hawley's 1993
Conversion Factors	Not applicable	Not applicable

Table 12 Chemical and Physical Data – Chromium Picolinate

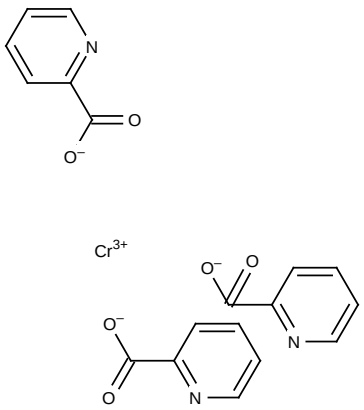
Parameter	Value	Reference
Molecular Formula	$C_{18}CrH_{12}N_3O_6$	Science Lab 2005d
Chemical Structure		ChemID Plus Advanced 2009
Molecular Weight	418.30 (g/mole)	Science Lab 2005d
Physical State	Solid, powdered solid	Science Lab 2005d
Color	Brownish red	Science Lab 2005d
Odor	Odorless	Science Lab 2005d
CAS Registry Number	14639-25-9	ATSDR 2009
Synonyms/Trade Names	Chromium (III) picolinate, chromium tripicolinate, CrPic, chromium 2-pyridinecarboxylate	Science Lab 2005d, ATSDR 2009
Solubility in water	Slightly soluble in cold water	Science Lab 2005d
Low K_{ow}	Not applicable	TD
Vapor Pressure	Not applicable	Science Lab 2005d
Vapor Density (air = 1)	Not available	Science Lab 2005d
Density (water = 1)	Not available	Science Lab 2005d
Melting Point	Decomposes	Science Lab 2005d
Boiling Point	Not available	Science Lab 2005d
Conversion Factors	Not applicable	Not applicable

Table 13 Chemical and Physical Data – Chromium Sulfate

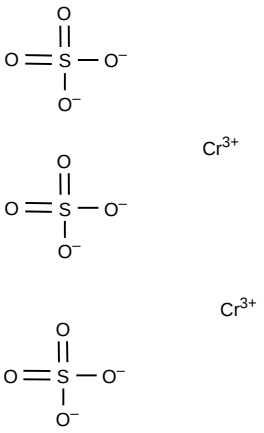
Parameter	Value	Reference
Molecular Formula	$Cr_2O_{12}S_3$	ChemID Plus Advanced 2009
Chemical Structure		ChemID Plus Advanced 2009
Molecular Weight	392.17 (g/mole)	Science Lab 2005e
Physical State	Crystals	J.T. Baker 2007b
Color	Violet or green	J.T. Baker 2007b
Odor	Odorless	J.T. Baker 2007b
CAS Registry Number	10101-53-8	Chemfinder 2004h, ATSDR 2009
Synonyms/Trade Names	Dichromium sulfate, dichromium trisulfate, chromic sulfate, chromium sulfate, sulfuric acid chromium (3+) salt, chromium sulfate 12-hydrate	Chemfinder 2004h, J.T. Baker 2007b
Solubility in water	Insoluble	Chemfinder 2004h
Low K_{ow}	Not applicable	TD
Vapor Pressure	Not available	J.T. Baker 2007b
Vapor Density (air = 1)	Not available	J.T. Baker 2007b
Density (water = 1)	3.012 (temp not specified)	J.T. Baker 2007b
Melting Point	90 ^{o}C (194 ^{o}F)	J.T. Baker 2007b
Boiling Point	Decomposes at red heat	J.T. Baker 2007b
Conversion Factors	Not applicable	Not applicable

Table 14 Chromium Compounds and CAS Numbers

Chromium Compound	Chemical Abstract Service Registry Number
Oxidation State 0 (Cr 0) Compounds	
Chromium carbonyl	13007-92-6
Dibenzene chromium	1271-54-1
Divalent (Cr II) Compounds	
Chromous acetate	628-52-4
Chromous chloride	10049-05-5
Chromous fluoride	10049-10-2
Chromous sulfate	13825-86-0
Trivalent (Cr III) Compounds	
Chromium acetate	1066-30-4
Chromium acetate monohydrate	25013-82-5
Chromium bromide	10049-25-9
Chromium carbide	12012-61-9
Chromium carbonate	29689-14-3
Chromium chloride	10025-73-7
Chromium chloride hexahydrate	10060-12-5
Chromium fluoride	7788-97-8
Chromium hydroxide	1308-14-1
Chromium nitrate	13548-38-4
Chromium nitrate nonahydrate	7789-02-8
Chromium oxide	1308-38-9
Chromium phosphate	7789-04-0
Chromium phosphate hexahydrate	13475-98-4
Chromium picolinate	14639-25-9
Chromium potassium sulfate	10141-00-1
Chromium sulfate	10101-53-8
Chromium sulfate n-hydrate	15244-38-9
Basic chromium sulfate	12336-95-7
Ferrochrome	11114-46-8
Sodium chromite	12314-42-0
Tetravalent (Cr IV) Compound	
Chromium (IV) oxide	12018-01-8

Appendix B: BMC Modeling Results for Derelanko *et al*. (1999)

Increased total lung and trachea weight in male and female rats (both absolute increases and increases relative to body weight) are the critical effects identified from Derelanko *et al*. (1999). Other critical effects also occurred at the same LOAEL, but were not amenable to BMC modeling. The terms BMC and BMCL are used instead of BMD and BMDL, respectively, since the data represents an inhalation exposure concentration in air, not an exposure dose. BMC analysis was conducted using USEPA BMDS (version 2.0) based on male and female rat total lung and trachea weight data and on total lung and trachea weight data normalized for body weight from Table 3 in Derelanko *et al*. (1999), respectively. Data not amenable to BMC modeling were carried through the entire ReV derivation process in parallel with the BMC modeling results using the LOAEL as the POD. The data that was amenable to modeling with USEPA BMDS software is presented in Table 15.

Table 15 Data from Derelanko *et al*. (1999) Amenable to BMC Modeling

Terminal sacrifice Sex	Dose (mg/m3)	Subjects (number)	Total Lung and Trachea weight (g) Mean Resp.	SD	Total Lung/Trachea weight/body weight (%x10) Mean Resp.	SD
Male	0	10	0.99	0.7	4.42	0.187
	17	10	1.26	0.071	5.6	0.271
	54	10	1.51	0.088	7.15	0.252
	168	10	1.86	0.89	10.69	0.688
Female	0	10	0.81	0.081	5.65	0.418
	17	10	0.98	0.094	6.99	0.619
	54	10	1.29	0.164	9.24	1.036
	168	10	1.66	0.084	12.89	1.134

* Dose of basic chromium sulfate

SD = standard deviation

Although both absolute and relative lung and trachea weight data were modeled, the analysis focused on the relative lung and trachea weight changes, since treatment effects resulted in some differences in body weight relative to controls. Therefore, BMD modeling results based on total lung and trachea weight relative to body weight were used for identification of a POD. Goodness-of-fit was evaluated by p-values > 0.1 (Test 4), visual inspection of the dose-response curves, and scaled residuals less than an absolute value of 2. Tests from the BMC continuous model were examined to evaluated the hypothesis that response and variance do not differ among

dose levels (Test 1) as well as whether a homogeneous (constant variance) (C-V) or nonhomogeneous variance (NH-V) were applicable (Tests 2 and 3).

The unrestricted power model (NH-V) was the only model with an adequate fit to the male rat data. The following models had an adequate fit to the female rat data: unrestricted power, polynomial, and linear with the high dose removed, with NH-V. Generally, the NH-V models fit the data better than the models with C-V, so the NH-V models are the focus of this discussion. Modeling results for each of the models with adequate fit are presented in Table 16.

Table 16 BMC Modeling Results for Relative Increases in Total Lung and Trachea Weights in Rats Based on Derelanko *et al*. (1999)

Model	Sex	BMC10 (mg/m3)	BMCL10 (mg/m3)	BMC1SD (mg/m3)	BMCL1SD (mg/m3)	Goodness-of-Fit p-value a	Test 1	Test 2	Test 3	Test 4	AIC Value b	Scaled Residual at BMCL10 c
Unrestricted Power (NH-V) Males	Male	4.488	3.451	1.214	0.735	0.855	Yes	Yes	Yes	Yes	-46.662	0.076
Unrestricted Power (C-V) Males	Male	4.476	2.899	3.652	2.344	0.955	Yes	No	No	Yes	-29.187	0.041
Polynomial (NH-V)	Female	7.251	6.070	5.646	3.976	0.756	Yes	Yes	Yes	Yes	23.388	0.232
Polynomial (C-V)	Female	7.493	5.891	10.788	8.436	0.800	Yes	No	No	Yes	31.222	0.203
Unrestricted Power (NH-V)	Female	3.862	2.134	2.817	1.350	0.153	Yes	Yes	Yes	Yes	25.331	-0.865
Unrestricted Power (C-V)	Female	3.477	1.498	6.225	3.231	0.259	Yes	No	No	Yes	32.429	-0.789
Linear, No High Dose (NH-V)	Female	8.371	7.069	6.057	4.251	0.339	Yes	Yes	Yes	Yes	9.421 [d]	0.745
Linear, No High Dose (C-V)	Female	8.757	7.300	10.771	8.540	0.451	Yes	No	No	Yes	15.128 [d]	0.599

a p-value > 0.1 indicates an adequate fit

b lower AIC values generally indicate a better fit

c scaled residuals less than an absolute value of 2 generally indicate an adequate fit in the dose region of interest

d AIC values for the Linear Model are not comparable to the other models because only 3 exposure concentrations were modeled

The only model that adequately modeled increases in total lung and trachea weight normalized for body weight in male rats was the unrestriced power model with a BMCL10 value of 3.451 mg/m^3. Figure 2 shows the plot and several output parameters for the unrestriced power model for male rat data.

The model selected for increases in total lung and trachea weight normalized for body weight in female rats was the polynomial model. For female rats, the polynomial model produced a lower AIC value than the other 4-concentration models, indicating a better fit. The linear model (no high concentration) also provided an adequate fit, but didn't include the highest dose level, so the results from the polynomial model (4-concentration) were used. Figure 2 shows the plot and several output parameters for the polynomial model for female rats, which produced a BMCL10 value of 6.070 mg/m3. Since data from Derelanko et al. (1999) indicates that male rats may be more sensitive to the effects of basic chromium sulfate exposure, the BMCL10 for male rats of 3.451 mg/m3 was selected for use as a potential POD for the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$.

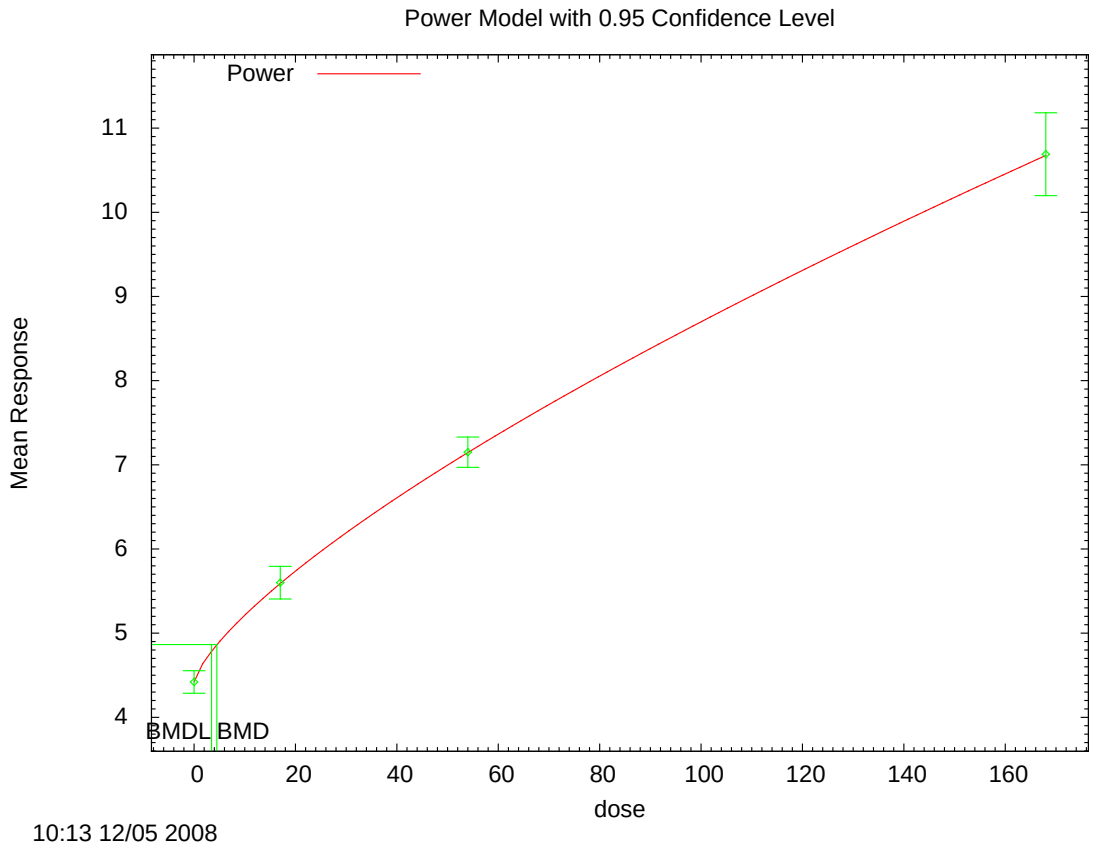


Figure 2 Plot and BMDM Output for Relative Lung and Trachea Weight Increases in Male Rats

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Relative risk
Confidence level = 0.95
BMC = 4.48844
BMCL = 3.45156

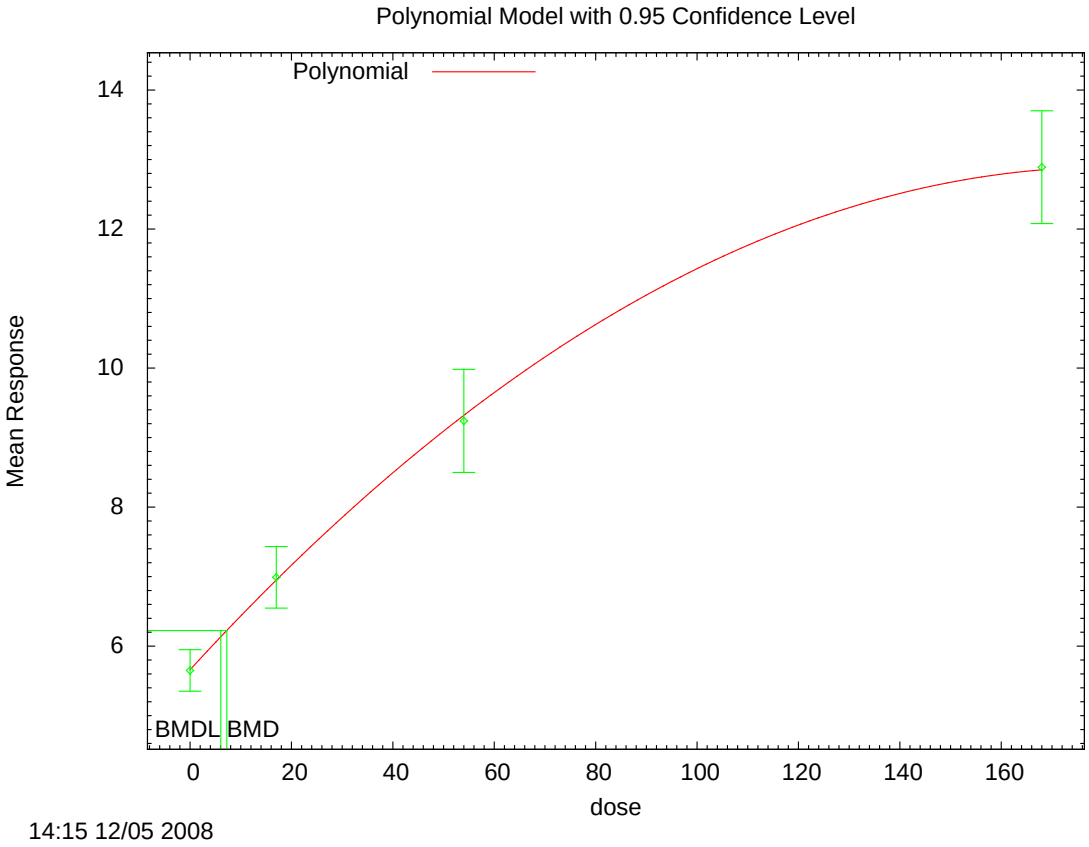


Figure 3 Plot and BMDM Output for Relative Lung and Trachea Weight Increases in Female Rats

Benchmark Dose Computation

Specified effect= 0.1
Risk Type = Relative risk
Confidence level = 0.95
BMC = 7.25156
BMCL = 6.06971

Appendix C: MPPD Program Output and Calculations for Basic Chromium Sulfate from Subchronic Study (Derelanko *et al.* 1999)

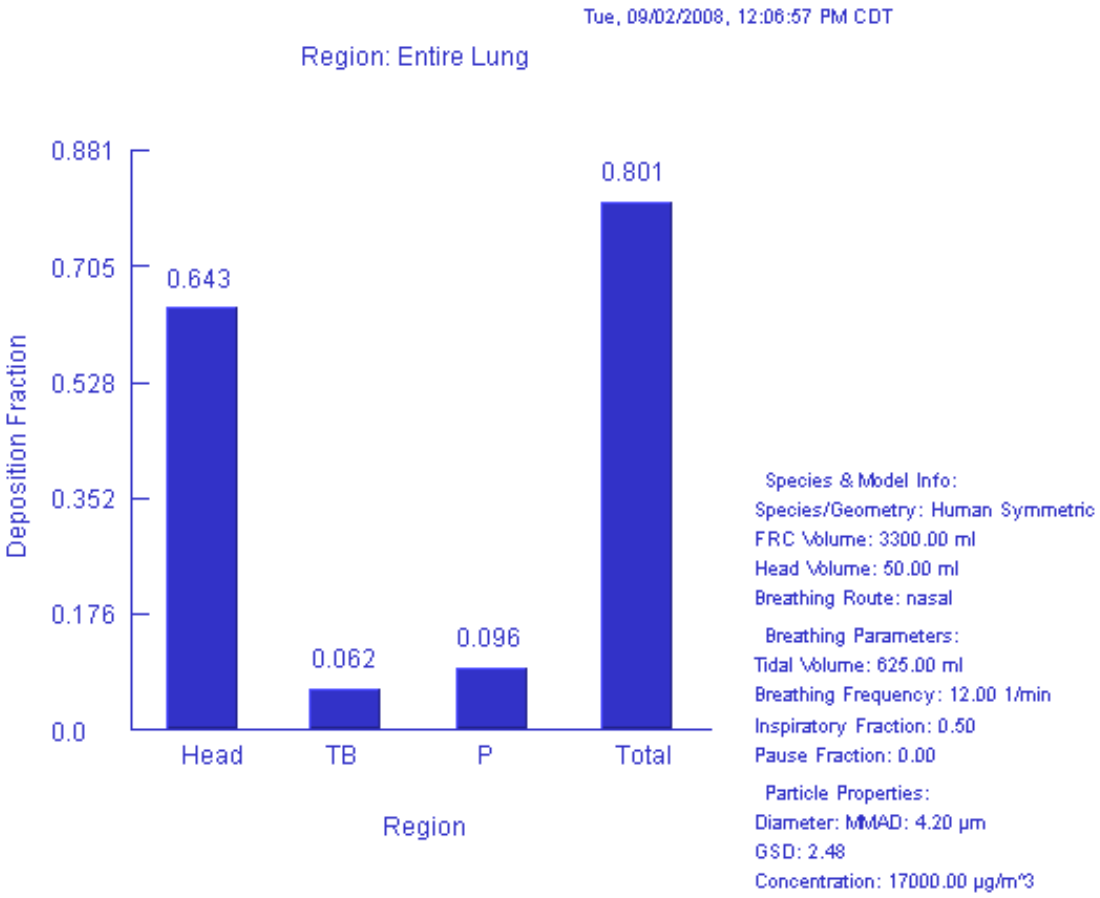


Figure 4 MPPD Model Output for Human (Derelanko *et al.* 1999)

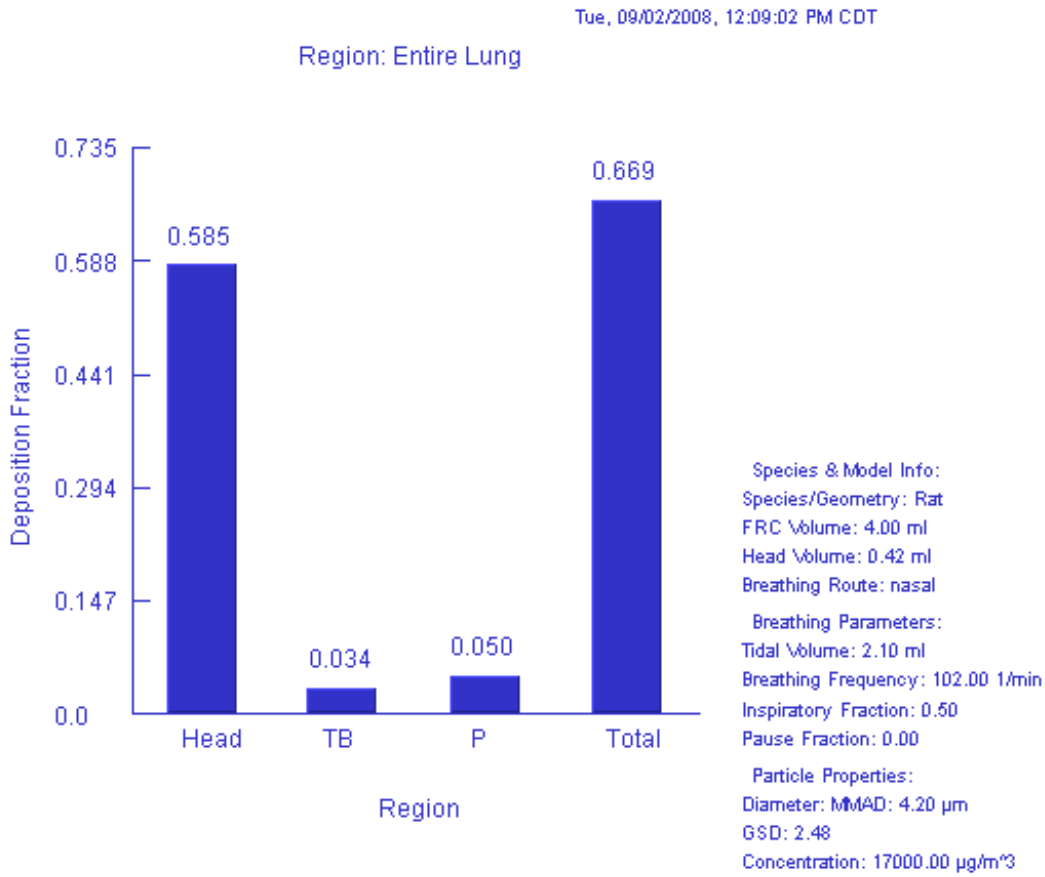


Figure 5 MPPD Model Output for Rat (Derelanko *et al*. 1999)

RDDR = $(Ve_A \times DF_A \times NF_H)/(Ve_H \times DF_H \times NF_A)$

= (137.3 mL/min x 0.669 x 543,400 cm^2) / (13,800 mL/min x 0.801 x 3437.5 cm^2)

= (49,913,300.58/39,997,437.5)

= 1.3135965

where: RDDR = Regional Depositional Dose Ratio

Ve = Minute ventilation

DF = Depositional fraction in the respiratory tract target region

NF = Normalizer factor

A = Animal

H = Human

Appendix D: Supporting Chronic Noncarcinogenic Approach Using Johannson *et al*. (1986a, 1986b, 1987)

Although the Johannson *et al*. (1986a, 1986b, 1987) studies were used to derive supporting chronic toxicity values for trivalent chromium, no other regulatory agency has developed values based on these studies. There was only a control group and one (1986a, 1986b) or two (1987) exposure concentrations, limited endpoints were evaluated, and similar mild effects were noted over different exposure durations and concentrations. The key study selected in this DSD (Derelanko *et al*. 1999) was a better study that examined two different forms of trivalent chromium in rats. In addition, Derelanko *et al*. (1999) looked at a wider range of endpoints, exposed subjects to more doses, and provided more statistical information about the significant effects. Overall, the deficiencies in the Johannson *et al*. (1986a, 1986b, 1987) studies, combined with the advantages of the Derelanko *et al*. (1999) study, make the Johansson *et al*. (1986a, 1986b, 1987) data less reliable for derivation of chronic toxicity values.

D.1 Dose Metric

In the supporting studies using rabbits (Johansson *et al.* 1986a, 1986b, 1987), data on exposure concentration of the parent chemical are available. The adverse effect for the key supporting studies is related to effects in the lung from exposure to the parent chemical. Other dose metrics are not available; therefore, the exposure concentration of the parent chemical is the appropriate dose metric (TCEQ 2006).

D.2 PODs for Key and Supporting Studies

The LOAEL of 0.6 mg/m^3 (Cr^{3+}) based on a 4 – 6 week exposure in rabbits (Johannson *et al*. 1986a, 1986b) and on a 17 – 21 week exposure in rabbits (Johannson *et al.* 1987) was used as the POD. Adequate information was not available to perform benchmark-dose modeling for trivalent chromium compounds.

D.3 Dosimetric Adjustments

D.3.1 Exposure Duration Adjustments

According to the ESL guidance (TCEQ 2006), the POD from the Johannson *et al*. (1986a, 1986b, 1987) studies was adjusted to a continuous exposure concentration:

$$POD_{ADJ} = POD \times D/24 \times F/7$$
$$= (0.6\ mg/m^3) \times (6\ h/24\ h) \times (5\ d/7\ d)$$
$$= 0.107\ mg/m^3$$

where: POD = point of departure in key study
D= h per day
F = days per week

POD_{ADJ} = point of departure adjusted for continuous duration

D.3.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

The USEPA RDDR model (version 2.3) was used to calculate the depositional fraction for trivalent chromium in the target respiratory region for the supporting subchronic studies (USEPA 1994). The RDDR model allows the adjustment of an animal dose to a human equivalent dose for PM and aerosolized compounds. The studies by Johansson *et al*. (1986a, 1986b, 1987) reported a MMAD of the $Cr(NO_3)_3$ aerosol of 1.0 µm, estimated with an impactor; however, a σ_g was not provided. In order to use the RDDR model, a σ_g was estimated using USEPA (1994) methods to predict a normally distributed range of particle sizes for various mists and fumes from Figure H-4 (0.1 to 10 µm) around the median from the study (1.0 µm), and the following equation:

$\sigma_g = e[(\ln(\text{upper bound/median}))/n]$

$= e[(\ln(10.0/1.0))/4]$

$= 1.78$ µm

where: e = irrational constant, base of ln

ln = natural logarithm

n = degrees of freedom

σ_g = geometric standard deviation

The MMAD and the σ_g were then used in the USEPA (1994) RDDR model (version 2.3), along with species specific information on the rabbit, to convert the rabbit dose to a human equivalent concentration (HEC). The input terms and the output from the RDDR model run using the Johansson et al. (1986a, 1986b, 1987) studies are presented in Figure D1.

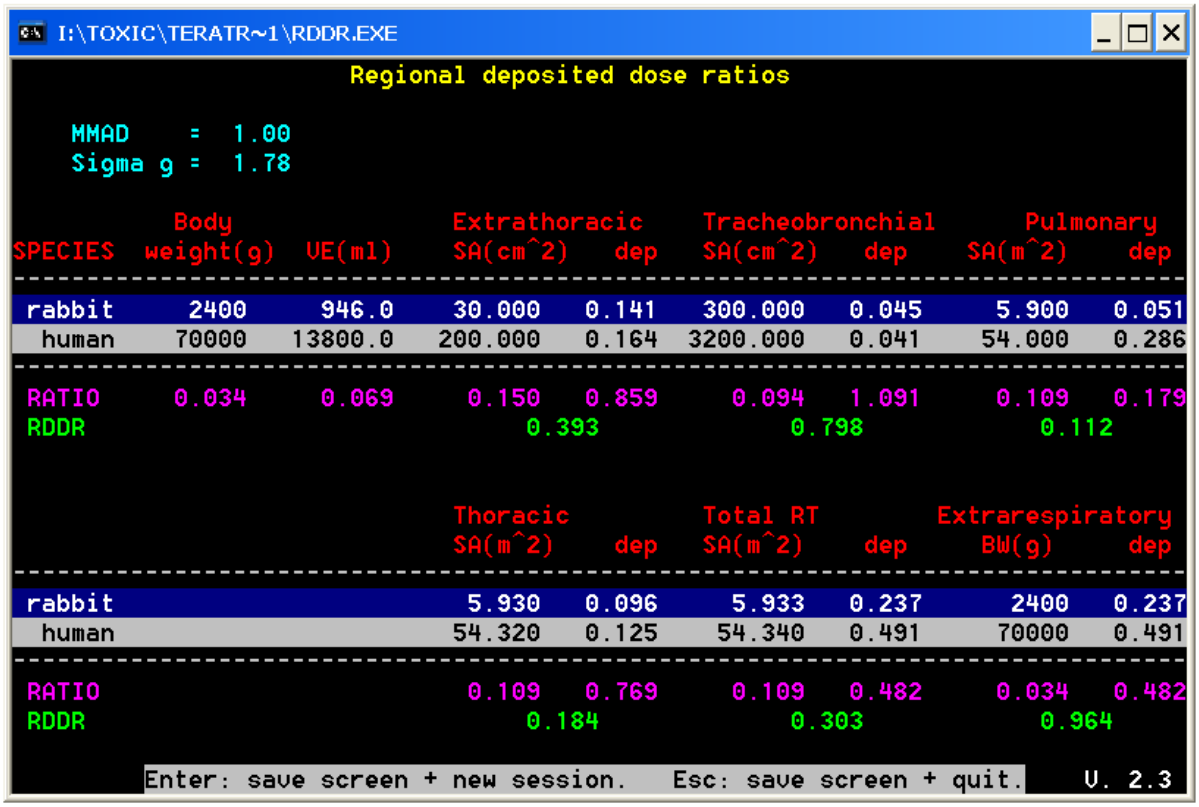


Figure 6 RDDR Model Run for $Cr(NO_3)_3$ (Johansson *et al.* 1986a, 1986b, 1987)

Since the particle diameter in the toxicity study was small enough that one would expect particle deposition in all respiratory tract regions, including the lower alveolar regions of the human lung, and because the mild adverse effect noted in the studies was to alveolar and lung tissue in this respiratory region, the RDDR of the pulmonary region was selected as the appropriate output to use to develop a human equivalent concentration. Therefore the RDDR for the pulmonary region was multiplied by the POD_{ADJ} for the Johansson *et al*. (1986a, 1986b, 1987) studies to get a POD_{HEC}.

$$POD_{HEC} = POD_{ADJ} \times RDDR$$
$$= 0.107 \text{ mg/m}^3 \times 0.112$$
$$= 0.0120 \text{ mg/m}^3$$

D.4 Critical Effect and Adjustments of the POD_{HEC}

The MOA by which trivalent chromium produces respiratory system toxicity is not understood (Section 3.1.2), so appropriate uncertainty factors (UFs) were applied to the POD to derive a chronic ReV. The POD_{HEC} of 0.0120 mg/m^3 based on Johansson *et al.* (1986a, 1986b, 1987) was

used to derive a supporting ReV. The ReV was calculated by applying the following UFs to the POD_{HEC}: an interspecies UF (UF_A) of 3 for extrapolation from animals to humans; an intraspecies UF (UF_H) of 10 to account for variability within the human population; a LOAEL-to-NOAEL UF (UF_L) of 1; a database UF (UF_D) of 3; and a subchronic to chronic UF (UF_{Sub}) of 10 (total UFs = 1000).

An UF_A of 3 was used because the RDDR program accounts for toxicokinetic differences and limits uncertainty between rabbit and human extrapolation but does not account for toxicodynamic differences. A full UF_H of 10 was applied because no information on variability in the human population to effects from trivalent chromium inhalation exposure was available (ATSDR 2009). According to the ESL Guidance (Table 18, TCEQ 2006), an additional UF_L was not applied since the noted effects are mild cytological, enzymatic, and physiological effects in lung tissue, and well within the range of effects essentially considered to be NOAELs. A UF_D of 3 was applied because the database on toxicity of trivalent chromium compounds lacks multigenerational reproductive and developmental studies. A subchronic to chronic uncertainty factor of 10 was applied because no chronic trivalent chromium studies were available, even though in general, trivalent chromium is relatively nontoxic and several subchronic studies identified similar mild LOAELs across a range of exposure durations (28 to 147 days).

D.5 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

As discussed in the previous section, UFs are applied to the POD_{HEC} to derive the supporting chronic ReV.

$$\text{Supporting chronic ReV} = [POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D \times UF_{Sub})] \times CF$$
$$= [0.0120 \text{ mg/m}^3 / (10 \times 3 \times 1 \times 3 \times 10)] \times 1000 \text{ µg/mg}$$
$$= (0.0000120 \text{ mg/m}^3) \times 1000 \text{ µg/mg}$$
$$= 0.0120 \text{ µg/m}^3$$

The supporting chronic ReV value was rounded to two significant figures at the end of all calculations. The rounded chronic ReV was then used to calculate the supporting $^{chronic}ESL_{nonlinear(nc)}$. Rounding to two significant figures, the supporting chronic ReV is 0.012 µg/m^3. At the target hazard quotient of 0.3, the supporting $^{chronic}ESL_{nonlinear(nc)}$ is 0.0036 µg/m^3 (Table 17).

Table 17 Derivation of a Supporting Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	**Summary**
Studies	Johansson et al. (1986a, 1986b, 1987)
Study Population	Eight rabbits per dose group
Study Quality	Medium
Exposure Methods	Inhalation of metal salt aerosol as ($Cr[NO_3]_3$) = (0.0, 0.6, 2.3 mg/m^3 Cr^{3+})
LOAEL	0.6 mg/m^3 Cr^{3+}
NOAEL	not available
Critical Effects	Macrophages characterized by round dark chromium rich inclusions, very large lysosomes with membranous fragments, increased numbers of lamellar inclusions, a frequent elongation of the cell profile, and nodular accumulation of macrophages with abnormal appearance.
POD	0.6 mg/m^3 Cr^{3+} (for mild effects)
Exposure Duration	4 – 21 weeks (5 day/week, 6 h/day)
POD_{ADJ} (extrapolated to continuous exposure)	0.107 mg/m^3
POD_{HEC}	0.0120 mg/m^3 (RDDR = 0.112 for pulmonary region)
Total UFs	1000
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL UF	*1*
Subchronic to Chronic UF	*10*
Incomplete Database UF	*3*
Database Quality	*Medium*
Supporting chronic ReV (HQ = 1)	**0.012 µg/m^3 as Cr^{+3}**
Supporting $^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**0.0036 µg/m^3 as Cr^{+3}**

Appendix E: Supporting Chronic Noncarcinogenic Approach Considering Total Chromium as an Essential Nutrient (NAS 2004)

Total chromium (as trivalent compounds) is an essential nutrient, as discussed in Section 2.2 of this DSD. Although the U.S. Food and Drug Administration has not identified a Recommended Daily Allowance (RDA) for chromium, the National Academy of Sciences (NAS 2004) has identified Adequate Intake Values (AIVs) for various life-stage-groups from infants to adults. Although there are valid concerns about trying to relate RDAs or AIVs to upper tolerance levels (UTLs) or toxic levels (Hanekamp and Bast 2008), the RDAs and AIVs can both be used as goals for individual intake and can conservatively be equated to NOAELs. The AIVs for chromium from NAS (2004) are presented in the second column of Table 18.

Mean inhalation rates for various life-stage-groups can be obtained from the Exposure Factors Handbook (USEPA 1997). The mean inhalation rates are presented in the third column of Table 18. The AIVs (µg/day) from NAS (2004) can be divided by the inhalation rates (m^3/day) from USEPA (1997) to arrive at air concentrations for each life-stage-group in µg/m^3. These air concentrations are presented in the fourth column of Table 18. They are an estimate of the amount of chromium in air, assuming average inhalation rates that each life-stage-group could breathe on a daily basis to obtain their respective AIVs. Admittedly, it is odd to think of the inhalation route as a means of obtaining ones recommended AIV, especially when it is well documented that the primary route of exposure to chromium is ingestion and systemic absorption from the inhalation route is limited.

Rather than examine each life-stage-group separately, or calculate a time-weighted average acceptable air concentration, a single conservative calculation can be done. Using the lower end of the chromium AIV range for adults (20 µg/day) and dividing by the upper end of mean inhalation rates (20 m^3/day) yields an air concentration of 1.0 µg/m^3. This comparison assumes that inhaled chromium is absorbed as efficiently as ingested chromium. A reasonable estimate of ingested chromium, regardless of valence state, is less than 5%, with trivalent forms much less readily absorbed than hexavelnt forms (USEPA 1984). Actual inhalation absorption is dependent on the size and solubility of the particular chromium compound, and on the valence state of chromium in the compound (Cr^{6+} or Cr^{3+}). Absorption of inhaled chromium is typically estimated to be about 3%, but as high as 12% for trivalent forms (CEPA 1994). Therefore, the assumption that inhalation absorption is equivalent to ingestion absorption may over- or under-estimate actual absorption. The air concentration of 1.0 µg/m^3 was divided by a relative source contribution (RSC) factor of 10 to account for daily dietary intake which occurs naturally.

$$\text{Supporting chronic ReV} = [POD_{HEC} / RSC_{AIV}]$$
$$= [1.0\ ug/m^3 / 10]$$
$$= 0.1\ \mu g/m^3$$

where: chronic ReV = chronic reference value

POD_{HEC} = point of departure (mg/m^3) from AIV comparison
RSC_{AIV} = relative source contribution factor

Table 18 Evaluation of Adequate Intake Values (AIVs) for Total Chromium

Life Stage Group	Chromium [a]	Inhalation Rate [b]	Air Concentration [c]
Infants	**(µg/day)**	**(m^3/day)**	**(µg/m^3)**
0 - 6 mo	0.2	4.5	0.04
7 - 12 mo	5.5	4.5	1.22
Children			
1 - 3 yr	11	8.3	1.33
4 - 8 yr	15	10	1.50
Males			
9 - 13 yr	25	15	1.67
14 - 18 yr	35	17	2.06
19 - 30 yr	35	15.2	2.30
31 - 50 yr	35	15.2	2.30
51 - 70 yr	30	15.2	1.97
> 70 yr	30	15.2	1.97
Females			
9 - 13 yr	21	12	1.75
14 - 18 yr	24	12	2.00
19 - 30 yr	25	11.3	2.21
31 - 50 yr	25	11.3	2.21
51 - 70 yr	20	11.3	1.77
> 70 yr	20	11.3	1.77
Pregnancy			
14 - 18 yr	29	12	2.42
19 - 30 yr	30	11.3	2.65
31 - 50 yr	30	11.3	2.65
Lactation			
14 - 18 yr	44	12	3.67
19 - 30 yr	45	11.3	3.98
31 - 50 yr	45	11.3	3.98
Range	0.2 - 45	4.5 - 17	0.04 - 3.98

[a] Recommended daily intakes for individuals (Adequate Intake Values [AIVs]), Food and Nutrition Board, Institute of Medicine (NAS 2004).

[b] Mean inhalation rates for Exposure Factors Handbook (EFH) (USEPA 1997).

[c] Air concentrations calculated by dividing the chromium AIVs by the mean inhalation rates from EFH.

The supporting chronic ReV (0.1 µg/m^3) was then used to calculate the supporting $^{chronic}ESL_{nonlinear(nc)}$. At the target hazard quotient of 0.3, the supporting $^{chronic}ESL_{nonlinear(nc)}$ is 0.03 µg/m^3 (Table 19). This approach is not recommended as the preferred approach for developing a ReV, as there is little precedent. As mentioned above, RDAs, AIVs, UTLs, and ReVs are in many ways incompatible standards due to differences in databases, application of uncertainty factors, and differences in the goal of setting each value (Hanekamp & Bast 2008). In addition, there is conceptual uncertainty in trying to evaluate a daily dose for intake in terms of inhalation exposure, particularly when the AIV is based on ingestion. However, the information is presented in this appendix gives some context to determine if the proposed chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ are not set so low as to be overly conservative for an essential nutrient.

Table 19 Derivation of a Supporting Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	**Summary**
Studies	NAS (2004)
Study Population	Human
Study Quality	High
Exposure Methods	AIVs in diet
NOAEL	1.0 µg/m^3 as Cr^{+3}
Critical Effects	Essential nutrient
POD	1.0 µg/m^3
Exposure Duration	Daily exposure for a lifetime (> 70 years)
POD_{HEC}	1.0 µg/m^3
Relative Source Contribution UF	*10*
chronic ReV (HQ = 1)	**0.1 µg/m^3** as Cr^{+3}
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**0.03 µg/m^3** as Cr^{+3}