Development Support Document
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# Hexavalent Chromium (Particulate Compounds)

## CAS Registry Numbers:

**Hexavalent chromium 18540-29-9**
**Ammonium dichromate 7789-09-5**
**Calcium chromate 13765-19-0**
**Sodium chromate 7775-11-3**
**Chromium trioxide 1333-82-0**
**Sodium dichromate 10588-01-9**
**Sodium dichromate, dihydrate 7789-12-0**
**Lead chromate 7758-97-6**
**Potassium chromate 7789-00-6**
**Potassium dichromate 7778-50-9**
**Strontium chromate 7789-06-2**
**Zinc chromate 13530-65-9**

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# Acronyms and Abbreviations

| Acronyms and Abbreviations | Definition |
|---|---|
| ATSDR | Agency for Toxic Substances and Disease Registry |
| AMCV | Air monitoring comparison values |
| BALF | bronchoalveolar lavage fluid |
| BMC | benchmark concentration |
| BMCL | benchmark concentration lower confidence limit |
| $BMCL_{10}$ | benchmark concentration lower corresponding to the 10% response level |
| BMD | benchmark dose |
| BMDL | benchmark dose lower confidence limit |
| BMDS | benchmark dose software |
| BMR | benchmark response |
| BW | body weight |
| C | concentration |
| CalEPA | California Environmental Protection Agency |
| CI | confidence interval |
| CrVI | hexavalent chromium |
| d | day |
| DAF | dosimetric adjustment factor |
| DF | deposition fraction in the target region of the respiratory tract |
| DNA | deoxyribonucleic acid |
| DSD | development support document |
| E | exposure level or concentration |
| ET | extrathoracic |
| ESL | Effects Screening Level |
| $^{acute}ESL$ | acute health-based Effects Screening Level for chemicals meeting minimum database requirements |
| $^{acute}ESL_{generic}$ | acute health-based Effects Screening Level for chemicals not meeting minimum database requirements |
| $^{acute}ESL_{odor}$ | acute odor-based Effects Screening Level |
| $^{acute}ESL_{veg}$ | acute vegetation-based Effects Screening Level |
| $^{chronic}ESL_{nonthreshold(c)}$ | chronic health-based Effects Screening Level for nonthreshold (i.e., linear) dose-response cancer effect |
| $^{chronic}ESL_{nonthreshold(nc)}$ | chronic health-based Effects Screening Level for nonthreshold (i.e., linear) dose-response noncancer effects |
| $^{chronic}ESL_{threshold(c)}$ | chronic health-based Effects Screening Level for threshold dose-response cancer effects |
| $^{chronic}ESL_{threshold(nc)}$ | chronic health-based Effects Screening Level for threshold dose-response noncancer effects |
| $^{chronic}ESL_{veg}$ | chronic vegetation-based Effects Screening Level |
| F | exposure frequency, ds per week |
| $FEV_1$ | Forced Expiratory Volume in one second |

| Acronyms and Abbreviations | Definition |
|---|---|
| h | hour |
| HEC | human equivalent concentration |
| HQ | hazard quotient |
| IARC | International Agency for Research on Cancer |
| IRIS | Integrated Risk Information System |
| LCL | lower confidence limit |
| LDH | lactate dehydrogenase |
| LEC | lowest effective concentration |
| LOEL | lowest-observed-effect-level |
| LOAEL | lowest-observed-adverse-effect-level |
| MLE | maximum likelihood estimate |
| MW | molecular weight |
| µg | microgram |
| µm | micrometer |
| Mm | millimeter |
| min | minute |
| MMAD | mass median aerodynamic diameter |
| MPPD | multiple pass particle dosimetry |
| MOA | mode of action |
| MRL | Minimal Risk Level |
| NOAEL | no-observed-adverse-effect-level |
| NTP | National Toxicology Program |
| PM | particulate matter |
| POD | point of departure |
| $POD_{ADJ}$ | point of departure adjusted for exposure duration |
| $POD_{HEC}$ | point of departure adjusted for human equivalent concentration |
| POE | portal of entry |
| PU | pulmonary |
| ppb | parts per billion (by volume) |
| ppm | parts per million (by volume) |
| RDDR | regional deposited dose ratio |
| ReV | Reference Value |
| RfC | Reference Concentration |
| RfD | Reference Dose |
| SE | Standard Error |
| SIR | standardized incidence ratio |
| SMR | standardized mortality ratio |
| $\sigma_g$ | geometric standard deviation |
| T | time or exposure duration |
| TB | trachiobronchial |
| TCEQ | Texas Commission on Environmental Quality |

| Acronyms and Abbreviations | Definition |
|---|---|
| TD | Toxicology Division |
| TH | thoracic |
| TRI | Toxics Release Inventory |
| TWA | Time-Weighted Average |
| TWA-TLV | Time-Weighted Average Threshold Limit Value |
| UCL | upper confidence limit |
| UF | uncertainty factor |
| $UF_A$ | animal to human uncertainty factor |
| $UF_H$ | interindividual or intraspecies human uncertainty factor |
| $UF_{Sub}$ | subchronic to chronic exposure uncertainty factor |
| $UF_L$ | LOAEL to NOAEL uncertainty factor |
| $UF_D$ | incomplete database uncertainty factor |
| USEPA | United States Environmental Protection Agency |
| VE | minute ventilation |
| $VE_{ho}$ | default occupational ventilation rate for an eight-hour d |
| $VE_h$ | default non-occupational ventilation rate for a 24-h d |

# Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from the acute and chronic evaluations of hexavalent chromium (CrVI) and compounds. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 presents chemical and physical properties of hexavalent chromium (CrVI) compounds.

**Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air [b]**

| Short-Term Values | Concentration | Notes |
|---|---|---|
| Acute ReV [24-h]<br>(HQ = 1.0) | **Short-Term Health**<br>1.3 µg/m$^3$<br>CrVI Particulate Compounds as CrVI | **Critical Effect(s):** Increase in relative lung weight based on a 30-d subacute study in rats |
| $^{acute}ESL_{odor}$ | - - - | Odorless |
| $^{acute}ESL_{veg}$ | - - - | Insufficient Data |
| **Long-Term Values** | **Concentration** | **Notes** |
| Chronic ReV<br>(HQ = 1.0) | 0.22 µg/m$^3$<br>CrVI Particulate Compounds as CrVI | **Critical Effect(s):** Increase in relative lung weight based on a 90-d subchronic study in rats |
| $^{chronic}ESL_{nonthreshold(c)}$ | **Long-Term Health**<br>0.0043 µg/m$^3$ [a], as CrVI | **Critical Effect(s):** Lung cancer in industrial workers |
| $^{chronic}ESL_{veg}$ | - - - | Insufficient Data |

[a] Based on an inhalation unit risk factor (URF) of $2.3 \times 10^{-3}$ per µg/m$^3$ and a no significant risk level of 1 in 100,000 excess cancer risk, and applicable to all forms of CrVI compounds (e.g., particulate, dissolved CrVI (e.g., chromic acid) mist).

[b] Chromium compounds are respiratory sensitizers

Abbreviations used in Tables 1 and 2: **µg/m$^3$**, micrograms per cubic meter; **h**, hour; **HQ**, hazard quotient; **ESL**, Effects Screening Level; **ReV**, Reference Value; **$^{acute}$ESL**, acute health-based ESL; **$^{acute}$ESL$_{odor}$**, acute odor-based ESL; **$^{acute}$ESL$_{veg}$**, acute vegetation-based ESL; **$^{chronic}$ESL$_{nonthreshold(c)}$**, chronic health-based ESL for nonthreshold dose-response cancer effects; **$^{chronic}$ESL$_{threshold(nc)}$**, chronic health-based ESL for threshold dose-response noncancer effects; and **$^{chronic}$ESL$_{veg}$**, chronic vegetation-based ESL.

**Table 2. Air Permitting Effects Screening Levels (ESLs)**

| **Short-Term Values** [d] | **Concentration** | **Notes** |
|---|---|---|
| $^{acute}ESL$ [24-h] (HQ = 0.3) | **0.39 µg/m$^3$** [a] **CrVI Particulate Compounds as CrVI** **Short-Term ESL for Air Permit Reviews** | **Critical Effect(s):** Increase in relative lung weight based on a 30-d subacute study in rats |
| $^{acute}ESL_{odor}$ | - - - | Odorless |
| $^{acute}ESL_{veg}$ | - - - | Insufficient Data |
| **Long-Term Values** [d] | **Concentration** | **Notes** |
| $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) | 0.066 µg/m$^3$ [b] CrVI Particulate Compounds as CrVI | **Critical Effect(s):** Increase in relative lung weight based on a 90-d subchronic study in rats |
| $^{chronic}ESL_{nonthreshold(c)}$ | **0.0043 µg/m$^3$** [c]**, as CrVI** **Long-Term ESL for Air Permit Reviews** | **Critical Effect(s):** Lung cancer in industrial workers |
| $^{chronic}ESL_{veg}$ | - - - | Insufficient Data |

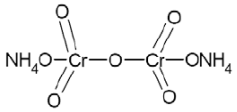
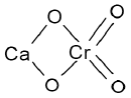
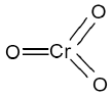
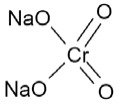
[a] Based on the CrVI particulate compound acute ReV of 1.3 µg/m$^3$ multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

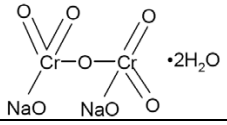
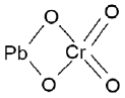
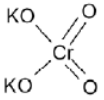
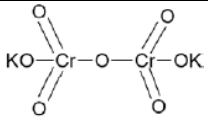
[b] Based on the CrVI particulate compound chronic ReV of 0.22 µg/m$^3$ multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

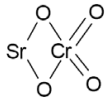
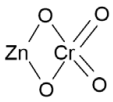
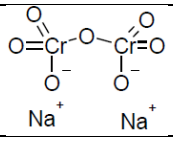
[c] Based on an inhalation unit risk factor (URF) of $2.3 \times 10^{-3}$ per µg/m$^3$ and a no significant risk level of 1 in 100,000 excess cancer risk, and applicable to all forms of CrVI compounds (e.g., particulate, dissolved CrVI (e.g., chromic acid) mist).

[d] In general, to protect against sensitization, exceedances of the acute (or chronic) ESL during the air permit review should be discouraged for any chemicals identified as respiratory sensitizers.

**Table 3. Chemical and Physical Properties of Hexavalent Chromium (CrVI) Compounds**

| **Parameter** | **Value** | **Value** | **Value** | **Value** |
|---|---|---|---|---|
| Name of Chemical | Ammonium dichromate | Calcium chromate | Chromium trioxide | Sodium chromate |
| Molecular Formula | $(NH_4)_2Cr_2O_7$ | $CaCrO_4$ | $CrO_3$ | $Na_2CrO_4$ |
| Chemical Structure |  |  |  |  |
| Molecular Weight | 252.07 | 156.07 | 99.99 | 161.97 |
| Physical State | Solid | Solid | Solid | Solid |
| Color | Orange | Yellow | Red | Yellow |
| Odor | Odorless | No data | Odorless | No data |
| CAS Registry Number | 7789-09-5 | 13765-19-0 | 1333-82-0 | 7775-11-3 |
| Synonyms | Chromic acid, diamonium salt | Chromic acid, calcium salt | Chromic acid, chromium anhydride | Chromic acid, disodium salt |
| Solubility in water (mg/L) | 26,670 at 20°C | 22,300 at 20°C | 617,000 at 0°C | 873,000 at 30°C |
| Log $K_{ow}$ | Not applicable | Not applicable | Not applicable | Not applicable |
| Vapor Pressure (mm Hg) | No data | No data | No data | No data |
| Density ($g/cm^3$) | 2.15 at 25°C | 2.89 at unspecified °C | 2.70 at 25°C | 2.723 at unspecified °C |
| Melting Point | Decomposes at 180°C | No data | 197°C | 792°C |
| Boiling Point | Not applicable | No data | Decomposes | No data |

| **Table 3. Chemical and Physical Properties (Continued)** | | | | |
|---|---|---|---|---|
| **Parameter** | **Value** | **Value** | **Value** | **Value** |
| Name of Chemical | Sodium dichromate, dihydrate | Lead chromate | Potassium chromate | Potassium dichromate |
| Molecular Formula | $NaCr_2O_7 \cdot H_2O$ | $PbCrO_4$ | $K_2CrO_4$ | $K_2Cr_2O_7$ |
| Chemical Structure |  |  |  |  |
| Molecular Weight | 298.00 | 323.19 | 194.19 | 294.18 |
| Physical State at 25°C | Solid | Solid | Solid | Solid |
| Color | Red | Yellow | Yellow | Red |
| Odor | No data | Odorless | Odorless | No data |
| CAS Registry Number | 7789-12-0 | 7758-97-6 | 7789-00-6 | 7778-50-9 |
| Synonyms | Chromic acid, disodium salt, dihydrate | Chromic acid, lead salt | Chromic acid, dipotassium salt | Chromic acid, dipotassium salt |
| Solubility in water (mg/L) | 2,300,000 at 0°C | 0.058 at 20°C | 629,000 at 20°C | 49,000 at 0°C |
| Log $K_{ow}$ | Not applicable | Not applicable | Not applicable | Not applicable |
| Vapor Pressure (mm Hg) | 0 at 20°C | No data | 0 at 20°C | No data |
| Density ($g/cm^3$) | 2.52 at 13°C | 6.12 at 15°C | 2.732 at 18°C | 2.676 at 25°C |
| Melting Point | 356.7°C | 844°C | 975°C | 398°C |
| Boiling Point | Decomposes at 400°C | Decomposes | No data | Decomposes at 500°C |

| **Parameter** | **Value** | **Value** | **Value** |
|---|---|---|---|
| Name of Chemical | Strontium chromate | Zinc chromate | Sodium dichromate |
| Molecular Formula | $SrCrO_4$ | $ZnCrO_4$ | $Na_2Cr_2O_7$ |
| Chemical Structure |  |  |  |
| Molecular Weight | 203.61 | 181.97 | 262 |
| Physical State at 25°C | Solid | Solid | Solid |
| Color | Yellow | Lemon-yellow | Bright orange-red |
| Odor | No data | Odorless | Odorless |
| CAS Registry Number | 7789-06-2 | 13530-65-9 | 10588-01-9 |
| Synonyms | Chromic acid, strontium salt | Chromic acid, zinc salt | Chromic acid, sodium salt (1:2) |
| Solubility in water (mg/L) | 1,200 at 15°C | Insoluble | 2,380,000 at 0°C |
| Log $K_{ow}$ | Not applicable | Not applicable | Not applicable |
| Vapor Pressure (mm Hg) | No data | No data | No data |
| Density ($g/cm^3$) | 3.895 at 15°C | 3.40 at unspecified°C | 2.52 at 13°C |
| Melting Point | No data | No data | 356.7°C |
| Boiling Point | No data | No data | Decomposes at 400°C |

# Chapter 2 Major Uses or Sources and Ambient Air Concentrations

## *2.1 Major Uses and Sources*

CrVI is an occupational respiratory carcinogen and environmental contaminant generated primarily by industrial processes (Nickens et al. 2010). The CrVI compounds most commonly encountered in industry are calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, lead chromate, strontium chromate, and zinc chromate (NTP 2011). The following information on uses and sources was taken, some verbatim, from ATSDR (2008) and NTP (2011).

Although chromium is currently mined in Oregon, the United States receives the majority of chromium ores from other countries. Thus, the Unites States is a major importer of chromium (hundreds of thousands of metric tons per year). From 2003 to 2006, chromium contained in chromite ore and chromium ferroalloys and metal was imported from South Africa (34%), Kazakhstan (18%), Russia (7%), Zimbabwe (6%), and other (35%). The Unites States is also a major producer of the end products of chromium for various uses, including wood preservation, leather tanning, chromium chemicals, metallurgy (e.g., ferroalloys, stainless steel, finishing), paint pigments, and other applications. For example, the refractory industry uses chromium as a component in chrome and chrome-magnesite, magnesite-chrome bricks, and granular chrome-bearing and granular chromite (linings for high temperature industrial furnaces), and the chemical industry uses both trivalent chromium (CrIII) and CrVI in pigments (ATSDR 2008).

However, the steel industry is the major consumer of chromium (NTP 2011). For example, in 2007, estimated consumption of chromium in the United States by end use was 78% in stainless and heat-resisting steel, 13.8% for other steel uses, 3.7% in superalloys, and 4.5% in other alloys and end uses. Alloys of stainless steel and chromium typically contain between 11.5% and 30% chromium. CrVI compounds are widely used as corrosion inhibitors, in the manufacture of pigments, in metal finishing and chrome plating, in stainless steel production, in leather tanning, and in wood preservatives. The use of CrVI compounds in wood preservatives increased dramatically from the late 1970s to the early 2000s; however, this use is expected to decrease because of a voluntary phase-out of all residential uses of wood treated with chromated copper arsenate (pressure- treated wood) that went into effect December 31, 2003. CrVI compounds are also used in textile-dyeing processes, printing inks, drilling muds, pyrotechnics, water treatment, and chemical synthesis (NTP 2011).

Additional information on the uses of specific CrVI compounds is provided by NTP (2011) and is quoted below.

> Calcium chromate is used primarily as a corrosion inhibitor and as a depolarizer in batteries. Chromium trioxide is used primarily in chrome plating and other metal finishing (particularly in the production of automobiles and military aircraft), in production of wood preservatives, as a corrosion inhibitor, and in production of

organic chemicals and catalysts. Lead chromate has been used in paints and printing inks and as a colorant in vinyl, rubber, and paper. Potassium chromate is used in production of dyes and in textile-dyeing processes. Potassium dichromate has largely been replaced by sodium dichromate in many applications; however, it is still used in photomechanical processes and production of pigments and wood preservatives. Sodium chromate is used as a corrosion inhibitor and in textile dyeing processes, inks, paints, leather tanning, wood preservatives, drilling muds, cutting oils, water treatment, and production of other chromium compounds. Sodium dichromate is the primary base material for the production of chromium compounds and is used as a corrosion inhibitor, in metal treatments, in drilling muds, and in the production of dyes, wood preservatives, synthetic organic chemicals, and catalysts. Strontium chromate is used as a corrosion inhibitor and metal conditioner, in aluminum flake coatings, as a colorant in polyvinyl chloride, in pyrotechnics, in chrome plating, and for sulfate ion control in electrochemical processes. Zinc chromates are used as corrosion inhibitors and metal conditioners and in paints, varnishes, and oil colors.

The main natural source of chromium in the atmosphere is continental dust flux; volcanic dust and gas flux are minor natural sources of chromium in the atmosphere. Chromium is released into the atmosphere primarily by anthropogenic stationary point sources such as industrial, commercial, and residential fuel combustion, and via the combustion of natural gas, oil, and coal. Metal industries, such as chrome plating and steel production, are also important anthropogenic stationary point sources of chromium emissions to air. Other potentially small sources of chromium air emissions include cement-producing plants, the incineration of municipal refuse and sewage sludge, and emissions from chromium-based automotive catalytic converters. Emissions from cooling towers that previously used chromate chemicals as rust inhibitors may also be atmospheric sources of chromium (ATSDR 2008).

## *2.2 Ambient Levels in Air*

Based on the US facilities required to report to the Toxics Release Inventory (TRI) in 2009, chromium releases to air account for less than 2% of the estimated total environmental releases (Tables 6-1 and 6-2 of ATSDR 2012). TRI data also indicate there are at least approximately 4,900 facilities that produce or process chromium in the US, including around 200-300 facilities in Texas (Tables 5-1 and 5-2 in ATSDR 2012). Major manufacturers of chromium compounds in Texas appear to include Elementis Chromium of Corpus Christi (chromic hydrate, chromium hydroxide, chromium(III) hydroxide, chromium oxide) and Elementis LTP of Amarillo (chromic sulfate, chromium(III) sulfate) (Table 5-3 of ATSDR 2012). Long-term CrVI average ambient concentrations (total suspended particulate or $PM_{10}$) measured at various sites in Texas range from approximately 5.9E-06 to 1.7E-04 µg CrVI/$m^3$ (Karnack: 0.00017 µg/$m^3$, Deer Park: 0.00014 µg/$m^3$, Midlothian: 5.9E-06 to 6.0E-05 µg/$m^3$), with maximum 24-hour (h) concentrations generally significantly less than 6.0E-03 µg/$m^3$.

# Chapter 3 Acute Evaluation

## *3.1 Health-Based Acute ReV and ESL*

Although acute ReVs are usually derived based on a 1-hour exposure duration, studies evaluating adverse effects due to such short-term exposure to CrVI are very limited. The shortest duration studies) available in the scientific peer-reviewed literature from which to identify an appropriate POD for derivation of short-term, health-protective air concentrations for CrVI involve intermediate (e.g., subacute) exposure duration. Additionally, the limited CrVI monitoring data the TCEQ collects are based on 24-h sampling. Thus, development of a 24-h acute ReV for CrVI will allow the TCEQ to more fully evaluate available monitoring data and is more consistent with the longer exposure duration studies available in the toxicological database for identification of a human point of departure ($POD_{HEC}$). Consequently, in this section the TCEQ develops a conservative 24-h reference value (ReV) and effects screening level (ESL) based on intermediate (e.g., subacute) exposure study results while considering any available information on adverse effects due to shorter-term exposure. The resulting values are considered sufficiently health-protective of not only 24-h exposure, but also the intermittent exposure which may occur over intermediate exposure duration downwind of a permitted facility or source. Consistent with TCEQ (2012), exceedances of the CrVI short-term ESL (or long-term ESL) should be discouraged during air permit reviews as CrVI has been identified as capable of causing respiratory sensitization (ATSDR 2012, Fernandez-Nieto 2006).

The TCEQ will develop both acute and chronic values based on the CrVI content of the compound used in the key study (i.e., on a CrVI equivalent basis (μg CrVI/$m^3$)). The CrVI equivalent for a given dose of a CrVI compound is based on the percent of the compound's molecular weight that CrVI represents (i.e., the compound's concentration in μg/$m^3$ × (MW of CrVI in compound / MW of compound)). From a protection of public health perspective, use of CrVI equivalents assumes that other forms are no more toxic than the compound used in the key study on a μg CrVI/$m^3$basis. This is a necessary science policy decision given the lack of available studies to derive separate values for every CrVI compound and is consistent with the approach of other agencies (e.g., USEPA, ATSDR). However, the derived acute ReV and ESL values are expected to be sufficiently health-protective regardless of the chemical form because they will be based on the CrVI compounds which have produced adverse effects at the lowest concentrations, the most conservative health-protective choice. For example, potassium chromate and barium chromate appear to produce adverse effects in rats at significantly higher concentrations in intermediate (e.g., subacute) exposure studies than sodium dichromate, which will be used to develop the acute ReV and ESL for CrVI particulates. Additionally, the acute values will incorporate appropriately conservative uncertainty factors.

### 3.1.1 Physical/Chemical Properties

Table 3 provides summary physical/chemical data for numerous hexavalent chromium (CrVI) compounds. The chemical/physical properties of CrVI compounds have toxicological

implications. Human and animal inhalation exposure toxicity data indicate that soluble CrVI compounds dissolved in the physical form of mists (e.g., chromium trioxide in water as chromic acid mist) and particulate CrVI compounds, which may be soluble or insoluble, have different adverse effect-inducing potencies and respiratory system target regions. The respiratory system is the most sensitive target for inhalation exposure to both types of CrVI compounds. However, the primary respiratory effects of chromic acid mist exposure occur in the nose, while the adverse effects of particulate CrVI compounds occur throughout the respiratory tract. There are also differences in potencies (e.g., LOAELs) and critical effects (e.g., nasal versus lower respiratory effects). Additionally, environmental exposure to chromium trioxide (e.g., chromic acid mist) and other soluble CrVI compounds in the form of mists is less likely than environmental exposure to particulate CrVI compounds (ATSDR 2012). Thus, similar to ATSDR (2012), CalEPA (2001), and USEPA (1998), the TCEQ will derive separate noncarcinogenic inhalation reference values (ReVs) for CrVI particulate compounds and dissolved CrVI mists (e.g., $CrO_3$ in water). *However, this development support document (DSD) only provides ReVs for CrVI particulate compounds, as those for CrVI compounds in the form of mists will be presented in a later DSD.*

The acid anhydride $CrO_3$ and acid chloride $CrO_2Cl_2$ and a wide variety of metal (M) chromates $MCrO_4$ (e.g., zinc chromate) and metal dichromates $MCr_2O_7$ (e.g., potassium dichromate) are typical CrVI compounds (Katz and Salem 1993). The following chemical/physical information concerning chromium in its various oxidation states was taken directly from ATSDR (2008).

> Chromium is a metallic element with oxidation states ranging from chromium(-II) to chromium(+VI). The important valence states of chromium are II, III, and VI. Elemental chromium, chromium(0), does not occur naturally. The divalent state (chromous) is relatively unstable and is readily oxidized to the trivalent (chromic) state. Chromium compounds are stable in the trivalent state and occur in nature in this state in ores, such as ferrochromite ($FeCr_2O_4$). The hexavalent (chromate) is the second most stable state. However, CrVI rarely occurs naturally, but is produced from anthropogenic sources. CrVI occurs naturally in the rare mineral crocoite ($PbCrO_4$).
>
> The solubility of chromium compounds varies, depending primarily on the oxidation state. Trivalent chromium (CrIII) compounds, with the exception of acetate, hexahydrate of chloride, and nitrate salts, are generally insoluble in water. The zinc and lead salts of chromic acid are practically insoluble in cold water. The alkaline metal salts (e.g., calcium, strontium) of chromic acid are less soluble in water. Some CrVI compounds, such as CrVI oxide (or chromic acid), and the ammonium and alkali metal salts (e.g., sodium and potassium) of chromic acid are readily soluble in water.

NTP (2011), quoted below, provides additional useful information on the chemical/physical properties of CrVI compounds.

> Calcium chromate occurs as yellow crystals or a bright-yellow powder. It is slightly soluble in water and soluble in dilute acids, and it reacts with acids and ethanol. Chromium trioxide (also known as chromic trioxide) occurs as dark-red or brown crystals, flakes, or granular powder and is soluble in water, ethyl alcohol, ethyl ether, sulfuric acid, and nitric acid. Lead chromate occurs as yellow, orange, or red crystals or a yellow or orange-yellow powder that is insoluble in water, acetic acid, and ammonia but soluble in dilute nitric acid. The term "lead chromate" is also used to refer to various commercial lead chromate pigments. Potassium chromate occurs as yellow crystals and is soluble in water but insoluble in ethanol. Potassium dichromate occurs as red or orange-red crystals and is soluble in water but insoluble in ethanol and acetone. Sodium chromate occurs as yellow crystals and is soluble in water and slightly soluble in methanol. Sodium dichromate occurs as bright orange-red or red hygroscopic crystals and is soluble in water and methanol. Strontium chromate occurs as yellow monoclinic crystals or a yellow powder. It is slightly soluble in water and soluble in dilute hydrochloric acid, nitric acid, and acetic acid. Zinc chromate occurs as lemon yellow crystals or powder. It is insoluble in cold water and acetone, sparingly soluble in hot water, and soluble in acid and liquid ammonia. The term "zinc chromate" is also used to refer to various commercial zinc and zinc potassium chromates.

Additional information and discussion on the chemical/physical properties of the various compounds of Cr, including CrVI, in relation to their toxicities may be found elsewhere (ATSDR 2012, Katz and Salem 1993).

## 3.1.2 Key Studies for CrVI Particulate Compounds

Toxicity data from human and animal inhalation exposure studies indicate adverse effects of CrVI particulate compounds occur throughout the respiratory tract (ATSDR 2012). Two studies were identified as key studies for CrVI particulate compounds (Glaser et al. 1990, 1985) and are described below.

### *3.1.2.1 Glaser et al. (1990) Key Study*

The Glaser et al. (1990) study was identified as one of the key studies and the increase in the mean lung weight relative to body weight (BW) was ultimately identified as the critical effect due to 30-d subacute exposure to sodium dichromate. It should be noted that some of the following summary information was taken verbatim from ATSDR (2012).

Glaser et al. (1990) was a well-conducted comprehensive study and evaluated several endpoints at different exposure durations. Specifically, in the study, 8-week old male Wistar rats (30 animals/group) were exposed 22 h/d, 7 d/week to sodium dichromate at 0, 50,100, 200, and 400

μg CrVI/$m^3$. Groups of 10 animals were sacrificed after 30 or 90 d of exposure or after 90 d of exposure with a 30-d recovery period. The respective mass median mean diameters (MMAD) and geometric standard deviations ($\sigma_g$) were 0.28 μm and 1.63 for the 50 and 100 μg CrVI/$m^3$ concentrations and 0.39 μm and 1.72 for the 200 and 400 μg CrVI/$m^3$ concentrations, respectively.

Glaser et al. (1990) conducted gross and histological examinations on the upper airway epithelia, left lung lobes, and kidneys. In addition, bronchoalveolar lavage fluid (BALF) was analyzed for total protein, albumin, and lactate dehydrogenase (LDH) activities. Other endpoints evaluated in the study included: BW gain in grams (g), lung weight normalized to the body weight (g dry weight/kg BW), leucocytes in blood per litre (l) ($10^9$/l), bronchoalveolar hyperplasia, lung fibrosis, lung histiocytosis, total macrophages in BALF ($10^6$), dividing macrophages in BALF (% of BALF cells), and viability of BALF cells (%).

While no deaths or abnormal clinical signs occurred at any of the exposures, obstructive respiratory dyspnea and reduced mean body weight gain were reported at ≥ 200 μg CrVI/$m^3$ after 30 and 90 d. Mean lung weight relative to BW and blood leucocyte counts were increased in all exposure groups and were statistically increased compared to the controls in all exposure groups starting at 50 μg CrVI/$m^3$. Histological examination revealed slight hyperplasia in high incidence at 50 μg CrVI/$m^3$ at 30-d.

Accumulation of macrophages (histiocytosis) was observed in all exposed rats, regardless of exposure concentration or duration. Histology of upper airways revealed focal inflammation. In addition, the authors describe increase in lung weight as a chromium-induced irritation effect and attribute it to lung histiocytosis. Results of BALF analysis provided further information on the reversible irritation effect. Total protein in BALF was significantly increased in all exposed groups, declining in the recovery period. Albumin in BALF increased in a dose-related manner at all concentrations in the 30-d exposure group, also declining during the 30-d recovery period. The activities of LDH and β-glucuronidase (measures of cytotoxicity) were elevated at exposures of 200 and 400 μg CrVI/$m^3$ for 30 and 90-d, returning to control levels during the recovery period. The number of macrophages in the BALF had significantly increased after 30 and 90 d, normalizing during the recovery period. Lung fibrosis occurred at a higher concentration (100 μg CrVI/$m^3$) after 30-d, but was not observed in rats exposed for 90-d.

Although LDH and β-glucuronidase are measures of cytotoxicity and were elevated in the study, they occurred at higher concentrations when compared to increase in mean lung weight and blood leucocyte count. Further, there is limited information in the scientific literature about what magnitude of biochemical change such as that documented by BALF analysis, accumulation of macrophages, and total protein in BALF should be considered adverse, particularly when extrapolating animal data to humans. The same is true for increases in blood leucocyte count.

On the other hand, such information exists for organ weight. A ten percent change in organ weight is commonly used to define adversity in regulatory chemical risk assessments. For that reason, increase in relative lung weight in Wistar rats at 50 μg CrVI/$m^3$ for 30-d was identified as the Lowest-Observed-Adverse-Effect-Level (LOAEL) and critical effect for deriving the acute ReV and ESL for a 24-h duration. The TCEQ conducted benchmark concentration (BMC) modeling for increase in lung weight to determine the point of departure (POD).

Additionally, the TCEQ also conducted BMC modeling for other endpoints from the 30-d exposure from Glaser et al. (1990) study and included: leucocytes counts, and total protein, total albumin, and LDH in BALF.

### *3.1.2.2 Glaser et al. (1985) Key Study*

Glaser et al. (1985) is another key study. The study design of Glaser et al. (1985) is very similar to the Glaser et al. (1990) study and included an exposure group (25 μg CrVI/$m^3$) that was lower than the lowest exposure group in the Glaser et al. (1990) study. In the 1985 study, 5-week-old male Wistar rats (20 per dose group) were exposed to sodium dichromate at concentrations of 25, 50, 100, and 200 μg CrVI/$m^3$, 22 h/d, 7 d/week in subacute (28-d) or subchronic (90-d) protocols. Similar to the Glaser et al. (1990) study, no deaths occurred in any exposure group and all exposed animals behaved similar to the control animals.

Normal histological findings were reported in the lung, kidney, liver, and stomach in all exposure groups. However, dose-dependent and significant increases in relative lung weight and spleen weight ($p < 0.05$ by Student's t test) were reported at concentrations greater than 25 μg CrVI/$m^3$ after both subacute and subchronic exposures, although the increases in spleen weight were not entirely monotonic (as they were for lung weight). The Glaser et al. (1985) study did not provide quantitative lung weight data for the 28-d subacute exposure duration. Therefore, the TCEQ could not conduct BMC modeling for the subacute exposure duration. However, a No-Observed-Adverse-Effect-Level (NOAEL) of 25 μg CrVI/$m^3$ was determined for increase in relative lung weight for the subacute exposure, which complements the LOAEL of 50 μg CrVI/$m^3$ for increased lung weight observed in both this study and Glaser et al. (1990).

### *3.1.2.3 Other Studies*

It should be noted that some of the following summary information was taken verbatim from ATSDR (2012). Most of the acute studies are 4-h lethality studies (American Chrome and Chemicals 1989; Gad et al. 1986) and nasal hemorrhage was observed in two of five rats after inhalation for 10 d to 1.15 mg CrVI/$m^3$ during a 13-week exposure study (Kim et al. 2004), with no nasal effects observed at 0.49 mg CrVI/$m^3$. However, only a small number of animals were evaluated and histopathological evaluations of the respiratory tract (or other tissues) were not conducted following the acute-duration period. Because nasal hemorrhage may be interpreted as a more severe effect, data are very limited, and the effect occurred at much higher concentrations than what was reported in the key studies chosen by the TCEQ, this endpoint was determined to be not suitable for defining NOAEL or LOAEL values for acute ReV development.

#### *3.1.2.4 Consideration of Developmental/Reproductive Effects*

Developmental effects are considered for derivation of the acute ReV and ESL (TCEQ 2012). No inhalation exposure developmental studies were located for CrVI in humans or laboratory animals. However, due to the lung's significant capacity to reduce CrVI to CrIII, essentially detoxifying it prior to (and limiting) absorption and systemic distribution (De Flora et al. 1997), developmental effects at inhalation exposure levels lower than the lowest inhalation LOAELs for point-of-entry effects (e.g., increased lung weight, nasal symptoms/irritation) are considered unlikely. For example, in oral studies in rats and mice, several developmental effects (e.g., decreased fetal weight and ossification, post-implantation losses, delayed sexual maturation) were observed at relatively high doses ≥35 mg CrVI/kg/d (Section 2.2 of ATSDR 2012), which appear to significantly exceed gastrointestinal reduction capacity (TCEQ 2010). Oral doses producing such effects in mice were around 50 mg/kg/d and equate to mouse daily inhalation exposure concentrations at tens of thousands µg CrVI/$m^3$, which are orders of magnitude higher than the levels producing the critical effects observed in key inhalation studies (e.g., increased relative lung weight). Thus, the acute ReV and ESL are expected to be protective of developmental effects.

Although human data on reproductive effects are limited and there is no evidence of such effects in people environmentally exposed, laboratory animal data from inhalation studies are useful. In regard to studies conducted by Glaser and colleagues, ATSDR (2012) indicates that histopathological examination of the testes of rats exposed to 0.2 mg CrVI/$m^3$ as sodium dichromate for 28 or 90 d (Glaser et al. 1985), to 0.1 mg CrVI/$m^3$ as sodium dichromate for 18 months, or to 0.1 mg Cr/$m^3$ as a 3:2 mixture of CrVI trioxide and CrIII oxide for 18 months (Glaser et al. 1986, 1988) revealed no abnormalities. 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 exposed to chromium dioxide at 15.5 mg CrVI/$m^3$for 2 years (Lee et al. 1989). ATSDR (2012) identified a NOAEL of 0.2 mg CrVI/$m^3$ for reproductive effects based on the Glaser et al. (1985) study 90-d exposure duration. This reproductive inhalation NOAEL (200 µg CrVI/$m^3$) is much higher than the lowest inhalation LOAELs for point-of-entry effects. Thus, the acute ReV and ESL are expected to also be protective of reproductive effects.

## 3.1.3 Mode-of-Action (MOA) Analysis and Dose Metric

This section contains MOA information relevant to CrVI-induced adverse effects. Additional MOA relevant to carcinogenesis is discussed in Section 4.2.2. The following information on mechanisms of CrVI toxicity was taken from ATSDR (2008) with references omitted [emphasis added].

> The respiratory tract is the major target of inhalation exposure to CrVI compounds in humans and animals. *Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact.* The toxic potency of

chromium is dependent on the oxidation state of the chromium atom, with CrVI more potent than CrIII. *The mechanisms of chromium toxicity and carcinogenicity are very complex. They are mediated partly through reactive intermediates during intracellular reduction of CrVI to CrIII and oxidative reactions, and partly mediated by CrIII which is the final product of intracellar CrVI reduction and forms deleterious complexes with critical target macromolecules.* CrIII may form complexes with peptides, proteins, and DNA, resulting in DNA-protein crosslinks, DNA strand breaks, and alterations in cellular signaling pathways, which may contribute to toxicity and carcinogenicity of chromium compounds.

*The greater toxic potency of CrVI relative to CrIII most likely is related to two factors: (1) the higher redox potential of CrVI; and (2) the greater ability of CrVI to enter cells.* Differences in molecular structure contribute the greater cellular uptake of CrVI compared to CrIII. At physiological pH, CrVI exists as the tetrahedral chromate anion, resembling the forms of other natural anions (e.g., sulfate and phosphate) which are permeable across nonselective membrane channels. CrIII, however, forms octahedral complexes and cannot easily enter through these channels. Therefore, the lower toxicity to CrIII may be due in part to lack of penetration through cell membranes. It follows that extracellular reduction of CrVI to CrIII may result in a decreased penetration of chromium into cells, and therefore, a decreased toxicity.

*The higher redox potential of CrVI contributes to the higher toxic potency of CrVI relative to CrIII, because once it is taken into cells, CrVI is rapidly reduced to CrIII, with CrV and CrIV as intermediates.* These reactions commonly involve intracellular species, such as ascorbate, glutathione, or amino acids. *CrVI, CrV, and CrIV have all been shown to be involved in Fenton-like oxidative cycling, generating oxygen radical species. It is believed that the formation of these radicals may be responsible for many of the deleterious effects of chromium on cells, including lipid peroxidation and alterations in cellular communication, signaling pathways and cytoskeleton.* Cellular damage from exposure to many chromium compounds can be blocked by radical scavengers, further strengthening the hypothesis that oxygen radicals play a key role in chromium toxicity.

To summarize, while the toxic potential of chromium following inhalation exposure is dependent on the oxidation state and any resulting adverse effects are probably due to the direct action of chromium at the site of contact, the mechanisms of chromium toxicity appear very complex and are mediated partly: (1) through reactive intermediates during intracellular reduction of CrVI to CrIII and oxidative reactions, and (2) by CrIII which is the final product of intracellular CrVI reduction and forms deleterious complexes with critical target macromolecules that may contribute to toxicity and carcinogenicity of chromium compounds. CrVI is more toxic than CrIII due to a greater ability to enter cells where it and its metabolic intermediates (CrV, CrIV)

formed during rapid reduction to CrIII generate oxygen radical species believed to be responsible for many of the deleterious effects of chromium on cells.

As with many chemicals, a complete and clear picture of the underlying mechanisms and/or MOA(s) producing the noncarcinogenic adverse effects of CrVI is yet to be fully elucidated. Consistent with TCEQ (2012), a threshold dose-response relationship is used for noncarcinogenic effects as a default. Additionally, as is often the case for inhalation studies, air concentration was the only dose metric available from the key studies for CrVI particulate compounds. Therefore, air concentration was used as the default dose metric for derivation of the acute ReV.

## 3.1.4 Evaluation of Potential PODs

### *3.1.4.1 Benchmark Concentration (BMC) Modeling*

Statistically increased relative lung weight occurred in male Wistar rats at a LOAEL of 50 μg CrVI/$m^3$ (30-d exposure duration) in the key studies of Glaser et al. (1990, 1985), with an associated NOAEL of 25 μg CrVI/$m^3$ from Glaser et al. (1985) and is determined to be the critical effect. While this NOAEL is a potential POD for derivation of the acute ReV and ESL, the data from Glaser et al. (1990) are amenable to BMC modeling. When possible, the TCEQ performs BMC modeling because of the potential advantages of this approach over the NOAEL/LOAEL approach (TCEQ 2012). Data for other endpoints (i.e., BALF analysis for total protein, total albumin, LDH, and increase in leucocyte number) lacking sufficient information on the level of change which should be considered adverse are also amenable to BMC modeling.

The 95% lower confidence limit on the BMC is abbreviated as the BMCL. Data on the critical effect of statistically significant increases in relative lung weight following 30-d exposure (Table 4) were modeled to determine the POD with benchmark dose (BMD) Software (USEPA BMDS Version 2.3.1) using continuous models (see Section 3.1.3.3). BMC modeling results for other endpoints were used as supporting information.

### *3.1.4.2 Critical Effect Size (CES)*

According to USEPA (2000), if there is a level of change in the endpoint that is considered to be biologically significant, then that amount of change is chosen for evaluation. 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), while for continuous data this level is expressed on a continuous scale.

Because the increase in lung weight relative to BW data are continuous, the TCEQ will use the term “critical effect size” (CES) instead of the term “BMR.” This is to distinguish continuous data from dichotomous data as recommended by Dekkers et al. (2001). Dekkers et al. (2001) recommended the term CES to define the demarcation between non-adverse and adverse changes in toxicological effect parameters for continuous data. For example, a CES of 10% or $CES_{10}$ for

continuous data corresponds to a 10% change in the mean of an exposed group parameter compared to the control mean.

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). Significant increases in mean lung weight occurred in all exposure groups when compared to controls after subacute exposure to sodium chromate in the key study of Glaser et al. (1990). A 16% increase in the mean lung weight was reported in the 50 μg CrVI/$m^3$ exposure group that was significantly different than the control group. The increase in lung weight also had a clear dose-response and was statistically increased in the other higher exposure groups (100, 200, and 400 μg CrVI/$m^3$). Therefore, for the Glaser et al. (1990) study, a $BMC_{10}$ and $BMCL_{10}$ were calculated for the $CES_{10}$ based on the critical effect of increased lung weight relative to BW in male Wistar rats to determine the POD (Table 5). 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 for comparison purposes as suggested by USEPA (2000).

BMC analyses for the other endpoints (i.e., BALF analysis for total protein, total albumin, LDH, and increase in leucocyte number) without sufficient information on the level of change which should be considered adverse were conducted using a default CES of 1SD (Table 6) and are provided to support the POD for the critical effect (i.e., increase in relative lung weight).

### *3.1.4.3 BMC Modeling Results for Increased Relative Lung Weight for 30-d Exposure*

Based on the key studies of Glaser et al. (1990, 1985), increase in mean lung weight relative to BW was identified as the critical effect upon which to base the POD. Expressing mean lung weight relative to BW is used to normalize changes in the lung. The specific data modeled from Table 1 of Glaser et al. (1990) are given in Table 4 (Glaser et al. 1985 did not provide specific data).

**Table 4. Increased Relative Lung Weight Data for 30-d Exposure (Glaser et al. 1990)**

| **Dose Group (μg CrVI/ $m^3$)** | **Relative Lung Weight (g lung dry weight/kg BW)** |
|---|---|
| Controls | 0.43 ± 0.04 |
| 50 | 0.50 ± 0.04*** |
| 100 | 0.54 ± 0.06*** |
| 200 | 0.55 ± 0.04*** |
| 400 | 0.61 ± 0.02*** |

*****p value <0.001**

Goodness of fit for BMC modeling results was evaluated by p-values > 0.1, visual inspection of the dose-response curves relative to data points, and scaled residuals less than an absolute value

of 2. Tests from BMC continuous models were examined to evaluate whether a homogeneous (constant) or nonhomogeneous variance was appropriate. A summary of acceptable BMC results (using constant variance) for relative mean lung weight is provided in Table 5.

**Table 5. BMC Modeling Results for Increased Relative Lung Weight for 30-d Exposure (Glaser et al. 1990)**

| Continuous Model | AIC | Scaled Residual | $BMC_{10}$ (μg CrVI/$m^3$) | $BMCL_{10}$ (μg CrVI /$m^3$) |
|---|---|---|---|---|
| Hill | -261.119785 | 0.282 | 29.6879 | 16.0631 |

Only the Hill model provided a satisfactory fit to the 30-d relative lung weight data with a goodness of fit p-value > 0.1. Visual inspection of model fit in the lower exposure range of most interest when extrapolating to lower exposures (e.g., 0 to 50 μg/$m^3$) also indicated good fit, which appeared slightly better for the constant variance model (Figure 1). The constant variance model also had lower AIC and scaled residual values than the nonconstant variance model. Therefore, constant variance was considered more appropriate and the results given in Table 5 were limited to those using constant variance. However, use of nonconstant variance resulted in very similar values ($BMC_{10}$ and $BMCL_{10}$ values of 34.1396 and 16.6246 μg CrVI/$m^3$, respectively). Also for comparison, the $BMCL_{1SD}$ of 15.7386 μg CrVI/$m^3$ was very similar to the Table 5 $BMCL_{10}$ value of 16.0631 μg CrVI/$m^3$ ($BMC_{1SD}$ = 27.9188 μg CrVI/$m^3$).

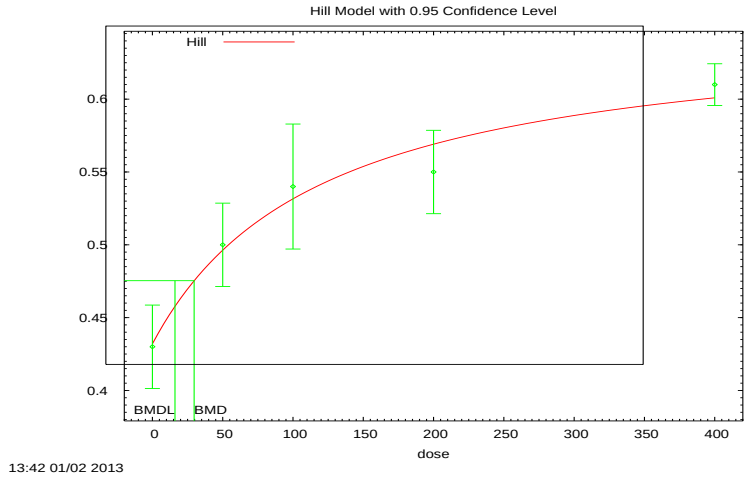



**Figure 1. Hill Model for Increase in Relative Lung Weight (Glaser et al. 1990)**

*The $BMCL_{10}$ of 16.0631 μg CrVI/$m^3$ for increase in relative lung weight due to 30-d exposure was conservatively used as the POD for deriving the acute ReV and ESL for a 24-h duration.*

### *3.1.4.4 BMC Modeling Results for the Other Endpoints*

There is limited information in the scientific literature about what magnitude of biochemical change (i.e., total protein, total albumin, LDH in BALF) and/or percent increase (i.e., leucocyte number) should be considered an adverse effect. Additionally, these endpoints are typically considered biomarkers of exposure as opposed to biomarkers of effects. Therefore, these endpoints were only evaluated from a weight-of-evidence approach to support the POD for critical effect (i.e., increase in relative lung weight) and are only briefly discussed below. BMC modeling was conducted with one standard deviation (1SD) as the default CES based on the Glaser et al. (1990) data presented in Table 6.

**Table 6. Leucocyte Count and BALF Analysis Data for 30-d Exposure (Glaser et al. 1990)**

| | **Dose Group 0 µg CrVI/ $m^3$** | **Dose Group 50 µg CrVI/ $m^3$** | **Dose Group 100 µg CrVI/ $m^3$** | **Dose Group 200 µg CrVI/ $m^3$** | **Dose Group 400 µg CrVI/ $m^3$** |
|---|---|---|---|---|---|
| **Total Protein in BALF (mg/l)** | 216 ± 34 | 309 ± 42*** | 387 ± 63*** | 468 ± 97*** | 607 ± 164*** |
| **Total Albumin in BALF (mg/l)** | 82 ± 15 | 150 ± 49*** | 179 ± 59*** | 233 ± 58*** | 270 ± 43*** |
| **LDH in BALF (mg/l)** | 28 ± 6 | 32 ± 3*** | 35 ± 7*** | 49 ± 8*** | 63 ± 10*** |
| **Leucocytes in Blood ($10^9$/l)** | 0.56 ± 0.31 | 1.03 ± 0.46* | 1.05 ± 0.21*** | 1.30 ± 0.60*** | 1.95 ± 0.91*** |

*****p value <0.001; * p value < 0/05**

BMC results based on the best fitting model (e.g., considering goodness of fit, AIC, visual inspection especially in the low-dose region, scaled residuals) for each of the endpoints are summarized in Table 7. For LDH in BALF, the Hill, Power, and Exponential 4 and 5 models (nonconstant variance) provided adequate fit to the data (goodness of fit p values > 0.1) with the lowest model AIC values, and with the lowest AIC the results for the Exponential 5 model are shown in Table 7. For leucocyte count, the linear model (nonconstant variance) provided adequate fit to the data (goodness of fit p value > 0.1) with the lowest model AIC value and likewise the results are given Table 7.

For total protein in BALF, the Hill and Exponential 5 models (nonconstant variance) provided adequate fit to the data (goodness of fit p values > 0.1) with the lowest model AIC values. However, since the $BMCL_{1SD}$ calculation failed for the Hill model with nonconstant variance, the results for the Exponential 5 model are shown in Table 7. The Hill model $BMCL_{1SD}$

calculation did not fail using constant variance. Both the Hill and Exponential 5 models also provided adequate fit to the data using constant variance but had higher AIC values. Using constant variance, the $BMC_{1SD}$ values ranged from 49.6748-52.701 μg CrVI/$m^3$ and the $BMCL_{1SD}$ values ranged from 30.0371-34.2993 μg CrVI/$m^3$. These ranges help put the Exponential 5 model results (nonconstant variance) and the Hill model $BMCL_{1SD}$ calculation failure using nonconstant variance into perspective for total protein in BALF and are provided in parenthesis in Table 7.

For total albumin in BALF, the Hill and Exponential 5 models (nonconstant variance) provided adequate fit to the data (goodness of fit p values > 0.1) with the lowest model AIC values. However, since the $BMCL_{1SD}$ calculation failed for the Hill model with nonconstant variance and the Exponential 5 model had the lowest scaled residual of interest, the results for the Exponential 5 model are shown in Table 7. The Hill model $BMCL_{1SD}$ calculation did not fail using constant variance. Both the Hill and Exponential 5 models also provided adequate fit to the data using constant variance but had slightly higher AIC values. Using constant variance, the $BMC_{1SD}$ values ranged from 32.6449-37.0088 μg CrVI/$m^3$ and the $BMCL_{1SD}$ values ranged from 19.3097-24.2117 μg CrVI/$m^3$. These ranges help put the Exponential 5 model results (nonconstant variance) and the Hill model $BMCL_{1SD}$ calculation failure using nonconstant variance into perspective for total albumin and are provided in parenthesis in Table 7.

**Table 7. BMC Modeling Results for Leucocyte Count and BALF Analysis for 30-d Exposure (Glaser et al. 1990)**

| | **AIC** | **Scaled Residual** | **$BMC_{1SD}$ (μg CrVI/$m^3$)** | **$BMCL_{1SD}$ (μg CrVI /$m^3$)** |
|---|---|---|---|---|
| **Total Protein in BALF (mg/l)** | 478.4989 | -0.2512 | 15.4162 | 10.4311 |
| **(constant variance models that also fit)** | (506.250781-506.3929) | (0.0437-0.1196) | (49.6748-52.701) | (30.0371-34.2993) |
| **Total Albumin in BALF (mg/l)** | 432.5644 | 0.2265 | 10.9985 | 5.9941 |
| **(constant variance models that also fit)** | (439.27746-439.3748) | (0.269-0.4887) | (32.6449-37.0088) | (19.3097-24.2117) |
| **LDH in BALF (mg/l)** | 247.8843 | -0.476 | 78.434 | 43.3173 |
| **Leucocytes in blood ($10^9$/l)** | -15.741256 | 0.248 | 95.2515 | 62.9147 |

The $BMCL_{1SD}$ values based on nonconstant variance for these endpoints which were not selected as the critical effects (for reasons discussed previously) ranged from 5.9941 μg CrVI/$m^3$ (total albumin in BALF) to 62.9147 μg CrVI/$m^3$ (leucocytes in blood). To put total protein and albumin $BMCL_{1SD}$ values with nonconstant variance into perspective, $BMCL_{1SD}$ values with constant variance ranged from 19.3097-34.2993 μg CrVI/$m^3$. These $BMCL_{1SD}$ values are fairly similar to the $BMCL_{10}$ of 16.0631 μg CrVI/$m^3$ for the critical effect (i.e., increase in relative lung weight). Thus, the BMCL results from these other endpoints support the POD for the critical effect, increase in relative lung weight, which has a defined level of change considered adverse.

## 3.1.5 Dosimetric Adjustments

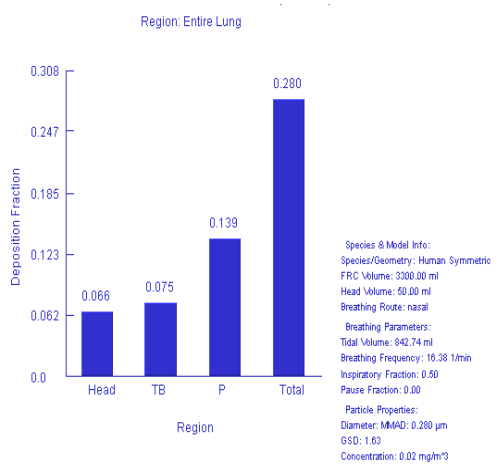
The POD (16.0631 μg CrVI/$m^3$) based on data from Glaser et al. (1990) is associated with exposure for 22 h/d, 7 d/week, for 30-d (660 h). The acute ReV duration of interest is much shorter at 24 h when compared to the exposure duration in the study. Due to the magnitude of such an extrapolation (i.e., 660 to 24 h), the TCEQ does not have confidence that Haber's rule could be used for upward adjustment of the key study POD to the duration of interest in a toxicologically predictive manner (TCEQ 2012). Therefore, conservatively no duration adjustment will be performed. The $POD_{ADJ}$ is therefore the $BMCL_{10}$ of 16.0631 μg CrVI/$m^3$.

### *3.1.5.1 Default Dosimetry Adjustment from Animal-to-Human Exposure*

Since Glaser et al. (1990) was conducted in laboratory animals, a dosimetric adjustment factor for particulate matter must be applied to the $POD_{ADJ}$ to convert the animal concentration to a $POD_{HEC}$. Per TCEQ (2012), the TCEQ uses the Multiple Pass Particle Dosimetry (MPPD) Model (version 2.11) (CIIT 2002) to derive a deposition fraction that is used in the regional deposited dose ratio (RDDR), which is an appropriate model for rats. Study-specific parameters necessary for the MPPD model were provided by Glaser et al. (1990), which included the MMAD and $\sigma_g$. The default minute ventilation ($V_E$) used by the MPPD model for humans (7,500 mL/min) does not correspond to the default value (13,800 mL/min) given by USEPA (1994), which is used in the RDDR calculation below. Neither USEPA (1994) nor cited USEPA background documents provide the human tidal volume (mL/breath) and breathing frequency (breaths/min) values which correspond to the default USEPA minute ventilation and are needed for input into the MPPD so that both the MPPD model and RDDR calculation use the same human minute ventilation. Therefore, the TCEQ used human tidal volume and breathing frequency values from de Winter-Sorkina and Cassee (2002) to determine the quantitative relationship between the two and calculate the tidal volume and breathing frequency values corresponding to the default USEPA minute ventilation for input into the MPPD model (TCEQ 2011). All remaining values used were default.

The RDDR for the pulmonary region was selected as the appropriate output to use to develop a $POD_{HEC}$ because the adverse effect noted in the key animal study is increase in mean lung weight. The human and rat MPPD modeling results for increase in relative lung weight are presented in Figure 2.

**Human Output**




**Rat Output**

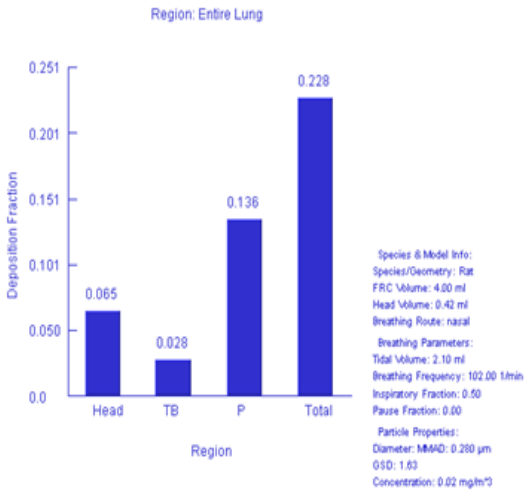



**Figure 2. MPPD Model Input and Output for Increase in Relative Lung Weight (Glaser et al. 1990)**

The deposition fractions determined from the MPPD program above were then used to calculate the RDDR for the key study:

$$RDDR = \frac{(V_E)_A}{(V_E)_H} \times \frac{DF_A}{DF_H} \times \frac{NF_H}{NF_A}$$

where:

$V_E$ = minute volume
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor
A =animal
H = human

$$RDDR = \frac{214.2 mL/min}{13{,}800\ mL/min} \times \frac{0.136}{0.139} \times \frac{54\ m^2}{0.34\ m^2} = 2.41$$

### *3.1.5.2 Calculation of the $POD_{HEC}$*

To derive a $POD_{HEC}$ for CrVI particulate compounds, the $BMCL_{10}$ of 16.0631 µg CrVI/$m^3$ was multiplied by the RDDR of 2.41 for the pulmonary region:

$POD_{HEC} = POD_{ADJ} \times RDDR$
$= 16.063$ µg CrVI/$m^3$ X 2.41
$= 38.71$ µg CrVI/$m^3$

where: $POD_{ADJ}$ = duration adjusted point of departure (µg/$m^3$)
RDDR = regional deposited dose ratio
$POD_{HEC}$ = dosimetrically adjusted point of departure (µg/$m^3$)

## 3.1.6 Adjustments of the $POD_{HEC}$ and Critical Effect

The $POD_{HEC}$ of 38.71 µg CrVI/$m^3$ is selected as the $POD_{HEC}$ based on the critical effect of increased lung weight (relative to BW). The acute ReV and ESL for a 24-h duration were derived based on this $POD_{HEC}$.

Although much information is available, the mechanisms of chromium toxicity appear very complex and the exact MOA by which CrVI produces toxicity is not fully elucidated (see Section 3.1.2). The default approach for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive the acute ReV (i.e., assume a threshold MOA) (TCEQ 2012).

A total UF of 30 was applied to the $POD_{HEC}$ of 38.71 µg CrVI/$m^3$ to derive the acute ReV: an $UF_A$ of 3 for extrapolation from animals to humans; an $UF_H$ of 10 to account for variability within the human population; and an $UF_D$ of 1. The following is more specific concerning the rational for the applicable UFs:

- A $UF_A$ of 3 was used for extrapolation from animals to humans because the MPPD program accounts for toxicokinetic differences and limits uncertainty for rat to human extrapolation but does not account for toxicodynamic differences;
- A $UF_H$ of 10 was used for interindividual variability because little information on variability in the human population to the effects of CrVI inhalation exposure was available and to account for potentially sensitive subpopulations such as children, the elderly, and those with pre-existing medical conditions;
- A $UF_D$ of 1 was used for database uncertainty because while the acute database is limited, database quality is medium to high for intermediate duration exposure (e.g., studies in more than one species; two rat strains, rabbits) and a much longer duration exposure study (30-d subacute exposure, 22 h/d) was used to determine a 24-h acute ReV. This is a very conservative (i.e., health-protective) approach that mitigates the lack of more acute (i.e., < 1 d) studies. Additionally, information is available regarding the potential for CrVI-induced developmental and reproductive effects (Section 3.1.1.4) which suggests that such effects are unlikely at inhalation exposure levels lower than the lowest inhalation LOAELs for point-of-entry effects. Thus, the acute ReV and ESL are expected to be protective of potential developmental and reproductive effects.

  24-h acute ReV = $POD_{HEC}$ / ($UF_H \times UF_A \times UF_D$)
  = 38.71 μg CrVI/$m^3$ / (10 × 3 × 1) = 1.29 μg CrVI/$m^3$ for CrVI particulates

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

The 24-h acute ReV for CrVI particulates rounded to two significant figures is 1.3 μg CrVI/$m^3$. The rounded 24-hour acute ReV was then used to calculate the 24-h $^{acute}$ESL. At the target hazard quotient (HQ) of 0.3, the 24-h $^{acute}$ESL for CrVI particulates is 0.39 μg CrVI/$m^3$ (Table 8).

**Table 8. Derivation of the 24-h Acute ReV and $^{acute}$ESL**

| **Parameter** | **Summary** |
|---|---|
| Key Study | Glaser et al. (1990) |
| Study Population | 8-week old male Wistar rats |
| Study Quality Confidence Level | Medium-High |
| Exposure Method | Inhalation |
| Critical Effect | Increase in relative lung weight |
| Exposure Duration | 22 h/d, 7 d/week, for 30 d |
| Extrapolation to 24-h | Conservatively, not performed |
| $BMCL_{10}$ | 16.06 µg CrVI/$m^3$ |
| $POD_{HEC}$ | 38.71 µg CrVI/$m^3$ |
| Total uncertainty factors (UFs) | 30 |
| *Interspecies UF* | *3* |
| *Intraspecies UF* | *10* |
| *Incomplete Database UF*<br>*Database Quality* | *1*<br>*Medium-High* |
| **24-Hour Acute ReV (HQ = 1)** | **1.3 µg CrVI/$m^3$** |
| **24-Hour $^{acute}$ESL (HQ = 0.3)** | **0.39 µg CrVI/$m^3$** |

## *3.2 Welfare-Based Acute ESLs*

### 3.2.1 Odor Perception

Odor information is available for several CrVI compounds and indicates these compounds are odorless (i.e., a lack of odor potential) (Table 3).

### 3.2.2 Vegetation Effects

No useful data were found regarding potential adverse vegetative effects due to direct exposure to airborne CrVI.

## *3.3 Acute Values for Air Permitting and Air Monitoring Evaluations*

This acute evaluation resulted in the derivation of the following acute values for CrVI particulate compounds:

- 24-h acute ReV = 1.3 µg CrVI/$m^3$
- 24-h $^{acute}$ESL = 0.39 µg CrVI/$m^3$

The 24-h $^{acute}$ESL for air permit evaluations is 0.39 µg CrVI/$m^3$ for CrVI particulate compounds (Table 8). The acute ReV of 1.3 µg CrVI/$m^3$ will be used for the evaluation of air monitoring data. In general, to protect against sensitization, exceedances of the acute (or chronic) ESL during the air permit review should be discouraged for any chemicals identified as respiratory sensitizers (TCEQ 2012).

## *3.4 Subacute Inhalation Observed Adverse Effect Level*

The key study for derivation of the 24-h ReV was a subacute animal study, which will be used to derive a subacute (i.e., not 24 h) inhalation observed adverse effect level. As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. The study by Glaser et al. (1990) had a $BMC_{10}$ of 29.6879 µg CrVI/$m^3$ (Table 5) for increased relative lung weight in rats. This animal $BMC_{10}$ was used as the animal acute inhalation observed adverse effect level for extrapolation to humans, although this may be conservative given that the subacute $BMC_{10}$ is very similar to the subchronic NOAEL of 25 µg CrVI/$m^3$ for this endpoint based on 90-d results from Glaser et al. (1985). No duration adjustment was made (TCEQ 2012). As discussed in Section 3.1.4.1, the applicable RDDR for animal-to-human dosimetric adjustment is 2.41. Thus, extrapolation of the animal study $BMC_{10}$ to humans results in a $POD_{HEC}$ of 71 µg CrVI/$m^3$ (rounded to two significant figures). Generally, an estimated subacute observed effect level would not be expected to be lower than a subchronic observed effects level, yet this subacute $POD_{HEC}$ of 71 µg CrVI/$m^3$ is somewhat lower than the subchronic $LOAEL_{HEC}$ derived in Section 4.5.1. However, this is due to the likely conservative nature of the subacute $BMC_{10}$ of 29.6879 µg CrVI/$m^3$, which is just above the clear subchronic NOAEL of 25 µg CrVI/$m^3$ for the same endpoint (increased relative lung weight). Consequently, the calculated subacute (i.e., not 24 h) inhalation observed adverse effect level may be conservative (i.e., over-predictive).

This $POD_{HEC}$ determined from an animal study represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study (22 h/d, 7 d/week, for 30 d) or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The estimated subacute (i.e., not 24 h) inhalation observed adverse effect level of 71 µg CrVI/$m^3$ is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the estimated subacute (i.e., not 24 h) inhalation observed adverse effect level of 71 µg CrVI/$m^3$ and the 24-h acute ReV of 1.3 µg CrVI/$m^3$ is a factor of approximately 55.

# Chapter 4 Chronic Evaluation

## *4.1 Noncarcinogenic Potential*

Few studies have evaluated the effects of chronic inhalation exposure to particulate CrVI compounds. Both USEPA (1998) and CalEPA (2001) utilize a subchronic rat study (Glaser et al. 1990) for derivation of a chronic inhalation value for CrVI particulate compounds based on BMC analyses of study results (e.g., Malsch et al. 1994). The TCEQ agrees that this study provides quality data on lower respiratory tract effects due to CrVI particulate compound exposure (sodium dichromate). In conjunction with a similar study by the same lead author that provides additional complementary information (Glaser et al. 1985), data from these studies (Glaser et al. 1990, 1985) are the best available for derivation of chronic inhalation values. *Thus, the noncarcinogenic chronic ReV and* $^{chronic}ESL_{threshold(nc)}$ *values for CrVI particulate compounds will be based on rats subchronically exposed in the key studies of Glaser et al. (1985 and 1990).*

As mentioned in Section 3.1, the TCEQ will develop chronic values (in addition to acute values) based on the CrVI content of the compound used in the key study (i.e., on a CrVI equivalent basis). The CrVI equivalent for a given dose of a CrVI compound is based on its CrVI content, that is, the percent of the compound's molecular weight that CrVI represents (e.g., the compound's concentration in $\mu g/m^3$ × (MW of CrVI in compound / MW of compound)). From a protection of public health perspective, use of CrVI equivalents assumes that other forms are no more toxic than the compound used in the key study on a CrVI equivalent basis. This is a necessary science policy decision given the lack of available studies to derive separate values for every CrVI compound is consistent with the approach of other agencies (e.g., USEPA, ATSDR). However, the derived chronic ReV and ESL values are expected to be sufficiently health-protective regardless of the chemical form because they will be based on the CrVI compounds which have produced adverse effects at the lowest concentrations, the most conservative (i.e., health protective) choice.

### 4.1.1 Key Studies for CrVI Particulate Compounds

Two studies were identified as key studies for CrVI particulate compounds (Glaser et al. 1990 and Glaser et al. 1985) and are described below. Data from these studies has previously been identified as the best basis for intermediate and chronic inhalation values (ATSDR 2012, USEPA 1998), and serve as the basis of ATSDR's intermediate inhalation MRL and USEPA's chronic reference concentration (RfC). An updated search of the peer-reviewed scientific literature did not reveal a more appropriate study for derivation of TCEQ's chronic ReV.

#### *4.1.1.1 Glaser et al. (1985) Key Study: 90-d Subchronic Exposure*

Glaser et al. (1985) is one of the key studies and the results of the 90-d subchronic exposure duration were used for the derivation of the chronic inhalation toxicity factors. In the 1985 study, 5-week-old male Wistar rats (20 per dose group) were exposed to sodium dichromate at

concentrations of 25, 50, 100, and 200 μg CrVI/$m^3$, 22 h/d, 7 d/week in subacute (28-d) or subchronic (90-d) protocols. There were no reports of abnormal histopathology in lung, kidney, liver, and stomach. No deaths were reported in any of the exposure groups, and all exposed animals behaved similar to control animals. There was no reported change in mean weight gain in any of the exposure groups when compared to the controls.

Dose-dependent and significant increases in mean lung weight relative to BW ($p < 0.05$ by Student's t test) were reported at concentrations greater than 25 μg CrVI/$m^3$ after both subacute and subchronic exposures. Increased mean spleen weight occurred only at 50 -100 μg CrVI/$m^3$, with a slight decrease in the mean spleen weight at 200 μg CrVI/$m^3$ (i.e., the dose-response was not entirely monotonic for spleen weight as it was for relative lung weight). A statistically significant nine percent increase in mean lung weight (normalized by BW) when compared to the control group was reported for subchronic exposure to 50 μg CrVI/$m^3$ (Table 9). Expressing mean lung weight relative to body weight is used in toxicity studies to normalize weight changes in the lung. A NOAEL of 25 μg CrVI/$m^3$ and a minimal LOAEL of 50 μg CrVI/$m^3$ can be determined for increased relative lung weight for the 90-d subchronic exposure from the Glaser et al. (1985) study. The TCEQ also conducted BMC modeling for increase in lung weight and the results are presented and discussed in the following sections.

The effect of CrVI sodium dichromate particulate exposure on alveolar macrophage was also evaluated. Decrease in macrophage cell count, a measure of cytotoxicity, was reported at concentrations ≥ 25 μg CrVI/$m^3$ and was statistically significant at exposure levels ≥ 50 μg CrVI/$m^3$. However, there is limited information in the scientific literature in regards to what percent decrease in macrophage cell count should be considered adverse. Therefore, the TCEQ did not select decrease in macrophage count as the critical effect but considered 50 μg CrVI/$m^3$ as the lowest observed effect level (LOEL), which although indicative of CrVI-induced cytotoxicity is not considered the critical adverse endpoint. Decreases in alveolar macrophage phagocytic activity and humoral immunity due to subchronic exposure only occurred in the highest dose group with a LOEL of 200 μg CrVI/$m^3$, with statistically significant increases occurring at lower exposure levels. *Based on the subchronic results reported in this study, increased relative lung weight (minimal LOAEL of 50 μg CrVI/$m^3$, NOAEL of 25 μg CrVI/$m^3$) is considered more clearly adverse and better suited for use as a critical adverse endpoint upon which to derive chronic toxicity factors.*

### *4.1.1.2 Glaser et al. (1990) Key Study: 90-dSubchronic Exposure*

The Glaser et al. (1990) study was also identified as a key study for derivation of the chronic ReV and ESL. The Glaser et al. (1990) study is very similar to the Glaser et al. (1985) study in terms of the exposure durations and exposure protocol. However, the Glaser et al. (1990) study included additional endpoints, a 30-d recovery period following the 90-d subchronic exposure, and a higher dose group (400 μg CrVI/$m^3$), although it omitted the lowest dose group (25 μg CrVI/$m^3$) of the Glaser et al. (1985) study.

It should be noted that some of the following summary information was taken verbatim from ATSDR (2012). Glaser et al. (1990) was a well-conducted comprehensive study and evaluated several endpoints at different exposure durations. Specifically, 8-week old male Wistar rats (30 animals/group) were exposed 22 h/d, 7 d/week to 0, 50,100, 200, and 400 μg CrVI/$m^3$ as sodium dichromate. Groups of 10 animals were sacrificed after 30 or 90 d of exposure or after 90 d of exposure with a 30-d recovery period. The MMAD and $\sigma_g$ were 0.28 μm and 1.63 for the 50 and 100 μg CrVI/$m^3$ concentrations and 0.39 μm and 1.72 for the 200 and 400 μg CrVI/$m^3$ concentrations, respectively.

Similar to the subacute scenario, the BALF was analyzed for total protein, albumin, and LDH activities. Other endpoints evaluated in the study included: BW, lung weight normalized by BW (g dry weight/kg BW), leucocytes in blood ($10^9$/l), bronchoalveolar hyperplasia, lung fibrosis, lung histiocytosis, total macrophages in BALF ($10^6$), dividing macrophages in BALF (% of BALF cells), and viability of BALF cells (%). In addition to obtaining data on several endpoints, Glaser et al. (1990) also performed urinalysis and obtained hematological and clinical chemistry data. Gross and histological examinations were performed on the upper airway epithelia, left lung lobes, and kidneys.

While no deaths or abnormal clinical signs occurred at any of the exposure levels, obstructive respiratory dyspnea and reduced mean BW gain were reported at ≥ 200 μg CrVI/$m^3$ after 30 and 90-d. Blood leucocyte counts were increased in all exposure groups and were statistically increased compared to the controls in all exposure groups starting at 50 μg CrVI/$m^3$. Similar to decreases in macrophage count that occurred at 50 μg CrVI/$m^3$ (increases occurred at the two highest doses), there is limited information in the scientific literature regarding what percent change in leucocyte count should be considered adverse. Therefore, 50 μg CrVI/$m^3$ is considered a LOEL for increase in blood leucocyte count, which is not considered a critical adverse endpoint.

An increase in the relative lung weight (normalized by BW) with increase in dose was reported similar to the Glaser et al. (1985) study. While the increase in lung weight began at 50 μg CrVI/$m^3$ in Glaser et al. (1990) with a nine percent increase, the increases achieved statistical significance only at 100 μg CrVI/$m^3$ and above where increases were 14 – 48 percent. Glaser et al. (1985), on the other hand, demonstrated significant lung weight increases at the LOAEL of 50 μg CrVI/$m^3$ and above, also with a nine percent increase at 50 μg CrVI/$m^3$. *Both Glaser et al. studies (1985, 1990) demonstrate a dose-response for increased relative lung weight starting at 50 μg CrVI/$m^3$, and when considered together support a minimal LOAEL of 50 CrVI/$m^3$ for increases in lung weight relative to BW for 90-d subchronic exposure.*

Accumulation of macrophages (histiocytosis) was observed in the higher exposure groups and showed a slight decrease in the 50 μg CrVI/$m^3$ exposure group, whereas dividing macrophages were increased in all the exposure groups except for the 400 μg CrVI/$m^3$ exposure group. Histology of upper airways revealed focal inflammation. In addition, the authors describe

increase in lung weight as a CrVI-induced irritation effect and attribute it to lung histiocytosis. Results of BALF analysis provided further information on the irritation effect. Total protein in BALF was significantly increased in all exposed group in the 90-d exposure, declining in the recovery period (Table 2 of Glaser et al. 1990). Albumin in BALF increased in a dose-related manner at all concentrations in the 90-d exposure group, although not statistically significant in the 100 μg CrVI/$m^3$ exposure group, also declining during the 30-d recovery period.

The activity of LDH was elevated at exposures of 50, 200, and 400 μg CrVI/$m^3$ for 90 d, but not in the 100 μg CrVI/$m^3$ group. The LDH levels returned to control levels during the 30-d recovery period. The number of macrophage in the BALF was significantly increased after 30 and 90 d, normalizing during the recovery period. Although LDH as well as β-glucuronidase are measures of cytotoxicity and were elevated in the study, the elevations only occurred consistently at higher concentrations (200 and 400 μg CrVI/$m^3$) compared to increases in relative lung weight at exposure levels ≥ 50 μg CrVI/$m^3$.

There is limited information in the scientific literature about what magnitude of biochemical change such as that documented by BALF analysis, accumulation of macrophage, total protein in BALF, and blood leucocyte count should be considered adverse, particularly when extrapolating animal data to humans (although some of these endpoints such as total protein in BALF generally support 50 μg CrVI/$m^3$ as an exposure level where potentially adverse effects begin to occur). On the other hand, such information exists for organ weight (i.e., a ten percent change in organ weight is commonly used to define adversity in regulatory chemical risk assessments). For that reason, increase in relative mean lung weight (normalized by BW) is identified as the critical adverse effect (i.e., adverse effect occurring at the lowest POD, resulting in the lowest adverse effect-associated $POD_{HEC}$), and 50 μg CrVI/$m^3$ is considered to be the minimal LOAEL for 90-d rat exposure based on Glaser et al. (1985, 1990).

### *4.1.1.3 Consideration of Developmental/Reproductive Effects*

Developmental and reproductive effects are considered for derivation of the chronic ReV and ESL (TCEQ 2012). However, such effects at low exposure levels are considered unlikely due to the lung's apparent significant capacity to reduce CrVI to CrIII, essentially detoxifying it prior to (and limiting) absorption and systemic distribution (De Flora et al. 1997). As discussed in Section 3.1.1.4 of the acute assessment, while no inhalation studies with developmental/ reproductive LOAELs are available to assess these endpoints, the oral doses producing such effects equate to daily inhalation exposure concentrations which are orders of magnitude higher than the levels producing the critical effects observed in key studies. In regard to reproductive effects more specifically, ATSDR (2012) indicates that histopathological examination of the testes of rats exposed to 0.2 mg CrVI/$m^3$ as sodium dichromate for 28 or 90 d (Glaser et al. 1985), to 0.1 mg CrVI/$m^3$ as sodium dichromate for 18 months, or to 0.1 mg Cr/$m^3$ as a 3:2 mixture of CrVI trioxide and CrIII oxide for 18 months (Glaser et al. 1986, 1988) revealed no abnormalities. 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 exposed to

15.5 mg CrVI/$m^3$ as chromium dioxide for 2 years (Lee et al. 1989). ATSDR (2012) identified a NOAEL of 0.2 mg CrVI/$m^3$ for reproductive effects based on the Glaser et al. (1985) study 90-d exposure duration. This reproductive inhalation NOAEL (200 µg CrVI/$m^3$) is much higher than the NOAEL to be used for point-of-entry effects (i.e., NOAEL of 25 µg CrVI/$m^3$ for increased relative lung weight) in the derivation of the chronic ReV and ESL. Thus, the chronic ReV and ESL are expected to be protective of developmental and reproductive effects.

## 4.1.2 Evaluation of Potential PODs

Statistically increased relative lung weight occurred in male Wistar rats exposed to the minimal LOAEL of 50 µg CrVI/$m^3$ for 90 d (Glaser et al. 1985) and was used as the critical adverse endpoint. Thus, the associated NOAEL of 25 µg CrVI/$m^3$ is a potential POD for the derivation of the chronic ReV and ESL for CrVI particulates, although BMC modeling was also conducted and is discussed below. *Ultimately, the NOAEL of 25 µg CrVI/$m^3$ from Glaser et al. (1985) was selected as the POD because the modeled shape of the dose-response curve was not adequately representative of the actual dose-response data in the low-dose region, which is critical for extrapolation to lower, more environmentally relevant regulatory concentrations.*

### *4.1.2.1 BMC Modeling*

The data on relative lung weight are amenable to BMC modeling, and the TCEQ performs BMC modeling when possible because of the potential advantages of this approach over the NOAEL/LOAEL approach (TCEQ 2012). The 95% lower confidence limit on the BMC is abbreviated as BMCL. Relative lung weight data were modeled with BMDS (USEPA Version 2.3.1) using continuous models (Section 3.1.4.2.1 BMC Modeling). In addition to the critical effect of increase in lung weight relative to BW based on Glaser et al. (1985), data for other endpoints from the Glaser et al. studies are also amenable to BMC modeling (see Section 4.1.2.1.2).

#### 4.1.2.1.1 CES

According to USEPA (2000), if there is a level of change in the endpoint that is considered to be biologically significant, then that amount of change is chosen for evaluation. For dichotomous data, this level is typically expressed as a certain increase in the incidence of adverse outcomes and is referred to as the BMR, while for continuous data this level is expressed on a continuous scale.

Because the increase in relative lung weight data are continuous, the TCEQ will use the term "CES" instead of the term "BMR." This is to distinguish continuous data from dichotomous data as recommended by Dekkers et al. (2001). Dekkers et al. (2001) recommended the term CES to define the demarcation between non-adverse and adverse changes in toxicological effect parameters for continuous data. For example, a CES of 10% or $CES_{10}$ for continuous data corresponds to a 10% change in the mean of an exposed group parameter compared to the control mean.

A 10% change in organ weight (e.g., lung) 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). Statistically significant increases in mean lung weight compared to the controls occurred after subchronic exposure to > 25 μg CrVI/$m^3$ (i.e., 50, 100, 200 μg CrVI/$m^3$) as sodium chromate in Glaser et al. (1985). In both the Glaser et al. studies (1985, 1990), a nine percent increase in mean lung weight was observed in the 50 μg CrVI/$m^3$ exposure group when compared to the controls. In addition to this increase achieving statistical significance in Glaser at el. (1985), increase in the mean lung weight was monotonic and significantly different than the control group in the higher exposure groups of both studies (100, 200, and 400 μg CrVI/$m^3$). For the Glaser et al. studies (1985, 1990), a $BMC_{10}$ and $BMCL_{10}$ were calculated for the $CES_{10}$ based on the critical effect of increased lung weight (relative to BW) in male Wistar rats.

#### 4.1.2.1.2 BMC Modeling Results

Data on increase in relative mean lung weight, leucocyte count, and BALF analysis from Glaser et al. (1985) and/or Glaser et al. (1990) are presented in Table 9. A summary of the BMC results for the critical effect of increase in relative lung weight is presented in Table 10. A summary of the BMC results for other endpoints (e.g., leucocytes in blood, LDH in BALF) lacking sufficient information on the level of change which should be considered adverse is provided in Table 11. BMC modeling results for other endpoints were used as supporting information.

**Table 9. Endpoint Data (90-d) for BMC Modeling (Glaser et al. 1985 and 1990)**

| | **Dose Group 0 µg CrVI/ $m^3$** | **Dose Group 25 µg CrVI/ $m^3$** | **Dose Group 50 µg CrVI/ $m^3$** | **Dose Group 100 µg CrVI/ $m^3$** | **Dose Group 200 µg CrVI/ $m^3$** | **Dose Group 400 µg CrVI/ $m^3$** |
|---|---|---|---|---|---|---|
| **Relative Lung Weight (µg/100g BW)** | 0.34 ± 0.02 | 0.33 ± 0.01 | 0.37 ± 0.03* | 0.38 ± 0.02* | 0.46 ± 0.04* | N/A |
| **Relative Lung Weight (g dry weight/kg BW)** | 0.44 ± 0.03 | N/A | 0.48 ± 0.05 | 0.50 ± 0.06** | 0.55 ± 0.04*** | 0.65 ± 0.05*** |
| **Total Protein in BALF (mg/l)** | 226 ± 30 | N/A | 396 ± 79*** | 326 ± 35*** | 703 ± 178*** | 975 ± 246*** |
| **Total Albumin in BALF (mg/l)** | 77 ± 13 | N/A | 115 ± 23 *** | 86 ± 13 | 117 ± 20*** | 184 ± 59*** |
| **LDH in BALF (mg/l)** | 29 ± 5 | N/A | 34 ± 3* | 31 ± 4 | 63 ± 11*** | 83 ± 17 *** |
| **Leucocytes in Blood ($10^9$/l)** | 0.54 ± 0.25 | N/A | 0.85 ± 0.30* | 0.92 ± 0.27** | 1.92 ± 0.96** | 2.56 ± 0.60*** |

***p value <0.001; ** p value <0.01; *p value < 0/05; N/A Not Applicable

### 4.1.2.1.3 BMC Modeling Results for Increase in Relative Lung Weight

Lung weight was modeled based on data from both the key studies. The models fit relative lung weight data from the Glaser et al. (1990) study better than data from the Glaser et al. (1985) study. However, this is primarily because no models could adequately fit a dose-response curve that accommodated the lack of response at the lowest exposure level of 25 µg CrVI/$m^3$ in the Glaser et al. (1985) study (Figure 3). This dose (25 µg CrVI/$m^3$) was not tested in Glaser et al. (1990), so it is not obvious on the BMD software-generated figure that the shape of the modeled dose-response curve in the low-dose region of interest for BMC calculation and downward extrapolation is not realistic (e.g., would over-predict the response, or lack thereof, at 25 µg CrVI/$m^3$ in Glaser et al. 1985). Although the BMC results are discussed below, this consideration ultimately precludes use of BMC modeling results for relative lung weight based on data from Glaser et al. (1990) as the POD. Adequate model fit to low dose data is critical to

informing the shape of the dose-response curve at lower exposure levels (closer to environmental levels), which in turn is a primary determinant of BMC values.

Based on both the key studies of Glaser et al. (1985, 1990), increase in relative lung weight was identified as the critical effect upon which to base the POD. BMC analysis was conducted for identification of potential PODs. The specific data that was modeled for relative lung weight are given in Table 9 and were obtained from Glaser et al. (1985) and Table 1 in Glaser et al. (1990). Goodness of fit was evaluated by p-values > 0.1, visual inspection of the dose-response curves relative to data points, and scaled residuals less than an absolute value of 2. Tests from BMC continuous models were examined to evaluate whether a homogeneous (constant) or nonhomogeneous variance was appropriate.

### *4.1.2.1.3.1 Glaser et al. (1985) study- Increase in Relative Lung Weight*

For increase in relative lung weight in this study, none of the models produced a satisfactory fit to the data. In addition to all goodness of fit p-values not being > 0.1, visual inspection also revealed poor model fit to the data. More specifically, all modeling results failed visual inspection of the critical low-dose region since no dose-response curve from any model fit the lowest dose (25 µg CrVI/$m^3$). That is, based on the actual dose-response data, the dose-response line between 0 and 25 CrVI/$m^3$ should essentially be flat (i.e., have no slope). Figure 3 provides an example of the inadequate fit in the low-dose region.

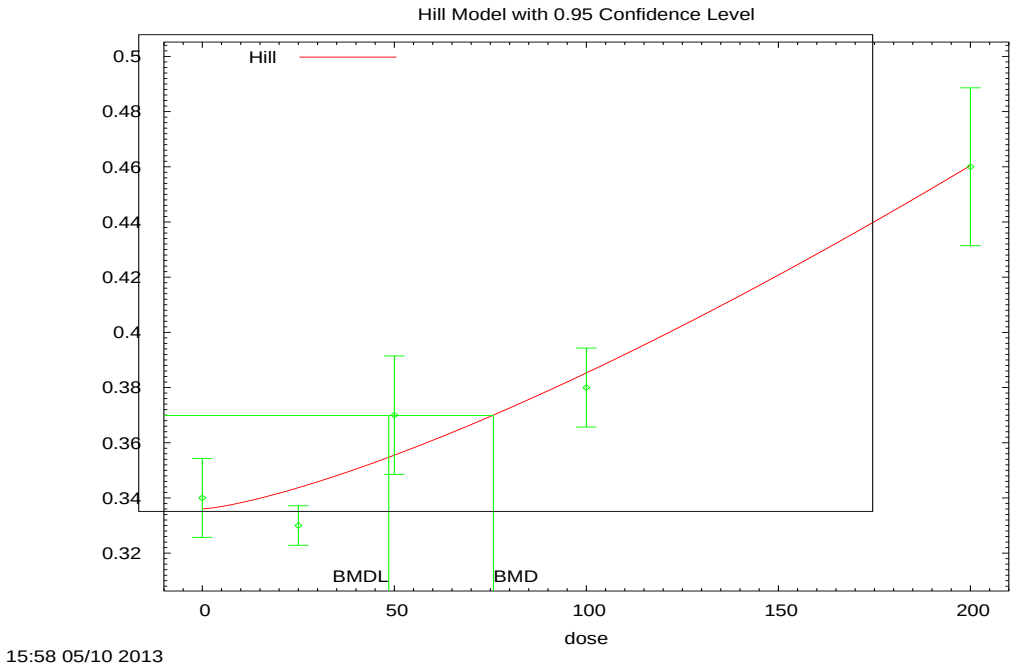



**Figure 3. BMC Output for Increase in Relative Lung Weight (Glaser et al. 1985)**

The modeled shape of the lung weight dose-response curve is simply not adequately representative of the actual dose-response data in the critical low-dose region. This is a significant limitation as the fit to study dose-response data in the lower exposure range (0 to 50 $\mu g/m^3$) is a primary determinant of the modeled BMC and extrapolation to lower, more environmentally relevant exposures, but is inadequate in this case. Therefore, the NOAEL for increased lung weight (25 $\mu g$ CrVI/$m^3$) will be the potential POD for deriving the chronic ReV and ESL based on this study.

#### *4.1.2.1.3.2 Glaser et al. (1990) study- Increase in Relative Lung Weight*

The Hill model and Exponential model 5 (constant or nonconstant variance) were the best fitting models (e.g., lowest AIC and scaled residual values). They provided similar satisfactory fits to the relative lung weight data from this study (due to the absence of the 25 $\mu g$ CrVI/$m^3$ dose group, unlike Glaser et al. 1985). The BMC/$BMCL_{10}$ values for these models using constant variance are provided in Table 10 and ranged from 47.4992-49.4567 $\mu g$ CrVI/$m^3$. These $BMCL_{10}$ values were evaluated further as potential PODs. [Although Tests 2 and 3 for constant variance and a good variance model passed, it is noted that the $BMCL_{10}$ values using nonconstant variance (not shown) were very similar and ranged from 46.472-48.6454 $\mu g$ CrVI/$m^3$.]

**Table 10. BMC Modeling Results for Increase in Relative Lung Weight for 90-d Exposure (Glaser et al. 1990)**

| Continuous Model | AIC | Scaled Residual | $BMC_{10}$ ($\mu g$ CrVI/$m^3$) | $BMCL_{10}$ ($\mu g$ CrVI/$m^3$) |
|---|---|---|---|---|
| Hill | -252.379691 | -0.0313 | 78.7312 | 47.4992 |
| Exponential 5 | -252.3767 | -0.02678 | 78.9931 | 49.4567 |

While representative of dose-response data from Glaser et al. (1990), based on the response at the lower dose (25 $\mu g$ CrVI/$m^3$) in Glaser et al. (1985), the shape of the modeled dose-response curve in Figure 4 based on Glaser et al. (1990) is known not to be representative of actual dose-response data in the critical low-dose region, which is of most interest for regulatory dose-response assessment as it is a primary determinant of the BMC. That is, based on the actual response at 25 $\mu g$ CrVI/$m^3$ in Glaser et al. (1985), a representative dose-response line between 0 and 25 CrVI/$m^3$ would essentially be flat (i.e., have no slope).

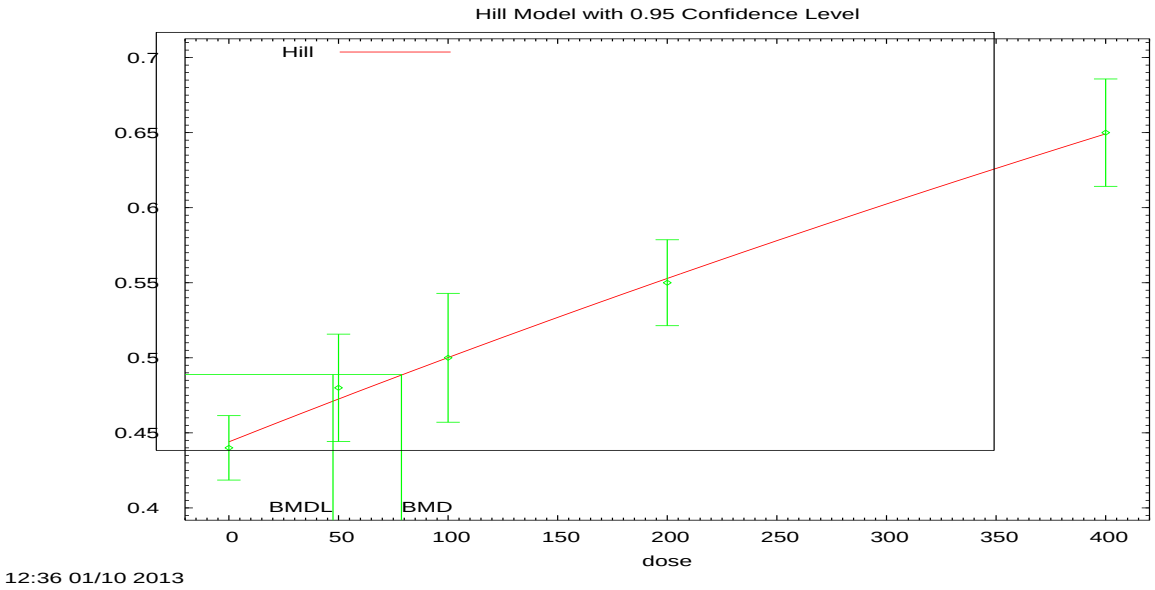



**Figure 4. BMC Output for Increase in Relative Lung Weight (Glaser et al. 1990)**

Since the shape of the modeled dose-response curve is not adequately representative of available dose-response data in the low-dose region, the NOAEL for increased lung weight (25 µg CrVI/$m^3$) will be the POD for deriving the chronic ReV and ESL based on the Glaser et al. studies (1985, 1990). Furthermore, this is conservative given that $BMCL_{10}$ values from the best fitting models for the Glaser et al. (1990) study (47.4992-49.4567 µg CrVI/$m^3$) are essentially equal to the LOAEL (50 CrVI/$m^3$) and approximately two times higher than the NOAEL (25 µg CrVI/$m^3$).

### 4.1.2.1.4 BMC Modeling Results for the Other Endpoints

Four more endpoints (LDH, total albumin, and total protein in BALF, and leucocytes in blood), lacking sufficient information on the level of change which should be considered adverse, were also modeled using the BMC approach with data obtained from the Glaser et al. (1990) study and a default CES of 1SD. Increase in protein, albumin, and LDH in BALF and leucocyte count have been used as biomarkers of chromium exposure, and there is some evidence to associate an increase in LDH to inflammation and subsequent cell damage. For example, LDH in BALF is found extracellularly upon cell damage (Malsch et al. 1994). However, similar to the other three endpoints, there is limited information regarding what percent increase in LDH should actually be considered adverse.

Leucocytes in blood showed a statistically significant increasing dose-response for all exposure groups, which made the data more amenable to modeling producing a dose-response curve with adequate fit compared to the data for the other three endpoints. The Exponential 5, Hill, and power models (constant variance) were considered to be best fitting for the leucocyte data based on lower AIC and scaled residual values and visual inspection of the model fit to the data. The

range of $BMC/BMCL_{1SD}$ values provided by these three models for leucocyte count is provided in Table 11. In contrast to leucocyte count, total protein, total albumin, and LDH in BALF data did not show a purely monotonic dose-response (i.e., there was an increasing dose-response except for the 100 μg $CrVI/m^3$ dose group), which made obtaining a satisfactory model fit to the data more problematic for these endpoints. For total protein and albumin in BALF, none of the models produced a satisfactory fit to the data (e.g., goodness of fit p-values not > 0.1, visual inspection revealed poor model fit to the data). For LDH in BALF, the Exponential model 5 (constant variance) was the only model to fit the data (goodness of fit p-values > 0.1), and $BMC/BMCL_{1SD}$ values are provided in Table 11.

The $BMCL_{1SD}$ values for these non-critical effect endpoints based on the best fitting models ranged from 62.8777μg $CrVI/m^3$ (leucocytes in blood) to 114.869μg $CrVI/m^3$ (LDH in BALF). These $BMCL_{1SD}$ values for endpoints without adequate information on the level of change considered adverse are higher than the NOAEL of 25 μg $CrVI/m^3$ for the critical effect of increased relative lung weight.

**Table 11. BMC Modeling Results for Leucocyte Count and BALF Analysis Results for 90-d Exposure (Glaser et al. 1990)**

| | AIC | Scaled Residual | $BMC_{1SD}$ (μg $CrVI/m^3$) | $BMCL_{1SD}$ (μg $CrVI/m^3$) |
|---|---|---|---|---|
| **LDH in BALF (mg/l)** | 282.3283 | 1.13E-06 | 183.27 | 114.869 |
| **Leucocytes in blood ($10^9$/l)** | -3.807573 to -4.525708 | -0.31 to -1.02 | 104.186 to 122.821 | 62.8777 to 84.0442 |

*****p value <0.001; * p value < 0/05**

As discussed previously, an increase in relative lung weight:

- is more clearly adverse for purposes of regulatory risk assessment;
- is relevant for this assessment;
- began occurring at the same exposure level (50 μg $CrVI/m^3$) as increases in endpoints lacking sufficient information on the level of change which should be considered adverse (e.g., LDH in BALF, leucocytes in blood);
- exhibited a dose-response that was entirely monotonic (i.e., progressively higher statistically significant increases occurred for all exposure levels ≥ 50 μg $CrVI/m^3$); and
- has a POD (NOAEL of 25 μg $CrVI/m^3$) that is lower than the potential PODs for endpoints without adequate information on the level of change considered adverse (e.g., $BMCL_{1SD}$ values of 62.8777-114.869μg $CrVI/m^3$).

*Based on these considerations, increase in relative lung weight (and not LDH increases or similar effects) is clearly the preferred critical endpoint for the development of a chronic ReV and ESL.*

## 4.1.3 MOA Analysis and Dose Metric

Please refer to Section 3.1.2 for a discussion on MOA. Similar to the acute ReV derivation, air concentration was the only dose metric available from the key studies for CrVI particulate compounds. Therefore, air concentration was used as the default dose metric for derivation of the chronic ReVs.

## 4.1.4 POD, Critical Effect, and Dosimetric Adjustments

Per the discussions above, the NOAEL of 25 µg CrVI/$m^3$ for increased lung weight (normalized by BW) from the Glaser et al. (1985) study is the POD for derivation of the chronic ReV and ESL.

### *4.1.4.1 Duration Adjustment*

This POD (25 µg CrVI/$m^3$) is based on exposure for 22 h/d,7 d/week, for 90 d, which very closely simulates a continuous exposure duration. Therefore, no duration adjustments will be performed. The $POD_{ADJ}$ is therefore the NOAEL of 25 µg CrVI/$m^3$.

### *4.1.4.2 Default Dosimetry Adjustment from Animal-to-Human Exposure*

Since Glaser et al. (1985) was conducted in laboratory animals, a dosimetric adjustment factor for particulate matter must be applied to the $POD_{ADJ}$ to convert the animal concentration to a $POD_{HEC}$. Per TCEQ (2012), the TCEQ uses the RDDR MPPD model (version 2.11) (CIIT 2002) to derive a deposition fraction that is used in the from the MPPD model, which is an appropriate model for rats. Study-specific parameters necessary for the MPPD model were provided by Glaser et al. (1985), which included the MMAD (0.2 µm) and σg (1.5). The default $V_E$ used by MPPD for humans (7,500 mL/min) does not correspond to the default value (13,800 mL/min) given by USEPA (1994), which is used in the RDDR calculation below. Neither USEPA (1994) nor cited USEPA background documents provide the human tidal volume (mL/breath) and breathing frequency (breaths/min) values which correspond to the default USEPA minute ventilation and are needed for input into the MPPD so that both the MPPD model and RDDR calculation use the same human minute ventilation. Therefore, the TCEQ used human tidal volume and breathing frequency values from de Winter-Sorkina and Cassee (2002) to determine the quantitative relationship between the two and calculate the tidal volume and breathing frequency values corresponding to the default USEPA minute ventilation for input into the MPPD model (TCEQ 2011). All remaining values used were default. The target region for CrVI was considered to be the pulmonary region (increased lung weight). The input and output terms are presented in Figure 5.

The deposition fractions determined from the MPPD program above were then used to calculate the RDDR for the key study:

$$RDDR = \frac{(V_E)_A}{(V_E)_H} \times \frac{DF_A}{DF_H} \times \frac{NF_H}{NF_A}$$

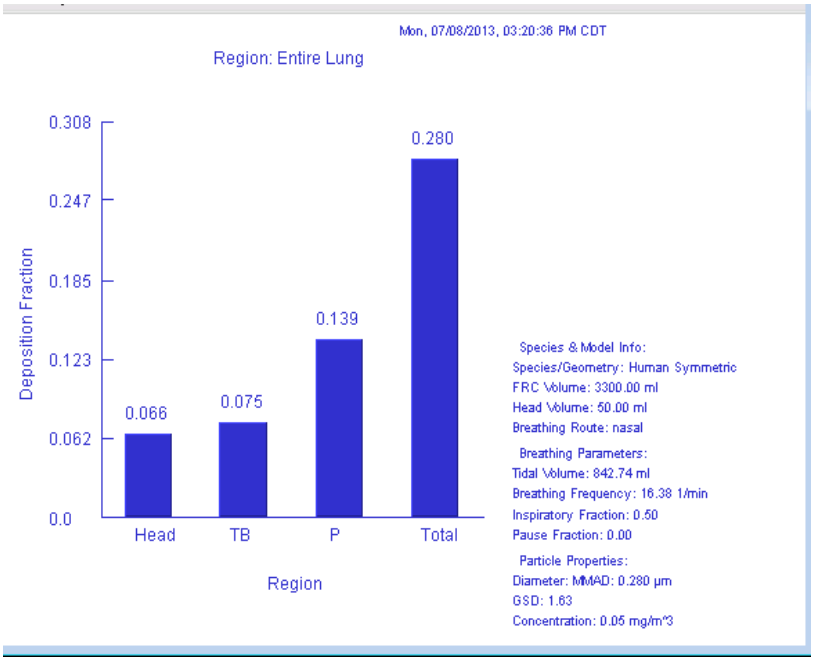
where:

$V_E$ = minute volume
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor
A =animal
H = human

$$RDDR = \frac{214.2 mL/min}{13{,}800\ mL/min} \times \frac{0.136}{0.139} \times \frac{54\ m^2}{0.34\ m^2} = 2.41$$

The RDDR for the pulmonary region was selected as the appropriate output to use to develop a $POD_{HEC}$ because the adverse effect noted in the key animal study is increase in relative lung weight.

**Human Output**




**Rat Output**

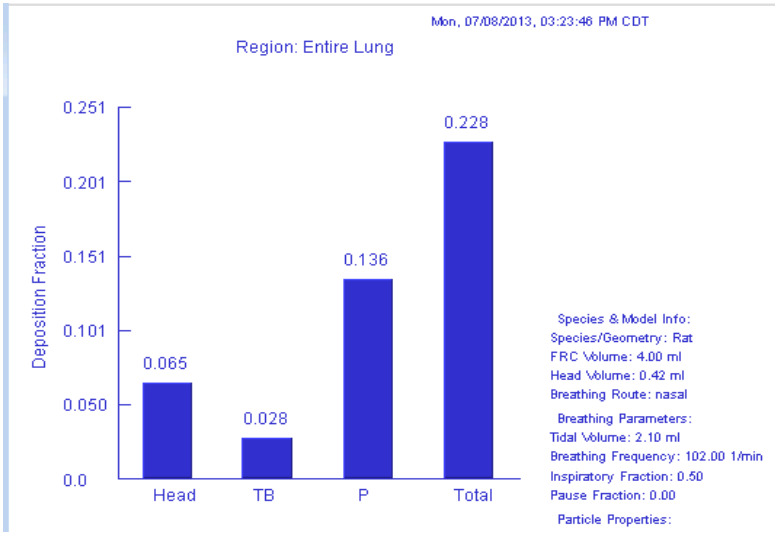



**Figure 5. MPPD Model Input and Output for Increase in Relative Lung Weight (Glaser et al. 1990)**

#### *4.1.4.3 Calculation of the $POD_{HEC}$*

To derive a $POD_{HEC}$ for CrVI, the NOAEL of 25 μg CrVI/$m^3$ was multiplied by the RDDR of 2.41 for the pulmonary region:

$$POD_{HEC} = POD_{ADJ} \times RDDR$$
$$= 25\ \mu g\ CrVI/m^3 \times 2.41$$
$$= 60.25\ \mu g\ CrVI/m^3$$

where: $POD_{ADJ}$ = duration adjusted point of departure (μg/$m^3$)
RDDR = regional deposited dose ratio
$POD_{HEC}$ = dosimetrically adjusted point of departure (μg/$m^3$)

### 4.1.5 Adjustments of the $POD_{HEC}$

The $POD_{HEC}$ of 60.25 μg CrVI/$m^3$ for the critical effect of increase in relative lung weight will be used to derive the chronic ReV.

Although much information is available, the mechanisms of chromium toxicity appear very complex and the exact MOA by which CrVI produces toxicity is not fully elucidated (see Section 3.1.2). The default approach for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive the chronic ReV (i.e., assume a threshold MOA) (TCEQ 2012).

A total UF of 270 was applied to the $POD_{HEC}$ of 60.25μg CrVI/$m^3$ to derive the chronic ReV: an $UF_A$ of 3 for extrapolation from animals to humans; an $UF_H$ of 10 to account for variability within the human population; an $UF_{Sub}$ of 3 because the study was a subchronic exposure study; and a $UF_D$ of 3. The following is more specific concerning the rational for the applicable UFs:

- An $UF_A$ of 3 was used for extrapolation from animals to humans because the MPPD program accounts for toxicokinetic differences and limits uncertainty for rat to human interspecies extrapolation but does not account for toxicodynamic differences;
- An $UF_H$ of 10 was used for interindividual variability to account for potentially sensitive subpopulations such as children, the elderly, and those with pre-existing medical conditions because little information was available on variability in sensitivity in the human population to the effects of CrVI inhalation exposure;
- An $UF_{Sub}$ of 3 was used because the study was a 90-d subchronic study; and
- An $UF_D$ of 3 was used for database uncertainty because the database quality on the toxicity of CrVI compounds is of medium to high quality. While the Glaser et al. (1985, 1990) studies were only conducted in male rats, chronic studies have also been conducted in mice and guinea pigs (e.g., Nettesheim and Szakal 1972, Nettesheim et al. 1971, Steffee and Baetjer 1965). Additionally, information is available regarding the potential for CrVI-induced developmental/reproductive effects (Section 4.1.1.3) which suggests that such effects are unlikely at inhalation exposure levels lower than the lowest inhalation LOAELs

for point-of-entry effects. Thus, the chronic ReV and ESL are expected to be protective of potential developmental/reproductive effects.

chronic ReV = $POD_{HEC}$ / ($UF_H \times UF_A \times UF_{Sub} \times UF_D$)
= 60.25 µg CrVI/$m^3$/ (10 × 3 × 3 × 3)
= 60.25 µg CrVI/$m^3$/ (270)
= 0.223 µg CrVI/$m^3$ for CrVI particulates

## 4.1.6 Health-Based Chronic ReV and $^{chronic}$ESL

The chronic ReV for soluble CrVI particulates rounded to two significant figures is 0.22 µg CrVI/$m^3$. The rounded chronic ReV was then used to calculate the $^{chronice}$ESL. At the target HQ of 0.3, the $^{chronic}$ESL for CrVI particulates is 0.066 µg CrVI/$m^3$ (Table 12).

**Table 12. Derivation of the Chronic ReV and $^{chronic}$ESL**

| **Parameter** | **Summary** |
|---|---|
| Key Study | Glaser et al. (1985) |
| Study Population | 8-week old male Wistar rats |
| Study Quality Confidence Level | Medium-High |
| Exposure Method | Inhalation |
| Critical Effect | Increase in Relative Lung Weight |
| Exposure Duration | 90-d subchronic exposure 22 h/d, 7d/week |
| POD | 25 µg CrVI/$m^3$ (NOAEL) |
| $POD_{HEC}$ | 60.25 µg CrVI/$m^3$ |
| Total uncertainty factors (UFs) | 270 |
| *Interspecies UF* | *3* |
| *Intraspecies UF* | *10* |
| *Extrapolation from subchronic to chronic* | *3* |
| *Incomplete Database UF*<br>*Database Quality* | *3*<br>*Medium-High* |
| **chronicReV (HQ = 1)** | **0.22 µg CrVI/$m^3$** |
| **$^{chronic}$ESL (HQ = 0.3)** | **0.066 µg CrVI/$m^3$** |

## 4.1.7 Comparison of Results for CrVI Particulate Compounds

ATSDR (2012), USEPA (1998), and California EPA (Cal EPA) (2001) have evaluated the noncancer inhalation toxicity data for CrVI and derived intermediate and/or chronic duration inhalation values. The ChemRisk Division of McLaren/Hart, for example, has also developed a chronic value (ChemRisk 1998) that underwent an independent peer review and meets the requirements to be on the International Toxicity Estimates for Risk website (http://www.tera.org/iter/), which is part of the National Library of Medicine's TOXNET compilation of databases (http://toxnet.nlm.nih.gov). Refer to Table 13 below for more details.

**Table 13. Chronic and Subchronic Noncarcinogenic Inhalation Toxicity Factors for CrVI Particulate Compounds**

| Agency or Entity | Key study | Critical endpoint | Total Uncertainty Factor | RDDR Value | Chronic Toxicity Factor |
|---|---|---|---|---|---|
| TCEQ | Glaser et al. (1985, 1990) | Increase in relative lung weight | 270 | 2.41 | 0.22 µg CrVI/$m^3$ |
| ATSDR | Malsch et al. (1994) analysis of Glaser et al. (1985, 1990) | Alterations in LDH levels in BALF | 30 | 0.630 | Intermediate inhalation MRL of 0.3 µg CrVI/$m^3$ |
| USEPA | Malsch et al. (1994) analysis of Glaser et al. (1985, 1990) | Lower respiratory effects in rat lung | 300 | 2.16 | 0.1 µg CrVI/$m^3$ |
| CalEPA | Glaser et al. (1990) | Brochchoalvelolar hyperplasia | 100 | | 0.2 µg CrVI/$m^3$ |
| ChemRisk | Malsch et al. (1994) analysis of Glaser et al. (1985, 1990) | Arithmetic Average of the benchmark concentrations for the pulmonary inflammation endpoint and includes lung weight, LDH in BALF, protein in BALF, albumin in BALF | 300 | 2.16 | 0.3 µg CrVI/$m^3$ |

While the TCEQ used increase in relative lung weight as the critical endpoint for derivation of the chronic ReV, USEPA's chronic assessment and ATSDR's subchronic assessment used LDH in BALF as the critical endpoint (although both agencies indicate that LDH in BALF did not generate the best fit on the regression curve of the endpoints considered in the BMC analysis). LDH in BALF is an indicator of cytotoxicity and may also reflect chronic lung inflammation. However, there is limited information in the literature to indicate what percent increase in LDH should actually be considered adverse. Similarly, ChemRisk selected the arithmetic average of BMCs for increase in lung weight and other pulmonary inflammation endpoints for which there is uncertainty about what level of change should be considered adverse (i.e., LDH, protein, and albumin in BALF). To avoid this uncertainty, the TCEQ used increased relative lung weight as the critical endpoint, which is associated with a level of change considered more clearly adverse. That is, a 10% change in organ weight relative to the mean in the control animals is typically considered an adverse effect in regulatory chemical risk assessments. The TCEQ used a total UF (270) whereas USEPA and ChemRisk used a total UF of 300 in their chronic toxicity factor derivations, and a similar RDDR value. However, the TCEQ chronic ReV of 0.22 μg CrVI/$m^3$ falls between USEPA's RfC (0.1 μg CrVI/$m^3$) and ChemRisk's chronic toxicity value (0.3 μg CrVI/$m^3$). This is primarily due to the difference in the PODs for the critical endpoints selected (e.g., USEPA used a BMC of 16 μg CrVI/$m^3$ based on Malsch et al. 1994). CalEPA considered the same key study as the other agencies but considered bronchoalveolar hyperplasia as the critical effect. Based on their POD ($BMC_{05}$ of 12.50 μg/$m^3$), CalEPA derived a chronic noncarcinogenic inhalation value (0.2 μg CrVI/$m^3$) essentially identical to the chronic ReV derived by the TCEQ (0.22 μg CrVI/$m^3$).

## *4.2 Carcinogenic Potential*

USEPA (1984) derived a unit risk factor (URF) of 1.2E-02 per μg/$m^3$ for environmental exposure to CrVI using lung cancer data from a now outdated occupational study (Mancuso 1975) and default linear low-dose extrapolation. The URF was not updated in USEPA (1998). Thus, the USEPA has not updated its URF value since USEPA (1984). However, new studies are available for dose-response assessment (e.g., Gibb et al. 2000, Crump et al. 2003). Thus, the TCEQ is performing an updated inhalation carcinogenic assessment for CrVI. Human studies were preferred per the TCEQ (2012) guidelines, and in addition to reviewing the epidemiological studies previously considered and/or utilized by other agencies (e.g., USEPA, OSHA, NIOSH) for URF/acceptable exposure level development, the TCEQ conducted a scientific literature search (through February 2013) for more recent CrVI inhalation epidemiological studies with adequate data for URF derivation. As with all chemicals for which a DSD is to be developed, external interested parties had ample opportunity to submit relevant information (e.g., published, unpublished studies). See Section 3.3.2 of TCEQ (2012) for additional information on the procedures and sources used to identify essential data.

## 4.2.1 Weight of Evidence (WOE) and Classifications

The causal relationship between the inhalation of Cr and lung cancer was suspected as early as the late 19th century (Jones 1990, McCarroll et al. 2009). Particulate forms of CrVI, relatively water insoluble compounds more specifically (e.g., moderate to low solubility compounds which remain in the lung longer delivering an intracellular dose), appear to be more potent lung carcinogens, with prolonged extracellular dissolution of the CrVI compound critical to potency (O'Brien et al. 2003, Holmes et al. 2008, ATSDR 2008, Nickens et al. 2010). Regarding evidence concerning the carcinogenicity of CrVI via inhalation, text in the following brief paragraph relevant to the carcinogenic WOE was adapted from ATSDR (2012) (*emphasis added*).

> Occupational exposure to CrVI compounds in various industries has been associated with increased risk of respiratory system cancers. Chromate production, chromate pigment production and use, chrome plating, stainless steel welding, ferrochromium alloy production, and leather tanning are among the industries investigated in retrospective mortality studies, but dose-response relationships have only been reported for chromate production workers. An increased risk of respiratory tract cancers has been found to be associated with increased cumulative exposure to CrVI in studies of chromate production workers. While studies of chrome platers exposed to CrVI and other carcinogenic chemicals (e.g., nickel) have found significant elevations in lung cancer risk in association with surrogate indicators of chromium exposure, estimates of risk specifically attributable to chromium exposure have not been reported. Study results for stainless steel welders and ferrochromium alloy workers exposed to CrVI and other chemicals (e.g., Cr(0) and CrIII) have been mixed and are inconclusive in regards to increased cancer risk. Leather tanners exposed to CrIII do not appear to have elevated cancer rates. *Occupational epidemiology studies, particularly chromate worker studies, clearly show that occupational exposure to CrVI is associated with an increased risk of respiratory cancer. Evidence is strongest for lung cancer, which has been used as the cancer endpoint and corroborated/quantified in numerous studies.* Chronic inhalation studies in animals also provide evidence that CrVI is carcinogenic (i.e., increases risk for lung tumors) (ATSDR 2012).

The USEPA considers CrVI as a known human carcinogen by the inhalation route of exposure based on occupational epidemiologic studies of chromium-exposed workers, dose-response relationships for CrVI exposure and lung cancer, and positive carcinogenic animal data for CrVI (but not CrIII) (USEPA 1998). The International Agency for Research on Cancer (IARC Monograph Volume 100C) has also determined that CrVI compounds are carcinogenic to humans (IARC 2012). Additionally, the National Toxicology Program (NTP) 12th Report on Carcinogens classifies CrVI compounds as known to be human carcinogens (NTP 2011). *Consistent with these WOE classifications, the TCEQ considers CrVI and CrVI compounds as a group to be carcinogenic to humans via inhalation (at least at sufficiently high long-term doses).*

The TCEQ's WOE classification and inhalation URF will be applied to all forms of CrVI. This includes dissolved CrVI mists (e.g., chromium trioxide in water, a.k.a. chromic acid mist) since although sparingly soluble forms are likely to represent a more significant cancer hazard (see Section 2.1), there is evidence suggesting that soluble CrVI (e.g., chromic acid mists in the plating industry) produces an increased risk of lung cancer (ATSDR 2012).

## 4.2.2 Carcinogenic MOA

As mentioned previously, human and animal studies have shown that CrVI has the ability to induce carcinogenicity. More specifically, high long-term, occupational and experimental animal inhalation exposure to CrVI concentrations several orders of magnitude higher than environmental levels has the ability to induce lung cancer (De Flora 2000, ATSDR 2012). This section provides a brief summary of information relevant to the MOA and various MOAs proposed for CrVI-induced lung carcinogenesis. As a thorough discussion of the MOA evaluations conducted to date are beyond the scope of this document, please refer to the cited references and scientific literature for detailed information. More detailed discussions of topics relevant to the carcinogenic MOA such as mechanisms of toxicity and toxicokinetics may be found elsewhere (e.g., ATSDR 2012, Holmes et al. 2008, Nickens et al. 2010, McCarroll et al. 2009, ToxStrategies 2012).

In regard to lung carcinogenesis, the chemical/physical properties of CrVI compounds affect toxicokinetics and subsequent carcinogenic potential. For example, the relatively smaller particle size in the chromate production industry (e.g., compared to the aerospace industry) is responsible for greater deposition in the tracheobronchial and alveolar regions of the lung, thus contributing to the excess lung cancer risk observed for this industry. CrVI-induced lung carcinogenesis generally involves localized regions of high CrVI tissue dose (ToxStrategies 2012). CrVI particulates do not distribute evenly throughout the lung but concentrate at major bifurcations, and "hot spots" particulate accumulation have been identified at the bifurcations of the bronchi of chromate workers (Nickens et al. 2010). This is consistent with lung cancers among CrVI workers as typically being bronchogenic carcinoma. Furthermore, some CrVI compounds are water soluble (chromic acid, chromium trioxide, chromates and dichromates of sodium, potassium, ammonium, lithium, cesium, rubidium) while others are rather insoluble (chromates of zinc, calcium, lead, barium, strontium, and sintered chromium trioxide) (Seidler et al. 2012). Human and animal data support chemical forms of CrVI with a long residency time in the lung (i.e., sparingly soluble forms such as zinc, strontium, and lead chromates and less soluble complex forms of calcium chromate) as representing a more significant cancer hazard (ToxStrategies 2012). Thus, it appears that a greater potential for occupational CrVI-induced lung cancer in exposed workers is generally associated with particle sizes resulting in greater deposition in the tracheobronchial and alveolar regions of the lung, and the longer lung residency time of sparingly soluble CrVI compounds resulting in a chronic CrVI dose due to slow *in situ* particle dissolution and toxic insult to the target lung tissue.

Various MOAs have been proposed for CrVI-induced carcinogenicity resulting from such chronic dosing to target lung tissue. For example, based on a review of relevant data (e.g., genetic characterization of CrVI-induced tumors, *in vivo* and *in vitro* genotoxicity/mutagenicity test results, epigenetic changes) in the context of possible carcinogenic mechanisms, Holmes et al. (2008) proposed a mechanism for CrVI-induced lung carcinogenesis that involves genomic instability due to DNA double strand break-induced G2 (post-DNA replication/pre-mitotic cell cycle phase) arrest (as opposed to mutation in multistage carcinogenesis) ultimately resulting in neoplastic transformation and cancer. Nickens et al. (2010) proposed cellular resistance to CrVI-induced death through dysregulated DNA repair and/or survival signaling and transcriptional repatterning. Other MOAs and mechanisms for CrVI-induced carcinogenicity (inhalation or oral route) have also been proposed (e.g., Zuo et al. 2012, Xie et al. 2008, Thompson et al. 2011). For example, a recent paper (ToxStrategies 2012) to evaluate the weight of evidence from available human, animal, and *in vitro* data (including *in vivo* genotoxicity) using the modified Hill Criteria supports that CrVI-induced lung carcinogenicity acts by a non-mutagenic MOA involving oxidative stress, oxidative DNA damage, tissue injury, and inflammation, with additional considerable evidence for epigenetic DNA modifications. McCarroll et al. (2009) and Zhitkovich (2011), on the other hand, indicate that the weight of evidence supports the plausibility that CrVI may act through a mutagenic MOA. However, TCEQ (2012) indicates that there should be a reasonably scientifically-rigorous standard for demonstration of a mutagenic MOA and the TCEQ believes such a standard has not been met for CrVI (i.e., merely demonstrating plausibility is not tantamount to an adequately robust demonstration that mutagenicity is in fact THE initiating event in target tissues) (see Section 4.2.3.1.8). Dose-dependent changes in the MOA may also be possible and have important implications for low-dose extrapolation and risk characterization. For example, linearity could occur at low doses due to mutagenicity with an additional contribution of oxygen radical/cellular damage-induced regenerative hyperplasia at high doses (i.e., a dual MOA could be possible), both of which could be reflected in dose-response modeling of the epidemiological data.

Thus, a complete and clear picture of the MOA(s) for CrVI-induced lung carcinogenesis is yet to be elucidated and no MOA has been widely accepted by the scientific community as definitive. While the proposed MOAs differ, what they have in common as the earliest key events is an assumption (inherent or explicitly stated) that CrVI has escaped extracellular reduction to enter cells of the target tissue, followed by the intracellular reduction of CrVI. Escaping the body's CrVI reductive capacity (to make absorption possible) is a necessary event regardless of whether downstream events are part of a non-mutagenic MOA such as oxidative stress, oxidative DNA damage, tissue injury and inflammation, or involve CrVI-induced genotoxicity/mutagenicity or other proposed key MOA events or mechanisms. Although inhalation CrVI doses well within extracellular (to lung tissue) reductive capacity have the opportunity to first be quickly reduced prior to absorption (e.g., reduction in the absence of reducing molecule depletion may be much more rapid than absorption and significantly minimize uptake), even at lower doses uptake cannot be excluded and can occur as extracellular lung reduction and target tissue absorption

rates compete concurrrently (Haney et al. 2012).In regard to the MOA more generally, based on available relevant information:

- The bioavailability and carcinogenic/toxic potential of Cr compounds are dependent on the oxidation state of the Cr atom, with CrVI readily able to cross cell membranes and potentially induce carcinogenicity whereas CrIII does not;
- CrVI carcinogenicity/toxicity appears to be mediated through reactive intermediates (e.g., CrIII, oxygen radicals) generated during the rapid intracellular reduction of CrVI to CrIII, which is the final product of intracellular CrVI reduction (ATSDR 2012) (although more information on the role of oxygen radicals in chromium-induced genotoxicity is needed, O'Brien et al. 2003); and
- The human body (e.g., alveolar macrophage, epithelial lining fluid, lung tissue) has a significant ability to reduce CrVI to CrIII, extracellular to target tissue as well as intracellularly (ATSDR 2012, De Flora et al. 1997).

However, as alluded to above, the scientific community has not reached a consensus on the specific MOA(s) for CrVI-induced lung carcinogenesis, or the role lung reductive capacity may play at low, environmentally-relevant concentrations in terms of risk.

According to ATSDR (2008),

> *The products of metabolic reduction of CrVI (free radicals and CrIV and V) and the newly generated CrIII are thought to be in part responsible for the carcinogenic effects seen in human and animal studies.* The interaction of free radicals, CrV, CrIV, and CrIII with DNA can result in structural DNA damage, functional damage, and other cellular effects. The types of chromium-induced structural damage include DNA strand breaks, DNA-protein crosslinks, DNA-DNA interstrand crosslinks, chromium-DNA adducts, and chromosomal aberrations. Functional damage includes DNA polymerase arrest, RNA polymerase arrest, mutagenesis, and altered gene expression. However, DNA double strand breaks may not be due to free radical formation, but due to the formation of chromium-DNA ternary adducts, which lead to repair errors and collapsed replication forks. Double strand breaks can also lead to alterations in cellular communication and effects on signaling pathways and cytoskeleton. In addition, results of recent studies in human lung cells suggest that chromosome instability is an important mechanism in the development of lung cancers; specifically, chromium-induced chromosome instability appears to be mediated through centrosome and spindle assembly checkpoint bypass.
>
> Location of particle deposition in the lung and extracellular dissolution of CrVI compounds (e.g., solubility) are also important considerations regarding the mechanism of CrVI-induced carcinogenesis. In chromate workers, analysis of bronchial tissues shows higher chromium concentrations in areas of bronchial

bifurcation compared to other areas in the bronchi. Also, autopsy results show that some precancerous bronchial lesions originated at bronchial bifurcations. *Solubility of CrVI compounds may also play a role in carcinogenic potency, with extracellular dissolution of the chromium compound critical to activity.* This hypothesis is supported by in vitro data suggesting that extracellular chromium ions are the proximate clastogen in Chinese hamster ovary cells.

CrIII can also interact with DNA to form adducts/complexes and DNA-protein crosslinks that interfere with DNA replication and transcription, and can promote the expression of regulatory genes such as nuclear factor-κβ, or may inhibit regulatory genes such as GRP78. Disruption of these pathways by other compounds has been implicated in carcinogenesis. The structural and functional damage can lead to growth arrest and apoptosis. Numerous studies show that chromium can induce apoptosis; although the mechanism by which chromium induces apoptosis is not fully understood, it is believed to involve oxidative stress and activation of the p-53 protein.

Lastly, products of the metabolic reduction of CrVI (free radicals and CrIV and V) and newly generated CrIII are thought to be partly responsible for CrVI-induced carcinogenic effects.

### 4.2.3 Carcinogenic Dose-Response Assessment Approach

The TCEQ (2012) guidelines for carcinogenic assessments employ the four-step risk assessment process formalized by the National Research Council (1983, 1994) and the procedures recommended in the most recent USEPA cancer guidelines (USEPA 2005a, 2005b) and scientific literature. Under TCEQ guidelines, the TCEQ evaluates and adopts low-dose extrapolation approaches (e.g., nonthreshold/linear, threshold) on a chemical-by-chemical basis in the context of the relevant data available. When data on the carcinogenic MOA support a nonthreshold (i.e., linear) dose-response extrapolation or sufficiently informative data on the carcinogenic MOA are lacking, a linear extrapolation is performed to estimate excess lifetime risk at lower environmentally-relevant doses. More specifically, the calculation of a health-protective air concentration based on carcinogenic effects due to inhalation is accomplished through the use of linear low-dose extrapolation to derive a URF. However, under the guidelines, information on the carcinogenic MOA indicating mechanisms or key events which may impart a nonlinear or threshold dose-response may sufficiently support conducting alternate approaches for comparison to results from linear low-dose extrapolation.

TCEQ staff recently published an exploratory nonlinear-threshold carcinogenic assessment (Haney et al. 2012) wherein available scientific data relevant to the carcinogenic MOA for CrVI are interpreted as adequate to support considering nonlinear-threshold assessments for inhalation carcinogenicity (although this is subject to scientific judgment and debate) for bounding uncertainty by comparison to default linear low-dose extrapolation approaches. More specifically, the assessment was performed for comparison of nonlinear-threshold assessment

results to the TCEQ policy-based 1 in 100,000 excess target risk air concentration calculated using the default linear low-dose URF approach. The Haney et al. (2012) study: (1) presents available summary MOA information and peer-reviewed scientific literature statistical evidence interpreted as supporting a potential practical threshold for CrVI-induced inhalation carcinogenicity, (2) conducts additional exploratory statistical dose-response analyses to identify potential carcinogenic thresholds and PODs in the context of supportive MOA information such as lung CrVI reductive capacity estimates, and (3) derives a potential cancer-based chronic nonlinear ReV of 0.24 µg CrVI/$m^3$ following dosimetric adjustments and application of appropriate UFs (total UF of 30). However, whether data relevant to the carcinogenic MOA and epidemiological analyses support consideration of nonlinear-threshold assessments for CrVI inhalation carcinogenicity is subject to scientific debate, and the uncertainties associated with the assessment (e.g., limited statistical power of epidemiological studies to detect increased risk at low exposure levels, lack of a statistically better fitting threshold model, lack of data on competing rates of extracellular CrVI reduction and lung tissue absorption) appear to preclude a robust scientific justification for deviation from the default linear low-dose extrapolation approach. Thus, the nonlinear-threshold assessment is not a focus of this document and the default linear low-dose extrapolation approach is utilized in the following sections to derive URF estimates based on various epidemiological studies.

#### *4.2.3.1 Default Linear Low-Dose Extrapolation Assessment*

The following sections discuss key steps in deriving an air concentration associated with a 1 in 100,000 excess risk, the TCEQ policy-based target risk used to set the cancer-based chronic ESL (i.e., $^{chronic}ESL_{nonthreshold(c)}$) when an alternative to using the default linear low-dose extrapolation URF approach is not better supported (TCEQ 2012).

##### 4.2.3.1.1 Cancer Endpoint

Lung cancer mortality will be considered the cancer endpoint of interest for the dose-response assessment consistent with the WOE for cancer endpoints (Section 4.2.1). Lung cancer mortality is the same endpoint used in the USEPA (1984) analysis and other analyses (e.g., Crump et al. 2003, Gibb et al. 2000, Applied Epidemiology 2002, Birk et al. 2006).

##### 4.2.3.1.2 Dose Metric

The key chromate production plant epidemiological studies discussed below and used for URF development all evaluated lung cancer mortality by cumulative exposure level (e.g., mg CrVI/$m^3$-yr). Thus, the dose metric used for the dose-response assessment is cumulative CrVI exposure not only because it is the only common measure available from the key studies, but also because cumulative exposure is the dose metric used for dose-response modeling based on epidemiological studies. Although target tissue dose in the lung (i.e., accounting for the kinetics of inhalation, deposition/retention, elimination/reduction, and dissolution over time to ultimately estimate absorbed dose) may be a better dose metric for dose-response assessment and accounting for the various forms of CrVI (i.e., sparingly soluble CrVI compounds are likely

more potent), currently no such model is available to estimate lung tissue dose among these CrVI-exposed workers. Application of the URF (derived using cumulative exposure to CrVI as the dose metric) to all CrVI compounds inherently treats all CrVI compounds as toxicologically equivalent based on CrVI content, consistent with the TCEQ considering CrVI compounds as a group to be "Carcinogenic to Humans."

### 4.2.3.1.3 Epidemiological Studies for Dose-Response Assessment

Human epidemiological studies are available and preferable over animal studies for the assessment of the carcinogenic potential of CrVI and the development of a URF. There are numerous epidemiological studies that have investigated the association of CrVI exposure and lung cancer, but not all of these studies are adequate to define the dose-response relationship. The Painesville, Ohio (e.g., Crump et al. 2003, Luippold et al 2003) and Baltimore, Maryland (e.g., Gibb et al. 2000, Park et al. 2004) chromate production worker cohorts have been used for quantitative risk assessment to derive occupational URFs for lung cancer previously (OSHA 2006). These cohorts are relatively large, have extensive follow-up, and documentation of historical CrVI exposure levels. Summary information for these key epidemiological studies, taken from ATSDR (2012), is presented below. Additionally, a cohort of workers from four low-dose chromate plants (Leverkusen and Uerdingen, Germany, Corpus Christi, Texas, and Castle Hayne, North Carolina) has been identified for a supporting quantitative dose-response assessment and is the subject of various studies (e.g., Applied Epidemiology 2002, Birk et al. 2006). Summary information for these supporting epidemiological studies is also provided below.

#### *4.2.3.1.3.1 Painesville, Ohio Key Cohort*

Several studies have found increased lung cancer mortality (standard mortality ratios or SMRs) among workers at the chromate production plant in Painesville, Ohio (e.g., Mancuso 1997). More recent studies of this cohort (Crump et al. 2003, Luippold et al. 2003) have reconstructed individual exposure histories to CrVI based on species-specific air monitoring data, and have attempted to quantify the potential lung cancer risk contribution of smoking. These studies included 482 workers employed for at least one year from1940 to 1972 and followed through 1997 (14,443 person-years). Cumulative exposure to CrVI was significantly associated with increased lung cancer risk. Using Poisson regression, Crump et al. (2003) estimated the slope of the linear relative risk model with multiplicative background as 0.636 per $mg/m^3$-yr (90% confidence interval (CI) of 0.401-0.920) and the slope for the analogous model with additive background as 0.00164 per $mg/m^3$-yr per person-year (90% CI 0.00110-0.00229). These estimates correspond to occupational unit risks (i.e., additional lifetime risk from 45-yr occupational exposure to 1 μg $CrVI/m^3$) of 0.00165 (90% CI 0.00104–0.00238) based on the relative risk Poisson model and 0.00220 (90% CI 0.00147–0.00306) based on the additional risk Poisson model (see Tables II and V of Crump et al. 2003). Study results indicated that smoking did not have a substantial effect on CrVI lung cancer risk results (i.e., smoking and CrVI appeared to contribute independently to cancer risk) since risk estimates were not appreciably

sensitive to smoking designation (for the 41% of the cohort that could be classified) (ATSDR 2012).

Crump et al. (2003) provide one of the best summary SMR datasets for dose-response assessment due to a relatively high number of exposure groups (10) evaluated for excess lung cancer risk. Additionally, study authors conducted statistical analyses in an attempt to identify potential thresholds for CrVI-induced lung carcinogenesis. Based on analysis of the Painesville, Ohio chromate production plant worker data, Crump et al. suggest a possible threshold at cumulative exposures (5-yr lag) possibly as high as 1.00-1.63 mg CrVI/$m^3$-yr because the dose-response trend was consistently statistically significant only after including exposure groups with cumulative exposure from 1.00-29 mg CrVI/$m^3$-yr (see Table IV of Crump et al. 2003). The cumulative exposure and SMR data which will be used to calculate the parameter (β) estimates based on Crump et al. (2003) are given in Table 8 below.

**Table 14. Cumulative Exposure and Lung Cancer Standardized Mortality Ratio (SMR) Data from Table IV of Crump et al. (2003)**

| Cumulative Exposure Range (mg CrVI/$m^3$-yr) [a] | Average Cumulative Exposure (mg CrVI/$m^3$-yr) [a] | Observed (O) | Expected (E) [b] | Lung Cancer SMR (O/E) | Trend p-Value |
|---|---|---|---|---|---|
| 0-0.06 | 0.00976 | 0 | 2.09 | 0 | --- |
| 0.06-0.18 | 0.115 | 3 | 2.19 | 1.4 | 0.35 |
| 0.18-0.30 | 0.233 | 3 | 2.19 | 1.4 | 0.26 |
| 0.30-0.46 | 0.386 | 5 | 2.13 | 2.3 | **0.04** |
| 0.46-0.67 | 0.563 | 0 | 2.20 | 0 | 0.45 |
| 0.67-1.00 | 0.817 | 4 | 2.22 | 1.8 | 0.18 |
| 1.00-1.63 | 1.27 | 12 | 2.23 | 5.4 | < **0.001** |
| 1.63-2.60 | 2.09 | 3 | 2.18 | 1.4 | < **0.001** |
| 2.60-4.45 | 3.37 | 10 | 2.18 | 4.6 | < **0.001** |
| 4.45-29.0 | 7.55 | 11 | 2.12 | 5.2 | < **0.001** |

[a] Exposure lagged 5 yrs.
[b] Based on Ohio rates.

Luippold et al. (2003) also evaluated the Painesville cohort, but only used 5 exposure groups. A trend test showed a strong relationship between lung cancer mortality (SMRs) and cumulative CrVI exposure. Lung cancer SMRs were increased for the two highest cumulative exposure categories (≥1.05 to <2.70 mg CrVI/$m^3$-yr with SMR of 3.65 (95% CI 2.08-5.92), ≥2.70 to 23 mg/$m^3$-yr with SMR of 4.63 (95% CI 2.83-7.16)), but not for the lowest three cumulative exposure groups. Similar to the findings of Crump et al., a stratified analysis of lung cancer mortality by cumulative exposure in Luippold et al. suggested a possible threshold effect as risk was significantly increased only at exposure levels over 1.05 mg CrVI/$m^3$-yr. However, because exposure was not lagged and fewer cumulative exposure groups are provided for dose-response

modeling, Crump et al. (2003) is considered to provide the best dose-response dataset for the Painesville, Ohio cohort and is used for the TCEQ assessment of this cohort. For completeness, modeled data and results for Luippold et al. (2003) may be found in Appendix A.

#### *4.2.3.1.3.2 Baltimore, Maryland Key Cohort*

Gibb et al. (2000) evaluated lung cancer mortality in a cohort of 2,357 male chromate production workers in Baltimore, Maryland hired during 1950 to1974, with mortality followed through 1992. Several earlier studies had found significantly increased lung cancer mortality (SMRs) among workers at the plant (e.g., Hayes et al. 1979). Cumulative exposures to CrVI or CrIII ($mg/m^3$-yr) were reconstructed for each worker from historical air monitoring data and job title records. As a group, the lung cancer SMR was 1.80 (95% CI of 1.49–2.14). Park et al. (2004) reanalyzed the cohort data using various dose-response models and found that in the preferred model (linear with cumulative chromium exposure and log-linear for age, smoking, race), the slope of the linear relative risk model was 2.78 per mg CrVI/$m^3$-yr. That is, the relative risk of lung cancer mortality increases by a factor of 2.78 per one unit of mg CrVI/$m^3$-yr (note that the cumulative $CrO_3$ exposure levels reported by Gibb et al. (2000) and Park et al. (2004) were converted to their CrVI equivalents for this document). Environ (2003) also reanalyzed the data using ten exposure groups (defined either by an equal number of observed lung cancer mortalities or equal number of person-years per group) with the addition of arguably more appropriate Baltimore lung cancer rates for SMR analyses (OSHA 2006). Additional analyses conducted by Park and Stayner (2006) attempted to estimate possible thresholds for excess lung cancer risk and reportedly excluded possible thresholds in excess of 16 µg CrVI/$m^3$ air concentration or 208 µg CrVI/$m^3$-yr (0.4 mg $CrO_3$/$m^3$-yr) cumulative exposure.

The TCEQ does, however, have concerns about the Baltimore cohort. Most notably, concerns regard the short exposure duration for many workers in this cohort. Forty-two percent of the Baltimore cohort worked in chromium production less than 3 months, with a median of around 4.5 months. Approximately 60% of the person-years at risk were from workers employed less than 6 months, with only about 15% of the cohort working for ≥ 5 years. By contrast, the median tenure for the Painesville workers was about 16 times longer at ≈ 6 years, with 17% working more than 20 years (as opposed to 15% working ≥ 5 years of the Baltimore cohort). Moreover, as can be seen from Figure 1, a large percentage of these short-term workers died of lung cancer. For example, 43% and 54% of lung cancer deaths occurred in those who worked for less than 6 months and 12 months, respectively. Because short-term workers (e.g., < 1 year) have been found more likely to lead an unhealthy lifestyle (e.g., abuse alcohol) and have a chronic disease such as cancer (Kolstad and Olsen 1999), have increased mortality (Kolstad and Olsen 1999, Steenland et al.1996), and have increased SMRs for respiratory and other cancers (Boffetta et al. 1997), their risk factors may differ from long-term workers (perhaps biasing risk low when short-term, low-dose workers are used as the referent) and the general population (perhaps biasing low-dose risk high when the general population is the referent as in Gibb et al. 2000). Additionally, the exposure scenario the Baltimore cohort experienced is most dissimilar to the lifetime, environmental exposure scenario of interest and therefore least relevant and likely most

uncertain for occupational-to-lifetime, low level environmental extrapolation. Consequently, the TCEQ and others (e.g., Kolstad and Olsen 1999, Steenland et al. 1996) consider inclusion of short-term workers as potentially problematic for assessing risk from long-term, low-dose exposure (although this was the reason these workers were included in Gibb et al.). Thus, the TCEQ's analysis for the Baltimore cohort will include a subset of workers exposed at least one year, which was also the worker inclusion criterion for the other cohorts evaluated herein. Other concerns about the Baltimore cohort, such as not controlling for smoking, have been discussed by other authors (e.g., Exponent 2002a,b).

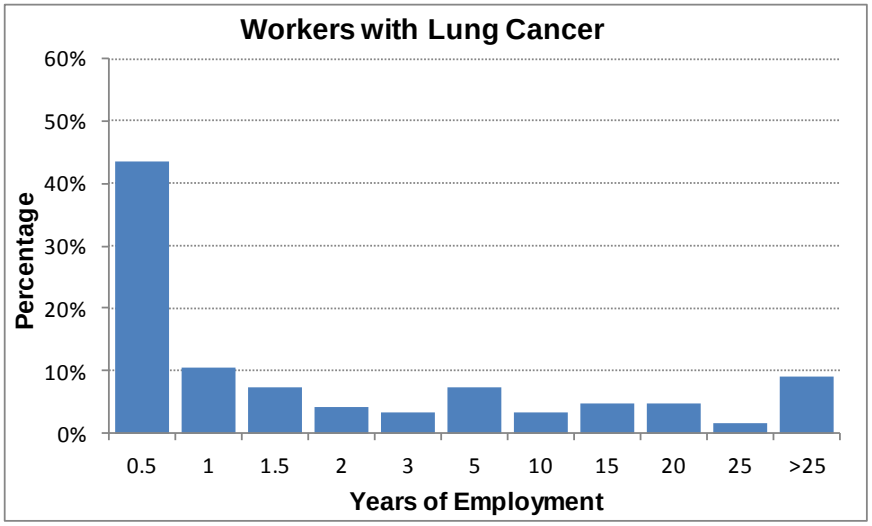



**Figure 6. Percentage of Workers with Lung Cancer Mortality by Work Duration**

Because of increased concerns about this cohort, Cox proportional hazards modeling will be performed using the Gibb et al. cohort individual data including smoking as a covariate. The Cox model is superior to Poisson regression modeling in that Cox modeling uses individual exposure estimates and optimally controls for the effect of age. However, for completeness and comparison to less refined modeling, modeled data and results for Gibb et al. (2000), Park et al. (2004), and Environ (2003) using maximum likelihood estimation procedures and Poisson regression modeling may be found in Appendix A.

#### *4.2.3.1.3.3 Low-Dose Supporting Cohorts: Germany and USA*

In addition to using the Painesville (Crump et al. 2003) and Baltimore (Gibb et al. 2000) cohorts for URF calculations, the TCEQ will utilize supporting dose-response data from 1,518 workers employed for at least one year who were exposed to low CrVI levels resulting from improved industrial hygiene practices and conversion to a low- or no-lime chromate production process. These low-exposed workers were followed through 1998 and are from four chromate production plants: Leverkusen and Uerdingen, Germany (total of 901 workers at these two plants), Corpus Christi, Texas (187 workers), and Castle Hayne, North Carolina (430 workers). Birk et al. (2006)

evaluated only the two German plants. However, Applied Epidemiology (2002) evaluated all four plants and will be the primary focus for this supporting assessment. The range of exposure durations for individual workers in the 4-plant study was 1.0-40.7 years, with mean exposure durations for the four plants ranging from 7.8-12.4 years and an overall mean exposure duration for the 4-plant study of 9.8 years.

For these low-exposed workers, cumulative exposure was reported as urinary chromium (µg Cr/L urine-yr). Therefore, cumulative urinary chromium was converted by the TCEQ to the cumulative air exposure equivalent dose metric (mg CrVI/$m^3$-yr) using the following biological exposure index (BEI)-type conversion established based on the relationship between urinary chromium and CrVI air concentration (Deutsche Forschungsgemeinschaft 1994):

mg CrVI/$m^3$-yr = µg Cr/L urine-yr /

[0.77 µg/L in urine per 1 µg CrVI/$m^3$ in the air × 1,000 µg/mg]

This BEI conversion is applicable to workers at the two German plants in Birk et al. (2006) and Applied Epidemiology (2002), and was used in Applied Epidemiology (2002) to covert CrVI air concentrations for the workers at the two American plants to urinary concentrations. Thus, for the American workers in Applied Epidemiology (2002), TCEQ using the reverse procedure simply converts cumulative urinary chromium back to the cumulative air exposure dose metric (mg CrVI/$m^3$-yr) for this assessment. Both Applied Epidemiology (2002) and Birk et al. (2006) found excess lung cancer risk in the highest unlagged exposure group (≥200 µg Cr/L-yr) based on SMR analyses (see Table 15 of Applied Epidemiology 2002 and Table 4 of Birk et al. 2006). Logistic regression analyses found increased odds ratios for the intermediate and/or high exposure groups after adjusting for smoking (see Table 18 of Applied Epidemiology 2002 and page 430 of Birk et al. 2006), and that adjusting for smoking did not materially change the relationship between CrVI exposure and lung cancer.

Although these supporting studies have some limitations (e.g., shorter follow-up time), the lower air concentration exposures (long-term plantwide geometric means generally <4 µg CrVI/$m^3$ for all four plants) are considered advantageous for assessing low-dose risk. The midpoint of the cumulative exposure range for the highest exposure group for these lower-exposed workers (509.74 µg CrVI/$m^3$-yr), for example, is approximately 33 times lower than that in the highest exposure group for the Painesville cohort (16,725 µg CrVI/$m^3$-yr) and would fall into the lower half of the cumulative exposure groups evaluated for that cohort (Crump et al. 2003). The 4-plant study (Applied Epidemiology 2002) has three times as many person-years (24,589 from Table 10 of Applied Epidemiology 2002) at these lower exposures (e.g., ≤ 0.67 mg CrVI/$m^3$-yr) as the Painesville cohort study (8,076 based on Table IV of Crump et al. 2003). Basing supporting risk estimates (i.e., URFs) on dose-response data from lower-exposed workers is considered more relevant for assessing risk associated with the lower environmental air concentrations to which the general public may be exposed (i.e., helps ensure generalizability to potential general public

exposures). It also reduces the magnitude of downward extrapolation and the uncertainty associated with low-dose extrapolation of risk far below the range of the data to a more environmentally-relevant 1 in 100,000 excess risk CrVI air concentration. Additionally, the US low-exposed workers provide diversity as less than 1% of the workers in the Painesville cohort were female, whereas 16% were women at these low-exposure US plants (also, 25% of the plant workers were African-American or Hispanic). Lastly, as potential CrVI emission sources, these types of chromate production plants are representative of current plants in the US.

Despite some advantageous attributes, the TCEQ limits use of the Applied Epidemiology (2002) 4-plant study to that of a supporting study due to the relatively short, mean follow-up time of 17.2 years (Table 9 of Applied Epidemiology 2002) compared to the latency for CrVI-induced lung cancer deaths (e.g., 86% of lung cancer deaths occurred ≥ 20 years after first exposure in the Painesville cohort, Luippold et al. 2003). Additionally, only 10.3% of the cohort was deceased (Table 10 of Applied Epidemiology 2002). These factors may limit the power of this study to detect increases in risk due to low cumulative exposure compared to the Baltimore cohort (30.0 years follow-up, 36% deceased) and Painesville cohort (30.4 years follow-up, 63% deceased) (Gibb et al. 2000, OSHA 2006, Luippold et al. 2003, Crump et al. 2003). The cumulative exposure and SMR data which will be used to calculate the parameter (β) estimates based on Applied Epidemiology (2002) are given in Table 9 below. For completeness, modeled data and results for the smaller 2-plant, low-dose study of Birk et al. (2006) may be found in Appendix A.

**Table 15. Lung Cancer Standardized Mortality Ratio (SMR) from Table 15 of Applied Epidemiology (2002)**

| Cumulative Exposure in Urine (µg Cr/L-yr) | Midpoint Converted to Air Cumulative Exposure Equivalent [b] (µg CrVI/$m^3$-yr) | No Lag SMR (O/E) [c] | 10-Yr Lagged Exposure SMR (O/E) [c] | 20-Yr Lagged Exposure SMR (O/E) [c] |
|---|---|---|---|---|
| 0-39.9 | 25.97 | 1.35 (4/2.96) | 1.34 (9/6.72) | 1.31 (17/12.98) |
| 40-99.9 | 90.91 | 0.95 (4/4.21) | 0.78 (3/3.85) | 1.01 (2/1.98) |
| 100-199.9 | 194.81 | 0.94 (5/5.32) | 1.31 (5/3.82) | 1.10 (2/1.82) |
| 200-585 [a] | 509.74 | 2.09 (12/5.74) | 2.05 (8/3.90) | 2.74 (4/1.46) |

[a] Upper end of exposure range based on Figure 23 in Applied Epidemiology (2002).
[b] Midpoint of cumulative urinary exposure converted to the air CrVI equivalent using the urine-to-air conversion factor of 1 µg CrVI/$m^3$ / 0.77 µg/L.
[c] Number of expected (E) calculated as number of observed (O)/SMR.

## 4.2.3.1.4 Slope Parameter (β) Estimates

### *4.2.3.1.4.1 Poisson Regression Modeling*

For lung cancer mortality in the studies evaluated, Poisson regression modeling was used to calculate the maximum likelihood estimate (MLE) of the slope parameter β (Appendix B). Maximum likelihood estimation with Poisson regression is preferred when the number of responses (i.e., observed and expected cases) is known (Section 8.3.3.2.1.1 of USEPA 1986; Crump and Allen 1985; Appendix B), as in this case. The multiplicative relative risk model used to calculate the β value included a term (α) to account for differences in lung cancer mortality background rates between the study population and the reference population used to determine the number of expected lung cancer mortalities. The use of this term may account for potential issues such as the healthy worker effect and any differences between internally- and externally-derived background rates. As discussed in Appendix B, incorporation of the α term into the relative risk model equation from USEPA (1986; p. 8-201) yields:

$$E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$$

where:

$E(O_j)$ = expected number of lung cancer mortality cases for exposure group j
$\alpha$ = accounts for differences in lung cancer mortality background rates between the study population and the reference population
$E_{oj}$ = expected number of background lung cancer mortality cases for exposure group j
$\beta$ = multiplicative factor by which background risk increases with cumulative exposure
$d_j$ = cumulative exposure for exposure group j

The linear multiplicative relative risk model, as opposed to an additive risk model, was used to calculate β estimates. The multiplicative relative risk model is preferred over the additive risk model for lung cancer because of more plausible assumptions concerning the increase in risk with age. For lung cancer, risk increases rapidly with age, which is better captured by the multiplicative relative risk model where risk increases over background rates multiplicatively. By contrast, the additive risk model assumes that cumulative exposure causes the same absolute increase in risk regardless of the age at which the risk is calculated, which is less plausible relative to actual observed age-related increases in lung cancer incidence and mortality.

For the studies evaluated, the mean or midpoint of each cumulative exposure group in units of µg CrVI/$m^3$-yr was used to estimate β values. Table 10 presents β estimates for Crump et al. (2003) and Applied Epidemiology (2002) evaluated in units of increase of relative risk per µg CrVI/$m^3$-yr.

**Table 16. β Values and Standard Error (SE) Based on Lung Cancer Mortality**

| Study | Lag | α | SE | β (95% LCL) [a, b] | β (MLE) [a] | β (95% UCL) [a, c] |
|---|---|---|---|---|---|---|
| **Crump et al. (2003) Painesville, OH** | 5-yr | 1.15 | 3.22E-04 | 1.05E-04 | **6.34E-04** | 1.16E-03 |
| **Applied Epidemiology (2002) Leverkusen and Uerdingen, Germany, Corpus Christi, TX and Castle Hayne, NC** | None | 0.88 | 2.58E-03 | -1.97E-03 | 2.27E-03 | 6.51E-03 |
| | 10-yr | 1.07 | 1.91E-03 | -1.60E-03 | **1.55E-03** | 4.69E-03 |
| | 20-yr | 1.17 | 2.44E-03 | -2.12E-03 | 1.90E-03 | 5.92E-03 |

[a] Estimates are excess relative risk per $\mu g/m^3$-yr.
[b] 95%LCL = β - (1.645 × SE).
[c] 95%UCL = β + (1.645 × SE).

Consistent with USEPA (2005a) and TCEQ (2012) guidelines, the standard error (SE), 95% lower confidence limit on the β (95%LCL β), and 95% upper confidence limit on the β (95%UCL β) were also calculated and are presented. As the 95%LCL β values for the 4-plant, low-dose worker study (Applied Epidemiology 2002) were negative, suggesting zero excess risk, these 95%LCL β values are not carried further in the dose-response assessment.

#### *4.2.3.1.4.2 Cox Proportional Hazards Modeling*

As previously indicated, Cox proportional hazards modeling was performed for a more extensive analysis of the Gibb et al. (2000) data for the Baltimore, MD cohort to offset some uncertainties about the use of this cohort for assessing risk from long-term (i.e., lifetime) exposure (e.g., 60% of the person-years at risk were from workers employed less than 6 months). Consequently, risk results for workers employed at least one year will be of primary interest and comparable to results based on the Painesville, OH cohort (Crump et al. 2003) and the supporting 4-plant, low-dose cohort (Applied Epidemiology 2002), both of which utilized at least 1 year of employment as a criterion for the inclusion of workers in the cohort. For completeness, however, results for the Baltimore, MD cohort are also presented for all workers regardless of employment duration and those employed at least one-half year.

Cox modeling is superior than Poisson regression modeling in that Cox modeling uses individual exposure estimates for each worker (as opposed to the average or midpoint for each exposure group) as well as the actual age of the worker (as opposed to age interval groupings), and does not make any assumptions about the functional form of the background hazard rate. This method avoids dependence on the partitioning of cumulative exposure and optimally controls for the effect of age on lung cancer. (The Poisson model was used for the Painesville cohort discussed in the previous section because the Cox model requires more information than the summary data that were available for the Painesville study.) The effect of smoking and the effect of race on the model fit to the lung cancer mortality were assessed separately and concurrently. The data were split into three strata (non-smoker, smoker, unknown smoking) to adjust the model parameters

for the effect of smoking and into two strata (white and non-white) to adjust the model parameters for the effect of race. The impact of these covariate effects were analyzed for the full cohort and the two subcohorts of workers employed at least one-half year and at least one year at the Baltimore plant (see Table 11 below).

More specifically, the log-linear form of the Cox proportional hazards model was used to fit the epidemiological data of the Baltimore cohort and to adjust for the effects of covariates. That Cox model can be specified as follows:

$$\ln(RR_{ij}) = s_i + r_j + \beta \times CumExp$$

where $s_i$ is the effect of smoking for the i-th smoking group relative to the reference smoking group, $r_j$ is the effect of race relative to the reference race group, and $\beta$ is the change in the $\ln(RR_{ij})$ per unit change in the cumulative exposure (CumExp). The Cox-proportional hazards model was fit to the Baltimore epidemiological data using Version 9.2 of the SAS System for Windows.

**Table 17. Statistics for the Baltimore Cohort and Two Subsets with Different Minimum Lengths of Employment Duration**

| Workers Included | Number of Workers | Workers without Lung Cancer | | | Workers that Died with Lung Cancer | | |
|---|---|---|---|---|---|---|---|
| | | Number | Smoker (%) | White (%) | Number | Smoker (%) | White (%) |
| **All** | 2,357 | 2,235 | 1,716 (76.78) | 1,134 (50.74) | 122 | 118 (96.72) | 71 (58.20) |
| **Employment Duration ≥ 0.5 Years** | 1,086 | 1,017 | 792 (77.88) | 531 (52.21) | 69 | 68 (98.55) | 38 (55.07) |
| **Employment Duration ≥ 1.0 Years** | 823 | 767 | 601 (73.03) | 413 (50.18) | 56 | 55 (98.21) | 29 (51.79) |

The impact of adding each of the covariate effects on the model fit to the data was evaluated using the improvement (i.e., reduction) of the deviance (deviance = -2×log likelihood) when the covariate was included in the model versus the deviance when the covariate was not included in the model. The decrease in the deviance was compared to a chi-square distribution to evaluate the statistical significance of the improvement of the model fit to the data. Table 12 shows the deviances for the models fit to the full cohort and two subcohorts. The deviance of the model adjusted for smoking is statistically significantly (p-value < 0.01) less than the deviance of the model not adjusted for any covariate for the full cohort and for the two subcohorts analyzed. In contrast, although the adjustment for race results in a statistically significant (p-value < 0.05) reduction in the deviance for the subcohort of workers employed at least one year, it does not result in a statistically significant reduction in the deviance for the full cohort and the subcohort of workers employed at least half a year. The deviance of the model adjusted for smoking and

race is statistically significantly (p-value < 0.01) less than the deviance of the model not adjusted for any covariate for the full cohort and the two subcohorts analyzed. However, the statistically significant decreases of the deviance when both covariates are included in the model are driven by the effect of smoking and only marginally due to the effect of race.

**Table 18. Deviance for Three Subsets of the Baltimore Cohort based on the Cox Proportional Hazards Model with Unlagged Exposure**

| Covariates in Addition to Cumulative CrVI Exposure | All Workers | Only Workers ≥ 0.5 Years of Employment | Only Workers ≥ 1.0 Years of Employment |
|---|---|---|---|
| None | 1629.256 [a] | 798.815 | 623.071 |
| Smoking [b] | 1609.261** | 784.358** | 611.721** |
| Race [c] | 1627.951 | 796.603 | 617.539* |
| Smoking & Race | 1608.128** | 782.61** | 606.531** |

* Deviance is statistically significantly < deviance of the model without covariates at the 5% significance level.
** Deviance is statistically significantly < deviance of the model without covariates at the 1% significance level.
[a] Deviance = -2×Log-Likelihood
[b] Smoking is a categorical covariate with three categories: "Non Smoking", "Smoking", and "Unknown Smoking."
[c] Race is a categorical covariate with two categories: "White" and "non-White."

Based on these results, the model without covariates and the model that included smoking as a covariate (which drove statistical significant decreases of the deviance) were analyzed further to determine the optimal exposure lag. That is, the effect of cumulative exposure lag on the model fit to the epidemiological data was analyzed. The lag adjusts the cumulative exposures to account for the potential latency and induction periods of lung cancer mortality in the cohort. The optimal lag was estimated for lung cancer mortality in the full cohort and in the two subcohorts.

Table 13 lists the deviances (-2×log likelihood) for each of the two models (without covariates and with smoking as a covariate), for each of the three subsets of the data (all workers, workers hired for at least half a year, and workers hired for at least one year), and for three lag periods (no lag, 5 years, and the lag with the minimum deviance which is the same as the lag that maximizes the likelihood). Both models fit the lung cancer mortality data better when the lag is set equal to 5 years than when no lag is used. Both models also find that the lag that maximizes the likelihood of the model fit to the lung cancer mortality data is between 6.3 and 7.4 years for the different subcohorts. The deviances for the models with exposure lag are less than the deviances for the models without exposure lag (although the improvements in the fit are not statistically significant at the 5% significance level).

**Table 19. Deviance for Three Subsets of the Baltimore Cohort based on the Cox Proportional Hazards Model with 0-Year, 5-Year, and Optimal Exposure Lag**

| Exposure Lag | All Workers | Only Workers ≥ 0.5 Years of Employment | Only Workers ≥ 1.0 Years of Employment |
|---|---|---|---|
| **Covariates: None** | | | |
| None | 1629.256 [a] | 798.815 | 623.071 |
| 5-yr | 1628.328 | 797.858 | 621.924 |
| Optimal Lag (MLE of the lag) | 1628.145 Lag=6.3 years | 797.653 Lag=6.7 years | 621.620 Lag=7.4 years |
| **Covariates: Smoking [b]** | | | |
| None | 1609.261 | 784.358 | 611.721 |
| 5-yr | 1608.407 | 783.502 | 610.705 |
| Optimal Lag (MLE of the lag) | 1608.259 Lag=6.3 years | 783.33 Lag=6.7 years | 610.456 Lag=7.4 years |

[a] Deviance = -2×Log-Likelihood
[b] Smoking is a categorical covariate with three categories: "Non Smoking", "Smoking", and "Unknown Smoking."

Table 14 presents β estimates for the Baltimore, MD cohort with smoking as a covariate (statistical significant decreases in model deviance are driven by the effect of smoking) and the optimal lag period in units of increase in relative risk per μg CrVI/$m^3$-yr, with β estimates for no lag and 5-year exposure lag provided for comparison. As can be seen from Tables 14 and 10, use of the better Cox model for the Gibb et al. (2000) data on the Baltimore, MD cohort provides β values fairly consistent with those of Crump et al. (2003) for the Painesville, OH cohort (e.g., 5-year lag β MLE range of 8.19E-04 to 1.00E-03 compared to the β MLE from Crump et al. of 6.34E-04). Since the statistically significant decrease of the deviance in the model is driven by the effect of smoking and the optimum exposure lag optimizes model fit, this will be the analysis of primary interest for workers employed at least one year (the preferred worker subset upon which to base risk estimates due to long-term exposure). The β MLE for the preferred analysis (i.e., workers employed ≥1 year, smoking as a covariate, optimum exposure lag) is bolded in the table below.

**Table 20. Cox Model β Values and Standard Error (SE) based on Gibb et al. (2000) Individual Data for the Baltimore Cohort with Smoking as a Covariate and Optimum, 5-, and 0-Year Exposure Lags**

| Worker Group | Exposure Lag | SE | β (95% LCL) [a, b] | β (MLE) [a] | β (95% UCL) [a, c] |
|---|---|---|---|---|---|
| All Workers | 6.3-yr (optimum) | 2.33E-04 | 6.37E-04 | 1.02E-03 | 1.40E-03 |
| | 5-yr | 2.31E-04 | 6.20E-04 | 1.00E-03 | 1.38E-03 |
| | None | 2.28E-04 | 5.72E-04 | 9.47E-04 | 1.32E-03 |
| Only Workers ≥ 0.5 Years of Employment | 6.7-yr (optimum) | 2.70E-04 | 3.99E-04 | 8.43E-04 | 1.29E-03 |
| | 5-yr | 2.67E-04 | 3.83E-04 | 8.22E-04 | 1.26E-03 |
| | None | 2.66E-04 | 3.19E-04 | 7.57E-04 | 1.19E-03 |
| Only Workers ≥ 1.0 Years of Employment | 7.4-yr (optimum) | 2.88E-04 | 3.78E-04 | **8.52E-04** | 1.33E-03 |
| | 5-yr | 2.84E-04 | 3.52E-04 | 8.19E-04 | 1.29E-03 |
| | None | 2.83E-04 | 2.72E-04 | 7.38E-04 | 1.20E-03 |

[a] Estimates are increase in relative risk per $\mu g/m^3$-yr.
[b] 95%LCL = β - (1.645 × SE).
[c] 95%UCL = β + (1.645 × SE).

## 4.2.3.1.5 Dosimetric Adjustments

Consistent with TCEQ (2012), occupational concentrations ($Concentration_{OC}$) were converted to environmental concentrations for the general population ($Concentration_{HEC}$) using the following equation:

$$Concentration_{HEC} = Concentration_{OC} \times (VE_{ho}/VE_h) \times (ds\ per\ week_{oc}/ds\ per\ week_{res})$$

where:

$Concentration_{HEC}$ = human equivalent concentration for the general public ($\mu g/m^3$)
$Concentration_{OC}$ = occupational exposure concentration ($\mu g/m^3$)
$VE_{ho}$ =occupational ventilation rate for an 8-h d (10 $m^3$/d)
$VE_h$ = non-occupational/environmental ventilation rate for a 24-h d (20 $m^3$/d)
$ds\ per\ week_{oc}$ = occupational weekly exposure frequency (5 ds per week)
$ds\ per\ week_{res}$ = residential weekly exposure frequency (7 ds per week)

## 4.2.3.1.6 Unit Risk Factors (URFs) and Air Concentrations at 1 in 100,000 Excess Lung Cancer Risk

URFs express cancer potency in units of excess risk per air concentration (e.g., excess risk per $\mu g/m^3$) assuming continuous lifetime exposure. They are calculated using linear low-dose extrapolation when the carcinogenic MOA is mutagenic, unknown, or sufficient information to justify an alternative extrapolation approach is not available (TCEQ 2012). Although there is not

a consensus on the specific MOA for CrVI, significant information relevant to the carcinogenic MOA for CrVI is known and justifies consideration of a nonlinear-threshold assessment in addition to the default linear low-dose extrapolation approach employed in this section. The implementation of nonlinear-threshold approach was published recently in Haney et al. (2012). However, as mentioned previously in Section 4.2.3, at this time the uncertainties associated with a nonlinear-threshold inhalation carcinogenic assessment for CrVI appear to preclude a robust scientific justification for deviation from the default linear low-dose extrapolation approach. Thus, the nonlinear-threshold assessment is not a focus of this document and the default linear low-dose extrapolation approach is utilized to derive URF estimates.

When a dose-response curve is modeled for tumor data (see Figure 2 below), the URF is the slope of a straight line from the POD to the origin, with the POD being the lowest tumor response level supported by the study data.

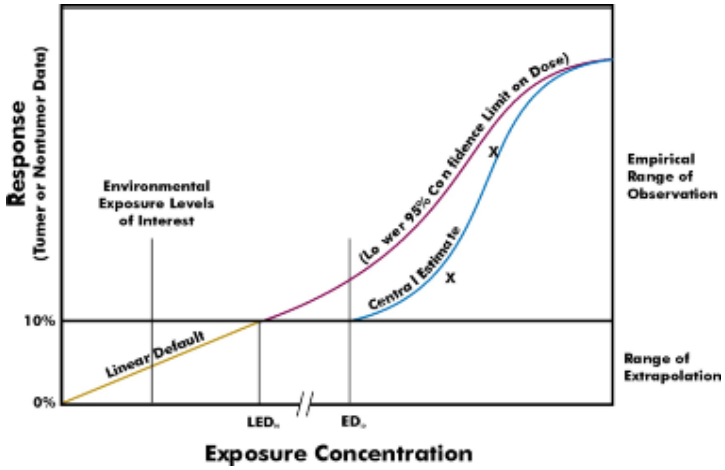



**Figure 7. Example of Linear Approach for Low-Dose Extrapolation**

Frequently in animal-based risk estimates, the lower statistical bounds on the concentration producing a 10% excess tumor response ($LEC_{10}$) is used as the POD for linear low-dose extrapolation and calculation of the URF since the limit of detection of tumor studies is often around 10%, and the resulting equation is:

$$URF = \text{risk per } \mu g/m^3 = 0.10 / LEC_{10} \text{ (where } LEC_{10} \text{ is expressed in } \mu g/m^3)$$

However, for this cancer assessment, the response data are based on humans and have already been fit to a linear equation (linear multiplicative relative risk model) for use with the BEIR IV methodology (NRC 1988). Therefore, consistent with TCEQ (2012) guidelines (e.g., meta-analysis approach, discussion of lung cancer mortality versus incidence in the next section), a URF is calculated using a central estimate of a POD within the range of the epidemiological data (i.e., $URF = 1/EC_{001}$) for this risk assessment.

Table 15 shows URFs estimated at an excess risk of 1 in 1,000 and extrapolated air concentrations corresponding to an excess cancer risk of 1 in 100,000 based on β (MLE), β (95% LCLs), and β (95% UCLs) from Table 10, which were calculated based on Crump et al. (2003) and the supporting study of Applied Epidemiology (2002) using maximum likelihood estimation with Poisson regression. For the Cox proportional hazards modeling of the Gibb et al. (2000) data for the Baltimore, MD cohort, Table 16 provides estimates of URFs and air concentrations at 1 in 100,000 excess cancer risk based on β (MLE), β (95% LCLs), and β (95% UCLs) from Table 14. Air concentrations are based on extra risk (as opposed to added risk) and a lifetime exposure of 70 years, the default used by TCEQ for exposure analysis (TCEQ 2012), and were solved iteratively with life-table analyses using the BEIR IV approach (NRC 1988). The following lung cancer mortality rates and survival probabilities were used in the primary (Texas rates) and supplementary (US rates) analyses:

- Texas-specific lung cancer mortality rates for 2005-2009 and Texas-specific survival rates for 2010 are the latest available (TDSHS 2010) (Appendix C);
- US lung cancer mortality rates for 2005-2009 are the latest available (Surveillance, Epidemiology, and End Results database (SEER 2012) (Appendix C); and
- US survival rates for 2008 are the latest available (Arias 2008) (Appendix C).

However, Texas background lung cancer mortality rates and survival probabilities are preferred by the TCEQ and were used for the results shown in Tables 15 and 16 below. For comparison purposes, the similar results obtained using US rates are provided in Appendix D.

**Table 21. URFs and Air Concentrations Corresponding to 1 in 100,000 Excess Lung Cancer Mortality**

| Study | Exposure Lag | Background Rates | URF (95% LCL) [a] Air Concentration @ 1 in 100,000 Excess Risk | URF (MLE) [a] Air Concentration @ 1 in 100,000 Excess Risk | URF (95% UCL) [a] Air Concentration @ 1 in 100,000 Excess Risk |
|---|---|---|---|---|---|
| Crump et al. (2003) Painesville, OH | 5-yr | TX | 3.21E-04 per µg/m$^3$ 3.11E-02 µg/m$^3$ | **1.94E-03 per µg/m$^3$ 5.16E-03 µg/m$^3$** | 3.55E-03 per µg/m$^3$ 2.82E-03 µg/m$^3$ |
| Applied Epidemiology (2002) Leverkusen and Uerdingen, Germany, Corpus Christi, TX and Castle Hayne, NC | None | TX | NA | 7.55E-03 per µg/m$^3$ 1.32E-03 µg/m$^3$ | 2.16E-02 per µg/m$^3$ 4.62E-04 µg/m$^3$ |
| | 10-yr | TX | NA | **4.33E-03 per µg/m$^3$ 2.31E-03 µg/m$^3$** | 1.31E-02 per µg/m$^3$ 7.63E-04 µg/m$^3$ |
| | 20-yr | TX | NA | 4.30E-03 per µg/m$^3$ 2.32E-03 µg/m$^3$ | 1.34E-02 per µg/m$^3$ 7.46E-04 µg/m$^3$ |

[a] Calculation of air concentrations at 1 in 100,000 excess risk used the unrounded URF.
NA = as the 95%LCL β value was negative, suggesting zero excess risk, calculation of an air concentration at 1 in 100,000 excess risk was not possible.

**Table 22. Cox Model URFs and Air Concentrations Corresponding to 1 in 100,000 Excess Lung Cancer Mortality based on Gibb et al. (2000) Data for the Baltimore Cohort with Smoking as a Covariate and Optimum, 5-, and 0-Year Exposure Lags**

| Worker Group | Exposure Lag | Background Rates | URF (95% LCL) [a] Air Concentration @ 1 in 100,000 Excess Risk | URF (MLE) [a] Air Concentration @ 1 in 100,000 Excess Risk | URF (95% UCL) [a] Air Concentration @ 1 in 100,000 Excess Risk |
|---|---|---|---|---|---|
| All Workers | 6.3-yr (optimum) | TX | 1.96E-03 per µg/m$^3$ 5.11E-03 µg/m$^3$ | 3.13E-03 per µg/m$^3$ 3.19E-03 µg/m$^3$ | 4.30E-03 per µg/m$^3$ 2.33E-03 µg/m$^3$ |
| | 5-yr | TX | 1.95E-03 per µg/m$^3$ 5.14E-03 µg/m$^3$ | 3.14E-03 per µg/m$^3$ 3.18E-03 µg/m$^3$ | 4.33E-03 per µg/m$^3$ 2.31E-03 µg/m$^3$ |
| | None | TX | 1.95E-03 per µg/m$^3$ 5.12E-03 µg/m$^3$ | 3.23E-03 per µg/m$^3$ 3.09E-03 µg/m$^3$ | 4.51E-03 per µg/m$^3$ 2.22E-03 µg/m$^3$ |
| Only Workers ≥ 0.5 Years of Employment | 6.7-yr (optimum) | TX | 1.22E-03 per µg/m$^3$ 8.22E-03 µg/m$^3$ | 2.57E-03 per µg/m$^3$ 3.89E-03 µg/m$^3$ | 3.93E-03 per µg/m$^3$ 2.54E-03 µg/m$^3$ |
| | 5-yr | TX | 1.20E-03 per µg/m$^3$ 8.31E-03 µg/m$^3$ | 2.58E-03 per µg/m$^3$ 3.87E-03 µg/m$^3$ | 3.96E-03 per µg/m$^3$ 2.53E-03 µg/m$^3$ |
| | None | TX | 1.09E-03 per µg/m$^3$ 9.18E-03 µg/m$^3$ | 2.58E-03 per µg/m$^3$ 3.87E-03 µg/m$^3$ | 4.06E-03 per µg/m$^3$ 2.46E-03 µg/m$^3$ |
| Only Workers ≥ 1.0 Years of Employment | 7.4-yr (optimum) | TX | 1.14E-03 per µg/m$^3$ 8.79E-03 µg/m$^3$ | **2.56E-03 per µg/m$^3$ 3.90E-03 µg/m$^3$** | 4.00E-03 per µg/m$^3$ 2.50E-03 µg/m$^3$ |
| | 5-yr | TX | 1.11E-03 per µg/m$^3$ 9.04E-03 µg/m$^3$ | 2.57E-03 per µg/m$^3$ 3.89E-03 µg/m$^3$ | 4.05E-03 per µg/m$^3$ 2.47E-03 µg/m$^3$ |
| | None | TX | 9.28E-04 per µg/m$^3$ 1.08E-02 µg/m$^3$ | 2.52E-03 per µg/m$^3$ 3.97E-03 µg/m$^3$ | 4.10E-03 per µg/m$^3$ 2.44E-03 µg/m$^3$ |

[a] Calculation of air concentrations at 1 in 100,000 excess risk used the unrounded URF.

### 4.2.3.1.7 Selection of Lung Cancer URFs

Based on the two key epidemiological studies (Crump et al. 2003, Gibb et al. 2000), two lung cancer URFs are selected in this section for combining into a final weighted URF. As indicated previously, Crump et al. (2003) provide one of the best summary SMR datasets for dose-response assessment due to a relatively high number of exposure groups (10) evaluated for excess lung cancer risk (14,443 person-years). Because exposure was not lagged and fewer

cumulative exposure groups are provided by Luippold et al. (2003) for dose-response modeling, Crump et al. are considered to provide the best dose-response dataset for the Painesville, Ohio cohort. Thus, the preferred URF for the Painesville, Ohio cohort (shaded in Table 15, associated β shaded in Table 10) will be based on the 5-year exposure lagged data from Crump et al. (2003).

For Gibb et al. (2000), URFs based on Cox proportional hazards modeling for workers employed at least one year are preferred given: (1) the superiority of the Cox model over Poisson regression, (2) TCEQ's reservations about inclusion of very short-term workers in Gibb et al. (2000) to assess the excess risk associated with long-term (e.g., lifetime) CrVI exposure, and (3) comparability considerations (i.e., Crump et al. 2003 and the supporting Applied Epidemiology 2002 study utilized one year of employment as a worker inclusion criterion). It is noted, however, that the URFs are fairly similar for the employment durations evaluated (e.g., the all worker 5-year lag MLE URF is only 22% higher than that for workers employed at least a year). Furthermore, use of the optimal exposure lag of 7.4 years is preferred as this lag maximizes the likelihood of the model fit to the data (although use of 5-year lag provides results within 4% and would result in an identical final weighted URF). The 7.4-year exposure lag is close to the 5-year lag results being used from Crump et al. (2003). Thus, the preferred URF for the Baltimore, Maryland cohort (shaded in Table 16, associated β shaded in Table 14) will be based on Cox modeling results for workers employed at least one year, 7.4-year exposure lagged data, and smoking as a covariate (as mentioned in Section 4.2.3.1.4).

Regarding the Applied Epidemiology (2002) supporting study, use of dose-response data from workers exposed to low levels of CrVI is considered advantageous for assessing low-dose risk as the magnitude of extrapolation below the range of data and the uncertainty associated with low-dose extrapolation is reduced. Thus, although the short follow-up time and low deceased percent for this cohort are important limitations, results from this supporting study are nevertheless considered to have value for comparison to the URFs based on the two key epidemiological studies. Three supporting URFs were calculated for Applied Epidemiology (2002) based on different exposure lag periods (0-, 10-, and 20-year lagged exposure). An exposure lag of 20 years appears too long considering that the mean time since first exposure for lung cancer mortality in the high cumulative exposure group which experienced excess risk in the SMR analysis was around 23 years (Figure 24 of Applied Epidemiology 2002) as this would assume that on average, only the first three years of CrVI exposure were potentially causative for the excess lung cancer mortality observed in this group. Along this line of reasoning, exposure lags of 0- and 10-years would seem to provide a more reasonable basis for a supporting URF. However, the 10-year lagged exposure data seem to provide a SMR exposure-response closer to linear than the 0-year lag data (Table 9) and produce a smaller β value variance (3.65E-06) than no lag (6.66E-06) (Table 10). Additionally, a 10-year lag is more similar to the exposure lags of 5- and 7.4-years, respectively, being used for the Crump et al. (2003) and Gibb et al. (2000) key studies. Based on these considerations, the preferred supporting URF for the 4-plant, low-dose worker cohorts (lightly shaded in Table 15, associated β lightly shaded in Table 10) will be based on the 10-year exposure lagged data from Applied Epidemiology (2002).

Lastly, as can be seen from Figure 3, lung cancer mortality is reasonably predictive of lung cancer incidence (i.e., five-year survival is only about 16% (American Cancer Society 2012)). Therefore, if incidence data were available, the lung cancer potency estimates would be expected to be very similar to those derived based on lung cancer mortality.

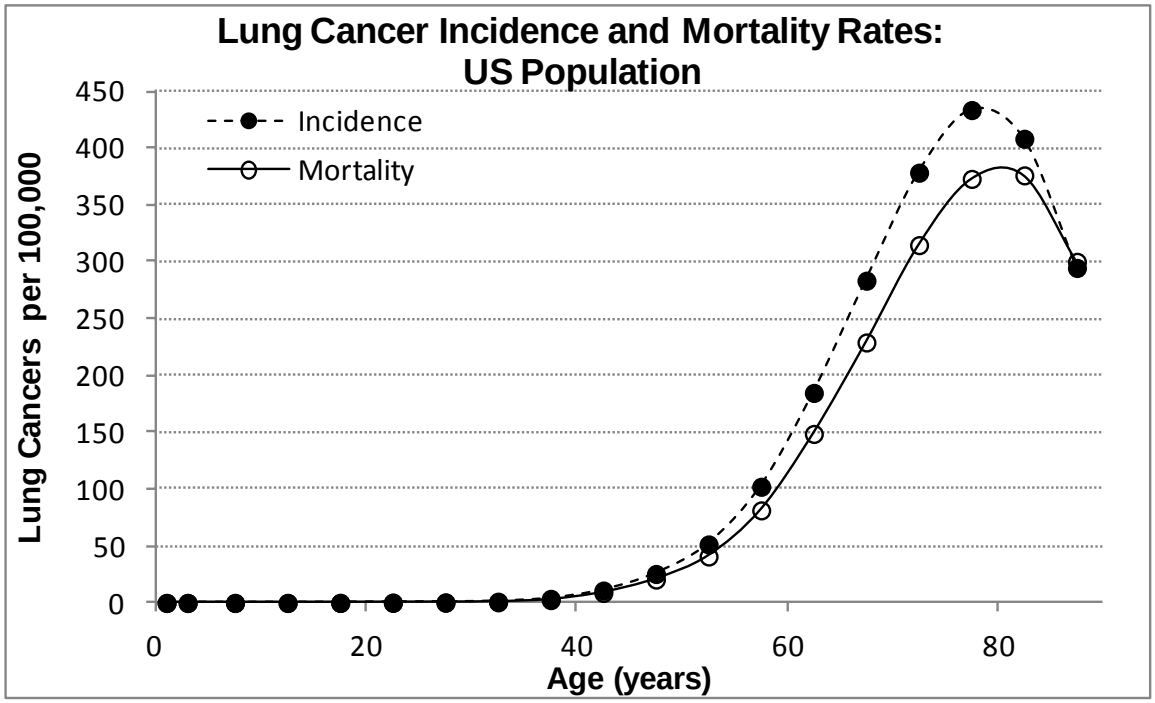



**Figure 8. Lung Cancer Incidence versus Mortality**

In such instances, the TCEQ selects the URF (MLE) as the best estimate of cancer potency (e.g., TCEQ 2011). Additionally, although values based on US rates are provided for comparison and are very similar (see Appendix D), the TCEQ uses Texas age-specific lung cancer mortality rates and survival probabilities to derive URFs.

Therefore, the URFs selected based on the key epidemiological studies of Crump et al. (2003) and Gibb et al. (2000) are 1.94E-03 and 2.56E-03 per µg CrVI/$m^3$, respectively (Tables 15 and 16). These URFs are very similar, a factor of only 1.3 apart. They are supported by a URF of 4.33E-03 per µg CrVI/$m^3$ based on data from Applied Epidemiology (2002). All three URFs are similar, within a factor of 2.2, although based on different cohorts and different lag periods in the cumulative exposure dose metrics. The URFs from the two key studies will be weighted following consideration of early-life exposures to calculate a final URF and the corresponding air concentration at the TCEQ policy-based excess risk level of 1 in 100,000, which is the $^{chronic}ESL_{nonthreshold(c)}$ value.

### 4.2.3.1.8 Evaluating Susceptibility from Early-Life Exposures

USEPA (2005) provides default age-dependent adjustment factors (ADAFs) to account for potential increased susceptibility in children due to early-life exposure when a chemical has been identified as acting through a mutagenic MOA for carcinogenesis. CrVI has not been demonstrated to have a mutagenic MOA for lung carcinogenicity considering the reasonably scientifically-rigorous standard set under TCEQ (2012) guidelines.

#### *4.2.3.1.8.1 Mutagenic Potential*

Occupational studies have reported mixed results on the genotoxic potential of CrVI compounds. However, some of the occupational studies were limited (e.g., low exposure or small exposure groups) and CrVI compounds are positive in the majority of genotoxicity tests, especially *in vitro* (e.g., mutation in E. coli and S. typhimurium; chromosomal aberrations, sister chromatid exchange, and DNA damage and strand breaks in mammalian cells) but also *in vivo* (e.g., mutation in D. melanogaster; chromosomal aberrations, sister chromatid exchange, micronuclei, and DNA damage and strand breaks in human lymphocytes). Genotoxicity in these tests is related to solubility and therefore bioavailability (see Tables 3-8 and 3-9 in ATSDR 2012). *In brief, the weight of evidence is that CrVI has genotoxic and mutagenic potential.* However, the determination that a chemical carcinogen is capable of producing genotoxicity and/or mutations is not sufficient to conclude that it causes specific tumors by a mutagenic MOA (or that mutation is the only key event in the pathway to tumor induction) (see Section 5.7.5.1.1 of TCEQ 2012 for additional information).

#### *4.2.3.1.8.2 Mutagenic MOA Considerations*

Once a carcinogen has been determined to have mutagenic potential, there are several important considerations in assessing evidence for a mutagenic MOA for cancer. For example: (1) whether the chemical-induced mutation occurs prior to the initiation of the carcinogenic process (i.e., early in relation to the key events that lead to cancer) in the target tissue (i.e., site and temporal concordance between mutagenicity and carcinogenicity), and if so (2) whether the chemical-induced mutation is THE key event that initiates the carcinogenic process in the target tissue. See Section 5.7.5.1.2 of TCEQ (2012) for additional information, including a hierarchy for types of relevant evidence. Consideration of possible dose-dependent changes in MOA may also have important implications for low-dose extrapolation and risk characterization (e.g., linearity at low doses due to mutagenicity with an additional contribution of oxygen radical/cellular damage-induced regenerative hyperplasia at high doses). *Most importantly, for a chemical to act by a mutagenic MOA, either the chemical or its direct metabolite must be the agent inducing THE mutations that initiate cancer in the target tissue.* As there is no default carcinogenic MOA, the scientific burden of proof is a reasonably robust demonstration through direct evidence (not just plausibly) that the specific mutation(s) caused by the chemical or its metabolite is in fact the first step in target tissue which initiates a cascade of other key events that are critical to the carcinogenic process in the specific tumors. Mere plausibility (whether or not information on other possible MOAs is available) based on the consistency of circumstantial evidence is not

tantamount to an adequately robust demonstration that mutagenicity is in fact THE initiating event in target tissues. *Thus, if the weight of evidence supports a chermical's mutagenic potential as in this case, for evaluation of the MOA emphasis should then be placed on evidence of the chemical's mutagenicity being the critical, initating carcinogenic event in target cells (at relevant doses if possible).* Finally, in the event scientifically convincing data on other possible carcinogenic MOAs are also lacking, the carcinogenic MOA may ultimately be judged simply to be unknown or not sufficiently elucidated or established (TCEQ 2012).

While Section 4.2.2 provides additional discussion, a comparative weight of evidence for various potential MOAs is beyond the scope of this document. However, ATSDR (2012) acknowledges that the mechanisms of CrVI carcinogenicity are very complex, being mediated partly through reactive intermediates (CrV, CrIV) during the intracellular reduction of CrVI to CrIII (also generating oxygen radical species and oxidative stress), and partly by CrIII forming deleterious complexes with critical targets such as peptides, proteins, and DNA. The intracellular metabolic reduction products of CrVI (free radicals, CrV, CrIV) and the newly generated CrIII are thought to be in part responsible for its carcinogenic effects, and their interaction with DNA can result in structural damage (e.g., breaks, crosslinks, adducts), functional damage (e.g., mutagenesis, altered gene expression), and other cellular effects (ATSDR 2012). However, direct and reactive oxygen species-mediated DNAdamage by CrV may only occur under conditions of limited ascorbate concentrations and more information on the role of oxygen radicals in chromium-induced genotoxicity is needed (Zhitkovich 2011, O'Brien et al. 2003). The formation of free radicals leading to oxidative stress may be responsible for deleterious cellular effects of chromium such as lipid peroxidation, alterations in cellular communication and signaling pathways, the induction and inhibition of transcription factors, etc. Also, recent human lung cell studies suggest that chromium-induced chromosome instability (mediated through centrosome and spindle assembly checkpoint bypass) is an important mechanism in the development of lung cancers (ATSDR 2012). Finally, a recent paper to evaluate the weight of evidence from available human, animal, and *in vitro* data (including *in vivo* genotoxicity) using the modified Hill Criteria supports that CrVI-induced lung carcinogenicity acts by a non-mutagenic MOA involving oxidative stress, oxidative DNA damage, tissue injury, and inflammation, with additional evidence for epigenetic DNA modifications (ToxStrategies 2012).

Although available information relevant to the MOA suggests multiple possible mechanisms, it does not elucidate whether chromium interactions with DNA induce a target tissue mutation which is THE key event that initiates the carcinogenic process. For example and more specifically, target (i.e., lung) tissue studies of induced mutation (or even genotoxicity), following *in vivo* CrVI exposure in particular, are of the highest hierarchial evidence but are lacking. Unfortunately, this precludes evaluation of a key issue, temporal and dose-response concordance between mutagenicity and carcinogenicity (TCEQ 2012). *Although plausible, the mutagenic/genotoxic potential of CrVI has simply not been demonstrated (robustly or otherwise) to result in lung tissue mutations that are THE mutations that initiate cancer in target tissue, the scientific burden of proof for a mutagenic MOA.*

Not to belabor the point more, the MOA(s) for CrVI carcinogenesis is yet to be fully elucidated, firmly established and widely accepted by the scientific community, although a variety of MOAs have been proposed as discussed in Section 4.2.2. The data are simply not sufficient to definitively determine the specific carcinogenic MOA(s). As the MOA for CrVI-induced lung cancer has not been sufficiently demonstrated to be mutagenic, consistent with TCEQ guidance (TCEQ 2012) ADAFs will not be applied to the final URF at this time. This issue will be reevaluated periodically as new scientific information on CrVI's carcinogenic MOA becomes available.

### *4.2.3.2 Final URF and $^{chronic}ESL_{nonthreshold(c)}$*

The final URF is derived here using a meta-analysis approach that combines the two preferred URFs based on the individual key epidemiological studies. Though meta-analyses usually combine results of primary research, herein the meta-analysis combines URFs estimated from published data of primary epidemiological research studies and from individual epidemiological data. The purpose of this meta-analysis is to integrate the findings based on the preferred individual studies into a final URF that objectively incorporates the significance of the results (measured by the precision or variance of the model fit to the data). More specifically, as discussed below and in TCEQ (2012), the two key URFs are weighted based on inverse variance ($1/SE^2$), a standard statistical procedure used in meta-analyses, to combine them and derive a final URF.

The two preferred URFs based on Crump et al. (2003) and Gibb et al. (2000) are 1.94E-03 and 2.56E-03 per µg CrVI/$m^3$, respectively. These URFs are similar and are considered appropriate estimates of the carcinogenic potency of CrVI based on their respective studies. The TCEQ believes that using either of these URFs would result in adequate protection of public health given available information. However, in order to incorporate the available information from both key epidemiological studies, the TCEQ combined these two URFs to derive a final URF using a weighting factor that reflects the relative statistical confidence in the URFs. Variance in the β values used to derive the preferred URFs reflects uncertainty in the β estimates and is used as a weighting factor. Since there is generally more confidence in β values with smaller variance, the reciprocal of the variance is used so that the resulting weighting factor is larger for the β value with the smallest variance (uncertainty). The URF based on a β with smaller variance receives greater weight as confidence is increased because a relatively lesser variance is an indication of higher statistical significance. The overall weight for a URF is the percentage of the sum of URF weighting factors that is represented by the reciprocal of the variance of the estimated β for that URF (i.e., (individual URF weighting factor/sum of weighting factors for URFs being weighted) × 100 = overall weight % for a given URF). As shown in Table 17 below, the variances associated with the β (MLE) values for the two studies are similar (less than 12% apart), resulting in similar weighting factors.

**Table 23. Weighting of Preferred URFs from Crump et al. (2003) and Gibb et al. (2000)**

| Study | Preferred URF (per µg CrVI/m$^3$) | Standard Error (SE) of β [c] | Weighting Factor (1 / SE$^2$) | Overall Weight of URF (%) [d] |
|---|---|---|---|---|
| Crump et al. (2003) | 1.94E-03 [a] | 3.22E-04 | 9.64E+06 | 44.4 |
| Gibb et al. (2000) | 2.56E-03 [b] | 2.88E-04 | 1.21E+07 | 55.6 |

[a] See Table 15.
[b] See Table 16.
[c] See Tables 10 and 14 for the values of the SE of β.
[d] Overall weight of URF (%) = (weighting factor/sum of weighting factors) × 100.

The final URF is equal to the weighted average (using weight percents expressed in decimal form) of the two individual URFs:

Final URF = Crump et al. (2003) URF × overall weight for Crump et al. (2003) +

Gibb et al. (2000) URF × overall weight for Gibb et al. (2000)

= 1.94E-03 × 0.444 + 2.56E-03 × 0.556

= 2.28E-03 per µg CrVI/m$^3$

Thus, the final URF when rounded to two significant figures is 2.3E-03 per µg CrVI/m$^3$. Based on the final URF, the air concentration corresponding to an excess lung cancer mortality risk of 1 in 100,000, rounded to two significant figures, is 0.0043 µg CrVI/m$^3$ (i.e., 0.00001 / 2.3E-03 per µg CrVI/m$^3$). Therefore, the $^{chronic}ESL_{nonthreshold(c)}$ is 0.0043 µg CrVI/m$^3$. As shown in Appendix D, using US lung cancer mortality and survival rates would result in a very similar URF (2.4E-03 per µg CrVI/m$^3$) and air concentration at a 1 in 100,000 excess risk (0.0042 µg CrVI/m$^3$).

### *4.2.3.3 Comparison of the Preferred and Final URFs to Other URFs*

As mentioned previously, the TCEQ selects the URF (MLE) using Texas age-specific lung cancer mortality rates and survival probabilities as the best (i.e., preferred) estimate of cancer potency when the cancer endpoint is lung cancer mortality (e.g., TCEQ 2011). Thus, the following discussion concerns comparisons of URF (MLE) values.

The preferred URF of 1.94E-03 µg CrVI/m$^3$ (5-year lagged exposure) for the Painesville, Ohio cohort based on Crump et al. (2003) is about 3 times more conservative than the other URF considered for the same cohort (7.05E-04 µg CrVI/m$^3$, no exposure lag) calculated based on Luippold et al. (2003) (Appendix A). The URF selected for the Baltimore, Maryland cohort based on the best analysis (i.e., Cox modeling) of the Gibb et al. data (2.56E-03 per µg CrVI/m$^3$)

is somewhat less conservative than other URFs that can be calculated for this cohort based on Poisson regression modeling and Park et al. (2004) and/or Environ (2003) data (Appendix A), and is within a factor of 4.3 of that based on Poisson modeling of Gibb et al. (2000).

The preferred URF from the supporting Applied Epidemiology (2002) study of four low-exposure chromate production plants (4.33E-03 per µg CrVI/$m^3$ based on 10-year lagged exposure) is very similar to (within a factor of 2.2 of) the URFs based on the two key epidemiological studies (Crump et al. 2003, Gibb et al. 2000), and to the other URFs calculated for this study with 20-year or no exposure lag. The 4.33E-03 per µg CrVI/$m^3$ value is essentially the same as the URF calculated based on 20-year lagged exposure (4.30E-03 per µg CrVI/$m^3$), and is less than a factor of 2 different than the URF based on no exposure lag (7.55E-03 per µg CrVI/$m^3$). The final URF would have been very similar to its current value had the supporting study also been included in the weighting since the weighting factor ($1/SE^2$) would have been only 1.2% (0.012 in the calculation above) due to a much higher variance ($SE^2$ = 3.65E-06) associated with the β (MLE) compared to those for the two key studies (i.e., 35- to 44-fold greater than the variances of 8.29E-08 and 1.04E-07 for Gibb et al. 2000 and Crump et al. 2003, respectively).

The USEPA has not finalized an updated toxicological review of CrVI since USEPA (1998), or a different inhalation URF value since USEPA (1984). Using default linear low-dose extrapolation and lung cancer data from a now outdated occupational study (Mancuso 1975) with several significant limitations which make it less suitable for CrVI risk assessment (e.g., exposure groups based on total Cr, no smoking data, lack of representative industrial hygiene survey data), USEPA (1984) derived a URF of 1.2E-02 per µg CrVI/$m^3$. This outdated USEPA URF is about five times greater than the final URF calculated by the TCEQ (2.3E-03 per µg CrVI/$m^3$) based on an updated carcinogenicity assessment using different key studies. See Appendix E for an uncertainty analysis concerning the derivation of the URF.

## *4.3 Welfare-Based Chronic ESL*

No useful data were found regarding potential adverse vegetative effects due to direct exposure to airborne CrVI.

## *4.4 Chronic Values for Air Permitting and Air Monitoring Evaluations*

The chronic evaluation resulted in the derivation of the following chronic values:

- chronic ReV = 0.22 µg CrVI/$m^3$ for CrVI particulate compounds
- $^{chronic}ESL_{threshold(nc)}$ = 0.066 µg CrVI/$m^3$ for CrVI particulate compounds
- $^{chronic}ESL_{nonthreshold(c)}$ = 0.0043 µg CrVI/$m^3$

The chronic ESL for air permit evaluations is the $^{chronic}ESL_{nonthreshold(c)}$ of 0.0043 µg CrVI/$m^3$ as it is lower than the $^{chronic}ESL_{threshold(nc)}$ of 0.066 µg CrVI/$m^3$ for CrVI particulate compounds (Table 2). As indicated previously, to protect against sensitization, exceedances of the chronic (or acute)

ESL during the air permit review should be discouraged for any chemicals identified as respiratory sensitizers (TCEQ 2012).

For evaluation of long-term ambient air monitoring data, the $^{chronic}ESL_{nonthreshold(c)}$ of 0.0043 µg CrVI/m$^3$ is lower than the chronic ReV of 0.22 µg CrVI/m$^3$ for CrVI particulate compounds (Tables 1 and 2). However, the ReV value may be used for the evaluation of air data as well as the URF of 2.3E-03 per µg CrVI/m$^3$. The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) value is not used to evaluate ambient air monitoring data.

## *4.5 Subchronic and Chronic Inhalation Observed Adverse Effect Levels*

### 4.5.1 Subchronic Noncarcinogenic Inhalation Observed Adverse Effect Level

The key studies for derivation of the chronic ReV were subchronic animal studies (Glaser et al. 1885 and 1990), with Glaser et al. (1985) ultimately providing the POD. This study will also be used to derive a subchronic inhalation observed adverse effect level. As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. The study by Glaser et al. (1985) had a LOAEL of 50 µg CrVI/m$^3$ for increased relative lung weight in rats. This animal LOAEL was used as the animal subchronic inhalation observed adverse effect level for extrapolation to humans. BMC results (e.g., $BMC_{10}$ of 78.7312 µg CrVI/m$^3$ (Hill model, Table 5) for increased lung weight based on Glaser et al. 1990) were not utilized for the same reasons discussed in Section 4.1.2.1.3.2 (e.g., shape of the dose-response curve not representative of available data in the low dose region). No duration adjustment was made (TCEQ 2012) (Section 4.1.4.1). As discussed in Section 4.1.4.2, the applicable RDDR for animal-to-human dosimetric adjustment is 2.41. Thus, extrapolation of the animal study LOAEL to humans results in a $LOAEL_{HEC}$ of 120 µg CrVI/m$^3$ (rounded to two significant figures). Generally, subchronic observed effects levels would not be expected to be higher than estimated subacute observed effects levels, yet this subchronic $LOAEL_{HEC}$ is somewhat higher than the subacute $POD_{HEC}$ of 71 µg CrVI/m$^3$ used for this purpose in Section 3.4. However, this is due to the likely conservative nature of the subacute $BMC_{10}$ of 29.6879 µg CrVI/m$^3$, which is very similar to the clear subchronic NOAEL of 25 µg CrVI/m$^3$ for the same endpoint (increased relative lung weight).

The $LOAEL_{HEC}$ of 120 µg CrVI/m$^3$ determined from an animal study represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study (22 h/d, 7d/week, for 90 d) or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The subchronic inhalation observed adverse effect level of 120 µg CrVI/m$^3$ is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the subchronic inhalation observed adverse effect level of 120 µg CrVI/m$^3$ and the chronic ReV of 0.22 µg CrVI/m$^3$ is a factor of approximately 545.

## 4.5.2 Chronic Carcinogenic Inhalation Observed Adverse Effect Level

A chronic (e.g., lifetime) carcinogenic effect level may be estimated based on an evaluation of the dose-response data. More specifically, the lowest air concentration/exposure corresponding to excess risk observed in the key epidemiological study(ies) can be considered the lowest level for which cancer effects in some individuals in the human population would be expected with reasonable certainty if exposed over a similar (or longer) exposure duration than those in the epidemiological study. In regard to cumulative CrVI exposure levels not associated with excess risk, Haney et al. (2012) indicate that cumulative exposures $\leq$ 0.817 mg CrVI/$m^3$-yr based on analyses of the Painesville cohort data do not appear to be associated with statistically increased risk and correspond to estimated average occupational air concentrations $\leq$ 88.8 µg CrVI/$m^3$. Conversely, based on these analyses, statistically elevated lung cancer risk appears to be associated with approximate average cumulative exposures $\geq$ 1.27 mg CrVI/$m^3$-yr (average cumulative exposure for the 1.00-1.63 mg CrVI/$m^3$-yr cumulative exposure group in Crump et al. 2003). This excess risk-associated cumulative exposure level is consistent with the finding of a statistically significant trend for increased lung cancer risk when the 0.5693-2.7352 mg CrVI/$m^3$-yr cumulative exposure group is included in the analysis of the Baltimore cohort data (Haney et al. 2012), although the midpoint of this range at 1.65 mg CrVI/$m^3$-yr is slightly higher. The lower cumulative exposure of $\geq$ 1.27 mg CrVI/$m^3$-yr based on analyses of the Crump et al. (2003) data corresponds to estimated average occupational air concentrations $\geq$ 138 µg CrVI/$m^3$ (i.e., 1.27 mg CrVI/$m^3$-yr / mean exposure duration of 9.2 years = 0.138 mg or 138 µg CrVI/$m^3$). This lower-end chronic (e.g., lifetime) carcinogenic effect level of 138 µg CrVI/$m^3$ is over 32,000 times greater than the $^{chronic}ESL_{nonthreshold(c)}$ of 0.0043 µg CrVI/$m^3$. An important caveat for observed adverse effect levels based on endpoints such as excess cancer risk which are demonstrated to result from long-term exposure is that they may only be appropriately compared to a long-term average air concentration over the same or longer exposure duration. The chronic carcinogenic inhalation observed adverse effect level of 138 µg CrVI/$m^3$ is provided for informational purposes only (TCEQ 2012).

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# Appendix A. Modeled Data and Results for Studies Not Included for Derivation of the URF

## *A.1 Painesville, Ohio: Luippold et al. (2003)*

Although not a preferred analysis due to fewer exposure groups than the Crump et al. (2003) analysis for dose-response assessment and the lack of any exposure lag, the cumulative exposure and SMR data which can be used with maximum likelihood estimation procedures and Poisson regression modeling to calculate the parameter (β) estimates based on Luippold et al. (2003) are given in Table 18 below. Beta (β) values and life-table (i.e., BEIR IV methodology , NRC 1988) analysis URF estimates with corresponding 1 in 100,000 excess risk air concentrations are given in Tables A-7 and A-8, respectively, at the end of this appendix.

**Table A-1. Cumulative Exposure and Lung Cancer Standardized Mortality Ratio (SMR) Data from Table 3 of Luippold et al. (2003)**

| Cumulative Exposure Range (mg CrVI/$m^3$-yr) [a] | Midpoint of Cumulative Exposure Range (mg CrVI/$m^3$-yr) [a] | Observed (O) | Expected (E) [b] | Lung Cancer SMR (O/E) | 95% Confidence Interval |
|---|---|---|---|---|---|
| 0-0.19 | 0.095 | 3 | 4.5 | 0.67 | 0.14-1.96 |
| 0.20-0.48 | 0.340 | 8 | 4.4 | 1.84 | 0.79-3.62 |
| 0.49-1.04 | 0.765 | 4 | 4.4 | 0.91 | 0.25-2.34 |
| 1.05-2.69 | 1.87 | 16 | 4.4 | 3.65 | **2.08-5.92** |
| 2.70-23 | 12.85 | 20 | 4.3 | 4.63 | **2.83-7.16** |

[a] Exposure not lagged.
[b] Based on Ohio rates.

## *A.2 Baltimore, Maryland: Gibb et al. (2000), Park et al. (2004), and Environ (2003)*

Due to concerns about this cohort (e.g., short exposure duration for many workers, confounding by smoking) and because the individual epidemiological data were available, more refined Cox proportional hazards modeling is preferred over using Poisson regression modeling on published summary data. However, for comparison and completeness the cumulative exposure and SMR data which can be used to calculate the parameter (β) estimates based on Gibb et al. (2000), Park et al. (2004), and Environ (2003) with maximum likelihood estimation procedures and Poisson regression modeling are given in Tables A-2, A-3, and A-4/5 below, respectively. Because Gibb et al. (2000) and Park et al. (2004) report cumulative exposure as $CrO_3$, the cumulative exposure levels were converted to their CrVI equivalents by multiplying the cumulative $CrO_3$ exposure by the ratio of the molecular weights (0.52 = 51.996 MW Cr / 99.99 MW $CrO_3$). While the preferred analysis is based on the preferred Cox proportional hazards modeling discussed within

the main body of this document, beta (β) values and life-table analysis URF estimates with corresponding 1 in 100,000 excess risk air concentrations are given in Tables A-7 and A-8, respectively, at the end of this appendix.

**Table A-2. Cumulative Exposure and Lung Cancer Standardized Mortality Ratio (SMR) Data from Table VI of Gibb et al. (2000)**

| Cumulative Exposure Range (mg $CrO_3/m^3$-yr) [a] | Mean of Cumulative Exposure Range (mg $CrO_3/m^3$-yr) [a] | Mean of Cumulative Exposure Range (µg CrVI/$m^3$-yr) [b] | Observed (O) | Expected (E) [c] | Lung Cancer SMR (O/E) |
|---|---|---|---|---|---|
| 0-0.00149 | 0.00045 | 0.234 | 26 | 27.1 | 0.96 |
| 0.0015-0.0089 | 0.0042 | 2.184 | 28 | 19.8 | 1.42 |
| 0.009-0.0769 | 0.030 | 15.60 | 30 | 19.1 | 1.57 |
| 0.077-5.25 | 0.449 | 233.5 | 38 | 17.0 | 2.24 |

[a] Exposure lagged 5 yrs.
[b] Mean of $CrO_3$ exposure range adjusted to CrVI content by multiplication by the ratio of molecular weights ($Cr/CrO_3$ or 51.996/99.99 = 0.52) and then to µg/$m^3$ by multiplying by 1000 µg/$m^3$ / 1 mg/$m^3$.
[c] Based on Maryland rates.

**Table A-3. Cumulative Exposure and Lung Cancer Standardized Mortality Ratio (SMR) Data from Table I of Park et al. (2004)**

| Cumulative Exposure Range (mg $CrO_3/m^3$-yr) [a] | Midpoint of Cumulative Exposure Range (mg $CrO_3/m^3$-yr) [a] | Midpoint of Cumulative Exposure Range (µg CrVI/$m^3$-yr) [b] | Observed (O) | Expected (E) [c] | Lung Cancer SMR (O/E) |
|---|---|---|---|---|---|
| 0-0.0282 | 0.0141 | 7.332 | 72 | 47.93 | 1.50 |
| 0.0282-0.0944 | 0.0613 | 31.88 | 14 | 7.64 | 1.83 |
| 0.0944-0.3715 | 0.23295 | 121.1 | 12 | 6.09 | 1.97 |
| 0.3715-1.0949 | 0.7332 | 381.3 | 12 | 5.13 | 2.34 |
| 1.0949-5.26 | 3.17745 | 1,652 | 12 | 1.90 | 6.32 |

[a] Exposure lagged 5 yrs.
[b] Midpoint of $CrO_3$ exposure range adjusted to CrVI content by multiplication by the ratio of molecular weights ($Cr/CrO_3$ or 51.996/99.99 = 0.52) and then to µg/$m^3$ by multiplying by 1000 µg/$m^3$ / 1 mg/$m^3$.
[c] Based on US rates.

**Table A-4. Cumulative Exposure and Lung Cancer Standardized Mortality Ratio (SMR) Data from Tables 3 and 4 of Environ (2003)**

| Cumulative Exposure Range (µg CrVI/$m^3$-yr) [a] | Mean of Cumulative Exposure Range (µg CrVI/$m^3$-yr) | Observed (O) | Expected (E) [b] | Lung Cancer SMR (O/E) |
|---|---|---|---|---|
| 0-0.151 | 0.0246151 | 12 | 13.37 | 0.898 |
| 0.151-0.686 | 0.394763 | 12 | 16.80 | 0.714 |
| 0.686-2.08 | 1.251266 | 12 | 13.55 | 0.886 |
| 2.08-4.004 | 2.962605 | 12 | 9.42 | 1.27 |
| 4.004-8.32 | 5.894943 | 12 | 7.32 | 1.64 |
| 8.32-18.2 | 12.405171 | 13 | 9.21 | 1.41 |
| 18.2-52 | 31.07919 | 13 | 9.05 | 1.44 |
| 52-182 | 104.809687 | 12 | 7.73 | 1.55 |
| 182-572 | 313.568768 | 12 | 7.66 | 1.57 |
| >572 | 979.307722 | 12 | 2.62 | 4.58 |

[a] Exposure lagged 5 yrs and groups based on approximately equal number of observed lung cancer mortalities.
[b] Based on Baltimore rates.

**Table A-5. Cumulative Exposure and Lung Cancer Standardized Mortality Ratio (SMR) Data from Tables 3 and 4 of Environ (2003)**

| Cumulative Exposure Range (µg CrVI/$m^3$-yr) [a] | Mean of Cumulative Exposure Range (µg CrVI/$m^3$-yr) | Observed (O) | Expected (E) [b] | Lung Cancer SMR (O/E) |
|---|---|---|---|---|
| 0.052 | 0.00531894 | 4 | 6.63 | 0.603 |
| 0.052-0.273 | 0.147145 | 11 | 11.58 | 0.950 |
| 0.273-0.65 | 0.455084 | 7 | 11.33 | 0.618 |
| 0.65-1.43 | 0.996418 | 11 | 9.58 | 1.15 |
| 1.43-3.12 | 2.189214 | 12 | 10.52 | 1.14 |
| 3.12-6.89 | 4.594251 | 11 | 8.95 | 1.23 |
| 6.89-16.12 | 10.722979 | 17 | 10.05 | 1.69 |
| 16.12-41.6 | 25.926783 | 12 | 8.57 | 1.40 |
| 41.6-143 | 81.508483 | 10 | 7.52 | 1.33 |
| >143 | 383.730927 | 27 | 11.99 | 2.25 |

[a] Exposure lagged 5 yrs and groups based on approximately equal number of person-yrs.
[b] Based on Baltimore rates.

## *A.3 Leverkusen and Uerdingen, Germany: Birk et al. (2006)*

Although not the preferred analysis due to including only two of the four low-dose plants (Applied Epidemiology 2002 includes all four), the cumulative exposure and SMR data which can be used with maximum likelihood estimation procedures and Poisson regression modeling to calculate the parameter (β) estimates based on Birk et al. (2006) are given in Table A-6 below. Beta (β) values and life-table analysis URF estimates with corresponding 1 in 100,000 excess risk air concentrations are given in Tables A-7 and A-8, respectively, at the end of this appendix.

**Table A-6. Lung Cancer Standardized Mortality Ratio (SMR) from Table 4 of Birk et al. (2006)**

| Cumulative Exposure in Urine (µg Cr/L-yr) | Midpoint Converted to Air Cumulative Exposure Equivalent [b] (µg CrVI/$m^3$-yr) | No Lag SMR (O/E) [c] | 10-Yr Lagged Exposure SMR (O/E) [c] | 20-Yr Lagged Exposure SMR (O/E) [c] |
|---|---|---|---|---|
| 0-39.9 | 25.97 | 0.36 (1/2.78) | 0.93 (6/6.45) | 1.10 (14/12.73) |
| 40-99.9 | 90.91 | 0.95 (4/4.21) | 0.78 (3/3.85) | 1.01 (2/1.98) |
| 100-199.9 | 194.81 | 0.94 (5/5.32) | 1.31 (5/3.82) | 1.10 (2/1.82) |
| 200-585 [a] | 509.74 | 2.09 (12/5.74) | 2.05 (8/3.90) | 2.74 (4/1.46) |

[a] Upper end of exposure range based on Figure 23 in Applied Epidemiology (2002).
[b] Midpoint of cumulative urinary exposure converted to the air CrVI equivalent using the urine-to-air conversion factor of 1 µg CrVI/$m^3$ / 0.77 µg/L.
[c] Number of expected (E) calculated as number of observed (O)/SMR.

## *A.4 β Values, URFs, and Corresponding 1 in 100,000 Excess Risk Air Concentrations for Non-Preferred Analyses*

The following Table A-7 contains the parameter (β values) estimated using maximum likelihood estimation procedures and Poisson regression modeling for study analyses not preferred due to use of a superior study or model for the given cohort (i.e., Crump et al. 2003 for the Painesville cohort, larger 4-plant Applied Epidemiology 2002 study for low-dose workers, better Cox proportional hazards modeling based on the individual epidemiological data for the Baltimore cohort).

**Table A-7. β Values and Standard Error (SE) for Non-Preferred Analyses Based on Lung Cancer Mortality**

| Study | Exposure Lag | SE | β (95% LCL) [a, b] | β (MLE) [a] | β (95% UCL) [a, c] |
|---|---|---|---|---|---|
| Luippold et al. (2003) Painesville, OH | None | 9.77E-05 | 5.12E-05 | 2.12E-04 | 3.73E-04 |
| Gibb et al. (2000) Baltimore, MD | 5-yr | 1.59E-03 | 9.56E-04 | 3.56E-03 | 6.17E-03 |
| Park et al. (2004) Baltimore, MD | 5-yr | 7.14E-04 | 6.60E-04 | 1.83E-03 | 3.01E-03 |
| Environ (2003) [d] Baltimore, MD | 5-yr | 1.10E-03 | 1.09E-03 | 2.89E-03 | 4.69E-03 |
| | | 1.25E-03 | 9.18E-04 | 2.98E-03 | 5.04E-03 |
| Birk et al. (2006) Leverkusen and Uerdingen, Germany | None | 8.81E-03 | -6.76E-03 | 7.74E-03 | 2.22E-02 |
| | 10-yr | 3.06E-03 | -1.94E-03 | 3.10E-03 | 8.13E-03 |
| | 20-yr | 3.10E-03 | -2.29E-03 | 2.82E-03 | 7.92E-03 |

[a] Estimates are increase in relative risk per unit of $\mu g/m^3$-yr.
[b] 95%LCL = β - (1.645 × SE).
[c] 95%UCL = β + (1.645 × SE).
[d] Top and bottom row values are based on data from exposure groups with approximately equal number of observed lung cancer mortalities and person-yrs per group, respectively.

The following Table A-8 contains the URFs and corresponding 1 in 100,000 excess risk air concentrations estimated using life-table (i.e., BEIR IV methodology , NRC 1988) analyses which are not preferred due to use of a superior study or model for the given cohort.

**Table A-8. URFs and Air Concentrations Corresponding to 1 in 100,000 Excess Lung Cancer Mortality for Non-Preferred Analyses**

| Study | Exposure Lag | Background Rates | URF (95% LCL) [a] Air Concentration @ 1 in 100,000 Excess Risk | URF (MLE) [a] Air Concentration @ 1 in 100,000 Excess Risk | URF (95% UCL) [a] Air Concentration @ 1 in 100,000 Excess Risk |
|---|---|---|---|---|---|
| Luippold et al. (2003) Painesville, OH | None | TX | 1.70E-04 per µg/m$^3$<br>5.87E-02 µg/m$^3$ | 7.05E-04 per µg/m$^3$<br>1.42E-02 µg/m$^3$ | 1.24E-03 per µg/m$^3$<br>8.06E-03 µg/m$^3$ |
| | | US | 1.83E-04 per µg/m$^3$<br>5.47E-02 µg/m$^3$ | 7.57E-04 per µg/m$^3$<br>1.32E-02 µg/m$^3$ | 1.33E-03 per µg/m$^3$<br>7.51E-03 µg/m$^3$ |
| Gibb et al. (2000) Baltimore, MD | 5-yr | TX | 2.93E-03 per µg/m$^3$<br>3.42E-03 µg/m$^3$ | 1.09E-02 per µg/m$^3$<br>9.17E-04 µg/m$^3$ | 1.89E-02 per µg/m$^3$<br>5.30E-04 µg/m$^3$ |
| | | US | 3.14E-03 per µg/m$^3$<br>3.18E-03 µg/m$^3$ | 1.17E-02 per µg/m$^3$<br>8.54E-04 µg/m$^3$ | 2.03E-02 per µg/m$^3$<br>4.93E-04 µg/m$^3$ |
| Park et al. (2004) Baltimore, MD | 5-yr | TX | 2.02E-03 per µg/m$^3$<br>4.95E-03 µg/m$^3$ | 5.60E-03 per µg/m$^3$<br>1.79E-03 µg/m$^3$ | 9.21E-03 per µg/m$^3$<br>1.09E-03 µg/m$^3$ |
| | | US | 2.17E-03 per µg/m$^3$<br>4.61E-03 µg/m$^3$ | 6.01E-03 per µg/m$^3$<br>1.66E-03 µg/m$^3$ | 9.89E-03 per µg/m$^3$<br>1.01E-03 µg/m$^3$ |
| Environ (2003) [b] Baltimore, MD | 5-yr | TX | 3.34E-03 per µg/m$^3$<br>3.00E-03 µg/m$^3$ | 8.84E-03 per µg/m$^3$<br>1.13E-03 µg/m$^3$ | 1.44E-02 per µg/m$^3$<br>6.97E-04 µg/m$^3$ |
| | | US | 3.58E-03 per µg/m$^3$<br>2.79E-03 µg/m$^3$ | 9.49E-03 per µg/m$^3$<br>1.05E-03 µg/m$^3$ | 1.54E-02 per µg/m$^3$<br>6.49E-04 µg/m$^3$ |
| Birk et al. (2006) Leverkusen and Uerdingen, Germany | None | TX | NA | 2.57E-02 per µg/m$^3$<br>3.89E-04 µg/m$^3$ | 7.38E-02 per µg/m$^3$<br>1.35E-04 µg/m$^3$ |
| | | US | NA | 2.76E-02per µg/m$^3$<br>3.62E-04 µg/m$^3$ | 7.93E-02per µg/m$^3$<br>1.26E-04 µg/m$^3$ |
| | 10-yr | TX | NA | 8.66E-03 per µg/m$^3$<br>1.15E-03 µg/m$^3$ | 2.27E-02 per µg/m$^3$<br>4.40E-04 µg/m$^3$ |
| | | US | NA | 9.29E-03 per µg/m$^3$<br>1.08E-03 µg/m$^3$ | 2.44E-02 per µg/m$^3$<br>4.10E-04 µg/m$^3$ |
| | 20-yr | TX | NA | 6.38E-03 per µg/m$^3$<br>1.57E-03 µg/m$^3$ | 1.79E-02 per µg/m$^3$<br>5.58E-04 µg/m$^3$ |
| | | US | NA | 6.84E-03 per µg/m$^3$<br>1.46E-03 µg/m$^3$ | 1.92E-02 per µg/m$^3$<br>5.21E-04 µg/m$^3$ |

[a] Calculation of air concentrations at 1 in 100,000 excess risk used the unrounded URF.
NA = as the 95%LCL β value was negative, suggesting zero excess risk, calculation of an air concentration at 1 in 100,000 excess risk was not possible.
[b] The β value with the lowest associated SE/variance was used as the best estímate of the parameter (β based on approximately equal number of observed lung cancer mortalities per exposure group).

# Appendix B. Linear Multiplicative Relative Risk Model (Crump and Allen 1985)

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This appendix provides a general overview of the multiplicative Poisson relative risk model. The multiplicative relative risk Poisson regression models are well-known models frequently used in the analyses of epidemiological data. This appendix is not a comprehensive study of multiplicative relative risk models or Poisson regression models. Rather, this appendix is meant as a simple exposition identifying the specific model applied to the nickel risk characterization in this DSD. For more Poisson regression modeling, Feldman and Valdez-Flores (2010) provide a basic introduction to Poisson regression models and include simple examples applied to engineering. Crump and Allen (1995) provide a more in-depth development of additive and multiplicative Poisson regression models applied to health risk assessment. This later reference also discusses calculations of excess risks once a model has been fitted to data and a target population, with its corresponding background hazard rates and risks from competing causes, has been defined.

## *B.1 Adjustments for Possible Differences Between the Population Background Cancer Rate and the Cohort's Cancer Rate in the Relative Risk Model*

The USEPA (1986) uses a relative risk model in their risk assessment for nickel to fit the observed number of cancer deaths in a cohort study. Section 8.3.3.2.1.1 in USEPA (1986) describes the equations used to find the slope and the variance of the slope in the relative risk model. The model presented by EPA can be easily solved analytically because it estimates only one parameter (i.e., the slope). This simple model, however, does not adjust for possible discrepancies between the cohort's cancer rate and the reference population background cancer rate. A model that uses reference population background cancer rates to fit the cohort's observed cancer rates should adjust for the possibility of discrepancies between the background cancer rates in the reference population and the cohort.

Crump and Allen (1985) discuss the relative risk model with an extra factor that accounts for the possibility of different background rates in an epidemiological cohort and its reference population. This extra factor may adjust for issues like the healthy worker effect, the difference between internally and externally derived background cancer rates, covariate effects not explicitly incorporated in the summary epidemiological data, etc. For example, EPA's model

with modified notation for the nickel carcinogenic assessment (USEPA 1986), the multiplicative or relative risk model can be extended from

$$E(O_j) = E_{oj} \times (1 + \beta \times d_j)$$

to

$$E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$$

where the $\alpha$ term adjusts for any possible difference between the population's background cancer rates and the cohort's observed cancer rates.

In the equations above the variables are:

$E(O_j)$ = expected number of lung cancer deaths for exposure group j predicted by the model;

$E_{oj}$ = expected number of background lung cancer deaths for exposure group j based on the reference population background cancer rates;

$\beta$ = multiplicative factor by which background risk increases with cumulative exposure;

$d_j$ = cumulative exposure for exposure group j;

$\alpha$ = multiplicative factor that accounts for differences in cancer mortality background rates between the study cohort and the reference population.

## *B.2 Estimating the Slope Parameter, β, in the Relative Risk Model Adjusting for Differences in Background Rates*

Poisson regression is a standard modeling technique in epidemiological studies. Poisson regression relies on the assumption that the number of cancer deaths in a dose group follows a Poisson distribution with mean equal to the expected number of cancer deaths and uses the maximum likelihood estimation procedure for the estimation for the parameters $\alpha$ and $\beta$ in the model.

The Poisson distribution that describes probabilistically the number of cancers observed in a group is given by:

$$P(x) = \lambda^x \times e^{-\lambda} / x!,$$

where P(x) is the probability of observing x cancers, x is the number of cancer deaths actually observed, x! = x ( x-1) (x-2) … 1, and $\lambda$ is the expected number of cancers in the group. Thus, for dose group j, $x_j=O_j$ and $\lambda_j= E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$. That is, for each group j of person-years with average dose $d_j$, the observed number of cancer deaths in the dose interval ($O_j$) follows a Poisson distribution with parameter $\lambda_j= E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$ and the likelihood of this is given by,

$$P(O_j) = \lambda_j^{Oj} \times e^{-\lambda j} / O_j!.$$

The likelihood (L) is given by the product of the likelihoods of observing the number of cancer deaths in each dose group. That is,

$$L = P(O_1) \times P(O_2) \times \ldots.$$

or, equivalently,

$$L = (\lambda_1^{O1} \times e^{-\lambda 1} / O_1!) \times (\lambda_2^{O2} \times e^{-\lambda 2} / O_2!) \times \ldots.$$

where $O_j$ is the number of cancer cases observed for the person-years with cumulative exposures equal to $d_i$. Substituting the value of $\lambda_j$ by $\alpha \times E_{oj} \times (1 + \beta \times d_j)$ in the equation above, the likelihood is expressed as follows:

$$L = \prod [\alpha \times E_{oj} \times (1 + \beta \times d_j)]^{Oj} \times \exp\{-[\alpha \times E_{oj} \times (1 + \beta \times d_j)]\} / O_j!$$

where the symbol $\prod$ indicates that it is the product over all dose groups j=1,2,… and exp{.} is the base of the natural logarithm (e) raised to the power in the braces.

The maximum likelihood estimates of $\alpha$ and $\beta$ can then be obtained by selecting the values of $\alpha$ and $\beta$ that maximize the value of L. Finding the values of $\alpha$ and $\beta$ that maximize the value of the likelihood L cannot be determined using a close-form solution as that offered by USEPA (1986), because here there are two variables, as opposed to only one being estimated by USEPA. However, any routine that can maximize non-linear functions of more than one variable can be used to calculate the maximum likelihood estimates of $\alpha$ and $\beta$.

The parameters $\alpha$ and $\beta$ that maximize the likelihood function given above also maximize the logarithm of the likelihood because the logarithm is a monotone function. The logarithm of the likelihood (LL) of the function given above is,

$$LL = \sum \{ O_j \times \ln[\alpha \times E_{oj} \times (1 + \beta \times d_j)] - [\alpha \times E_{oj} \times (1 + \beta \times d_j)] - \ln(O_j!) \}$$

where the symbol $\sum$ indicates that it is the sum over all dose groups j=1,2,… and ln(x) is the natural logarithm of x. The LL function can also be written as,

$$LL = \sum \{ O_j \times \ln(\alpha) + O_j \times \ln(E_{oj}) + O_j \times \ln(1 + \beta \times d_j) - [\alpha \times E_{oj} \times (1 + \beta \times d_j)] - \ln(O_j!) \}.$$

Note that the terms $O_j \times \ln(E_{oj})$ and $\ln(O_j!)$ do not depend on the values of $\alpha$ and $\beta$, and hence, the values of $\alpha$ and $\beta$ that maximize the LL also maximize the following simplified LL function:

$$LL = \sum \{ O_j \times \ln(\alpha) + O_j \times \ln(1 + \beta \times d_j) - [\alpha \times E_{oj} \times (1 + \beta \times d_j)] \}.$$

Finally, the maximum likelihood estimates of $\alpha$ and $\beta$ can also be obtained by solving for $\alpha$ and $\beta$ in the following system of equations:

$$\frac{\partial LL}{\partial \alpha} = \sum \{ O_j/\alpha - E_{oj} \times (1 + \beta \times d_j) \} = 0$$

$$\frac{\partial LL}{\partial \beta} = \sum \{ (O_j \times d_j) / (1 + \beta \times d_j) - \alpha \times E_{oj} \times d_j \} = 0$$

where $\partial LL/\partial\alpha$ and $\partial LL/\partial\beta$ are the partial derivatives of the logarithm of the likelihood with respect to $\alpha$ and $\beta$, respectively.

## *B.3 Estimating the Asymptotic Variance for the Slope Parameter in the Relative Risk Model*

The system of equations of the partial derivatives of the logarithm of the likelihood given in the previous section can be used to estimate the asymptotic variance of the maximum likelihood estimates of $\alpha$ and $\beta$. The variance-covariance matrix of the parameters $\alpha$ and $\beta$ is approximated by

$$Cov(\alpha,\beta) = -\begin{pmatrix} \partial^2 LL/\partial\alpha^2 & \partial^2 LL/\partial\alpha\partial\beta \\ \partial^2 LL/\partial\alpha\partial\beta & \partial^2 LL/\partial\beta^2 \end{pmatrix}^{-1}$$

where $[.]^{-1}$ is the inverse of the matrix, $\partial^2 LL/\partial\alpha^2$ is the second partial derivative of the logarithm of the likelihood with respect to $\alpha$, $\partial^2 LL/\partial\beta^2$ is the second partial derivative of the logarithm of the likelihood with respect to $\beta$, and $\partial^2 LL/\partial\alpha\partial\beta$ is the partial derivative of the logarithm of the likelihood with respect to $\alpha$ and $\beta$. The approximation of the covariance is then given by

$$Cov(\alpha,\beta) = -\begin{pmatrix} \partial^2 LL/\partial\beta^2 & -\partial^2 LL/\partial\alpha\partial\beta \\ -\partial^2 LL/\partial\alpha\partial\beta & \partial^2 LL/\partial\alpha^2 \end{pmatrix} / \text{Determinant}$$

where

$$\text{Determinant} = 1 \; / \; [\; \partial^2 LL/\partial\alpha^2 \times \partial^2 LL/\partial\beta^2 - (\partial^2 LL/\partial\alpha\partial\beta)^2 \;]$$

The second-order derivatives used for the estimation of the variance-covariance matrix are:

$$\frac{\partial^2 LL}{\partial \alpha^2} = \sum -O_j/\alpha^2$$

$$\frac{\partial^2 LL}{\partial \beta^2} = \sum -(O_j \times d_j^2) / (1 + \beta \times d_j)^2$$

$$\frac{\partial^2 LL}{\partial \alpha \partial \beta} = \sum -E_{oj} \times d_j$$

A better asymptotic variance calls for substituting the variance-covariance matrix of $\alpha$ and $\beta$ by the expected value of the above matrix. That is, by replacing the observed number of cancer deaths in a dose group j ($O_j$) by its expected value (i.e., $E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$). After substituting $O_i$ by $\alpha \times E_{oj} \times (1 + \beta \times d_j)$ in the second-order derivatives and the variance-covariance matrix given above and some simplification, the better approximation of $Cov(\alpha,\beta)$ is given by:

$$Cov(\alpha,\beta) = \begin{pmatrix} \sum E_{oj} \times (1 + \beta \times d_j)/\alpha & \sum E_{oj} \times d_j \\ \sum E_{oj} \times d_j & \alpha \times \sum (E_{oj} \times d_j^2) / (1 + \beta \times d_j) \end{pmatrix}^{-1}$$

The determinant for the matrix is

$$\text{Determinant} = [ \sum E_{oj} \times (1 + \beta \times d_j) ] \times [ \sum (E_{oj} \times d_j^2) / (1 + \beta \times d_j) ] - ( \sum E_{oj} \times d_j )^2$$

and the variance of the maximum likelihood estimate of $\alpha$ is

$$var(\alpha) = [ \alpha \times \sum (E_{oj} \times d_j^2) / (1 + \beta \times d_j) ] \ / \text{Determinant},$$

while the variance of the maximum likelihood estimate of $\beta$ is

$$var(\beta) = [ \sum E_{oj} \times (1 + \beta \times d_j)/\alpha ] / \text{Determinant},$$

and the standard errors (SE) of the estimated parameters are the square root of their respective variances.

## *References*

Crump, KS and BC Allen. 1985. Methods of Quantitative Risk Assessment Using Occupational Studies. *The Am* Stat 39: 442-450.

Feldman, R. M and C. Valdez-Flores, Applied Probability and Stochastic Processes, Second Edition, Springer-Verlag Berlin Heidelberg, 2010.

United States Environmental Protection Agency (USEPA). 1986 Health Assessment Document for Nickel and Nickel Compounds. EPA/600/8-83/012FF.

# Appendix C. Lung Cancer Mortality Rates and Survival Probabilities

| | US Total Population 2005-2009 | Texas Statewide Population 2005-2009 |
|---|---|---|
| | Total Lung Cancer Mortality Rates per 100,000 [1] | Total Lung Cancer Mortality Rates per 100,000 [2] |
| Years | Rate | Rate |
| 00 | 0.0 | 0.0 |
| 01-04 | 0.0 | 0.0 |
| 05-09 | 0.0 | 0.0 |
| 10-14 | 0.0 | 0.0 |
| 15-19 | 0.0 | 0.0 |
| 20-24 | 0.1 | 0.0 |
| 25-29 | 0.2 | 0.0 |
| 30-34 | 0.5 | 0.4 |
| 35-39 | 1.8 | 1.4 |
| 40-44 | 6.8 | 5.5 |
| 45-49 | 19.2 | 15.7 |
| 50-54 | 39.1 | 33.6 |
| 55-59 | 69.5 | 62.0 |
| 60-64 | 128.6 | 119.5 |
| 65-69 | 210.7 | 203.1 |
| 70-74 | 290.7 | 276.1 |
| 75-79 | 356.0 | 349.1 |
| 80-84 | 376.9 | 357.6 |
| 85+ | 314.9 | 295.4 |

[1] Table 15.10, Surveillance, Epidemiology, and End Results, Cancer Statistics Review 1975-2009. Available at http://seer.cancer.gov/csr/1975_2009_pops09/results_merged/sect_15_lung_bronchus.pdf.

[2] Texas age-specific lung and bronchus 2005-2009 cancer rates, Texas Department of State Health Services (Available at http://www.dshs.state.tx.us/tcr/data.shtm).

| 2008 US All Life Tables [1] | | 2010 Total Texas Population Life Tables [2] | |
|---|---|---|---|
| **Age** | **Survival** | **Age** | **Survival** |
| 0 | 1 | 0 | 1 |
| 1 | 0.99341 | 1 | 0.99388 |
| 5 | 0.99228 | 5 | 0.99277 |
| 10 | 0.99167 | 10 | 0.99222 |
| 15 | 0.99089 | 15 | 0.9915 |
| 20 | 0.98804 | 20 | 0.98901 |
| 25 | 0.98341 | 25 | 0.98456 |
| 30 | 0.97863 | 30 | 0.97999 |
| 35 | 0.97328 | 35 | 0.97489 |
| 40 | 0.96639 | 40 | 0.96814 |
| 45 | 0.95602 | 45 | 0.95876 |
| 50 | 0.93999 | 50 | 0.94351 |
| 55 | 0.91635 | 55 | 0.91963 |
| 60 | 0.88356 | 60 | 0.88587 |
| 65 | 0.8372 | 65 | 0.83994 |
| 70 | 0.77153 | 70 | 0.77564 |
| 75 | 0.68006 | 75+ | 0.68848 |
| 80 | 0.55562 | | |
| 85 | 0.39797 | | |

[1] Arias, E., United States Life Tables, 2008. National Vital Statistics Reports. 2012. 61(3): 5, Table C. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_03.pdf.

[2] Table 4, Life Tables, Texas 2010. Texas Department of State Health Services. Available at http://www.dshs.state.tx.us/chs/vstat/vs10/t24.shtm.

# Appendix D. Supplementary URF and 1 in 100,000 Excess Risk Air Concentration Calculations based on US Lung Cancer Mortality Rates and Survival Probabilities

## *D.1 URFs Based on US Rates*

Texas background lung cancer mortality rates and survival probabilities are preferred by the TCEQ for calculating a URF and the corresponding 1 in 100,000 excess air concentration. However, similar results are obtained using US rates and are provided in Tables 26 and 27 below for comparison purposes (shaded values represent the preferred analyses based on the key and supporting studies as discussed in Section 4.2.3.1.6).

**Table D-1. URFs and Air Concentrations Corresponding to 1 in 100,000 Excess Lung Cancer Mortality**

| Study | Exposure Lag | Background Rates | URF (95% LCL) [a]<br><br>Air Concentration @ 1 in 100,000 Excess Risk | URF (MLE) [a]<br><br>Air Concentration @ 1 in 100,000 Excess Risk | URF (95% UCL) [a]<br><br>Air Concentration @ 1 in 100,000 Excess Risk |
|---|---|---|---|---|---|
| Crump et al. (2003) Painesville, OH | 5-yr | US | 3.45E-04 per µg/m$^3$<br>2.90E-02 µg/m$^3$ | **2.08E-03 per µg/m$^3$**<br>**4.80E-03 µg/m$^3$** | 3.81E-03per µg/m$^3$<br>2.62E-03 µg/m$^3$ |
| Applied Epidemiology (2002) Leverkusen and Uerdingen, Germany, Corpus Christi, TX and Castle Hayne, NC | None | US | NA | 8.11E-03 per µg/m$^3$<br>1.23E-03 µg/m$^3$ | 2.33E-02 per µg/m$^3$<br>4.30E-04 µg/m$^3$ |
| | 10-yr | US | NA | **4.65E-03 per µg/m$^3$**<br>**2.15E-03 µg/m$^3$** | 1.41E-02 per µg/m$^3$<br>7.11E-04 µg/m$^3$ |
| | 20-yr | US | NA | 4.61E-03 per µg/m$^3$<br>2.17E-03 µg/m$^3$ | 1.44E-02 per µg/m$^3$<br>6.97E-04 µg/m$^3$ |

[a] Calculation of air concentrations at 1 in 100,000 excess risk used the unrounded URF.
NA = as the 95%LCL β value was negative, suggesting zero excess risk, calculation of an air concentration at 1 in 100,000 excess risk was not possible.

**Table D-2. Cox Model URFs and Air Concentrations Corresponding to 1 in 100,000 Excess Lung Cancer Mortality based on Gibb et al. (2000) Data for the Baltimore Cohort with Smoking as a Covariate and Optimum, 5- and 0-Year Exposure Lags**

| Worker Group | Exposure Lag | Background Rates | URF (95% LCL) [a] Air Concentration @ 1 in 100,000 Excess Risk | URF (MLE) [a] Air Concentration @ 1 in 100,000 Excess Risk | URF (95% UCL) [a] Air Concentration @ 1 in 100,000 Excess Risk |
|---|---|---|---|---|---|
| All Workers | 6.3-yr (optimum) | US | 2.10E-03 per µg/m$^3$ 4.77E-03 µg/m$^3$ | 3.35E-03 per µg/m$^3$ 2.98E-03 µg/m$^3$ | 4.60E-03 per µg/m$^3$ 2.17E-03 µg/m$^3$ |
| | 5-yr | US | 2.09E-03 per µg/m$^3$ 4.79E-03 µg/m$^3$ | 3.37E-03 per µg/m$^3$ 2.97E-03 µg/m$^3$ | 4.64E-03 per µg/m$^3$ 2.15E-03 µg/m$^3$ |
| | None | US | 2.09E-03 per µg/m$^3$ 4.78E-03 µg/m$^3$ | 3.47E-03 per µg/m$^3$ 2.89E-03 µg/m$^3$ | 4.83E-03 per µg/m$^3$ 2.07E-03 µg/m$^3$ |
| Only Workers ≥ 0.5 Years of Employment | 6.7-yr (optimum) | US | 1.30E-03 per µg/m$^3$ 7.67E-03 µg/m$^3$ | 2.75E-03 per µg/m$^3$ 3.63E-03 µg/m$^3$ | 4.21E-03 per µg/m$^3$ 2.37E-03 µg/m$^3$ |
| | 5-yr | US | 1.29E-03 per µg/m$^3$ 7.76E-03 µg/m$^3$ | 2.77E-03 per µg/m$^3$ 3.61E-03 µg/m$^3$ | 4.24E-03 per µg/m$^3$ 2.36E-03 µg/m$^3$ |
| | None | US | 1.17E-03 per µg/m$^3$ 8.57E-03 µg/m$^3$ | 2.77E-03 per µg/m$^3$ 3.61E-03 µg/m$^3$ | 4.35E-03 per µg/m$^3$ 2.30E-03 µg/m$^3$ |
| Only Workers ≥ 1.0 Years of Employment | 7.4-yr (optimum) | US | 1.22E-03 per µg/m$^3$ 8.20E-03 µg/m$^3$ | **2.75E-03 per µg/m$^3$ 3.64E-03 µg/m$^3$** | 4.29E-03 per µg/m$^3$ 2.33E-03 µg/m$^3$ |
| | 5-yr | US | 1.18E-03 per µg/m$^3$ 8.44E-03 µg/m$^3$ | 2.76E-03 per µg/m$^3$ 3.63E-03 µg/m$^3$ | 4.34E-03 per µg/m$^3$ 2.30E-03 µg/m$^3$ |
| | None | US | 9.95E-04 per µg/m$^3$ 1.00E-02 µg/m$^3$ | 2.70E-03 per µg/m$^3$ 3.70E-03 µg/m$^3$ | 4.39E-03 per µg/m$^3$ 2.28E-03 µg/m$^3$ |

[a] Calculation of air concentrations at 1 in 100,000 excess risk used the unrounded URF.

## *D.2 Final URF based on US Rates*

Similar to Section 4.2.3.2, a final URF based on US lung cancer mortality and survival rates may be calculated. This URF is equal to the weighted average (using weight percents expressed in decimal form) of the two individual preferred URF analyses:

Final URF = Crump et al. (2003) URF × overall weight for Crump et al. (2003) + Gibb et al. (2000) URF × overall weight for Gibb et al. (2000)

= 2.08E-03 × 0.444 + 2.75E-03 × 0.556

= 2.45E-03 per µg CrVI/$m^3$

Thus, the final URF based on US rates when rounded to two significant figures is 2.4E-03 per µg CrVI/$m^3$. Based on this URF the resulting air concentration at a 1 in 100,000 excess lung cancer risk rounded to two significant figures is 0.0042 µg CrVI/$m^3$.

# Appendix E. Uncertainty Analysis

This appendix presents an uncertainty analysis concerning the derivation of the inhalation URF and the $^{chronic}ESL_{nonthreshold(c)}$. Many of the areas discussed are common to risk assessments utilizing epidemiological studies.

## *E.1 Dose-Response Modeling*

The $^{chronic}ESL_{nonthreshold(c)}$ of 4.3E-03 µg CrVI/$m^3$ is based on best estimates of parameters in models fit to the most appropriate available epidemiological data of workers exposed to CrVI. The derivation of the final $^{chronic}ESL_{nonthreshold(c)}$ includes the use of the best TCEQ statistical analyses for the given epidemiological data (e.g., Cox model, optimal exposure lag) so as not to increase the uncertainty and variability already present in the epidemiological data. In regard to the remaining variability and uncertainty, the final $^{chronic}ESL_{nonthreshold(c)}$ includes some degree of variability and uncertainty inherent in all epidemiological studies that cannot be eliminated or further reduced with the available data. The excess risk of lung cancer mortality for the final $^{chronic}ESL_{nonthreshold(c)}$ could be as high as approximately 1.6 in 100,000 if the URF (95% UCL) values from the preferred analyses were weighted for the final URF instead of the maximum likelihood estimates, and could be as low as around 0.33 in 100,000 if the β (95% LCL) values from the preferred analyses were weighted for the final URF instead of the maximum likelihood estimates. The sections below highlight particular areas of uncertainty due to different dose-response modeling methods.

For the Crump et al. (2003) study, dose-response modeling was conducted with a multiplicative relative risk model and linear Poisson regression modeling including a term to account for differences between study and reference population background mortality rates. Linear Poisson regression is commonly used to investigate dose-response relationships derived from occupational cohort epidemiologic studies based on mortality and is generally considered to be biologically-plausible for lung cancer. The MLE of the intercept for the fitted model is greater than one (1.15), suggesting that the reported SMRs may be slightly elevated due to factors other than CrVI exposure. For the Gibb et al. (2000) study, a better Cox proportional hazards model was used with smoking as a covariate as the TCEQ had concerns about the data including a large portion of very short-term workers (e.g., < 6 months) and the study not having adjusted for smoking in their SMR analysis. On the other hand, Crump et al. had evaluated available smoking data and did not find that smoking had an appreciable effect on CrVI carcinogenic potency estimates for the Painesville, Ohio cohort.

The respective models for these cohorts were used to calculate the MLE β using cumulative exposure as the dose metric. Cumulative exposure is the only common measure available from the key studies. While target tissue dose in the lung (i.e., accounting for the kinetics of inhalation, deposition/retention, elimination/reduction, and dissolution over time to ultimately estimate absorbed dose) may be a better dose metric for dose-response assessment and

accounting for the various forms of CrVI, currently no such model is available to estimate lung tissue dose among these CrVI-exposed workers. Application of the URF derived using cumulative exposure to CrVI as the dose metric inherently treats all CrVI compounds as toxicologically equivalent based on CrVI content. Although this practice is consistent with the TCEQ considering CrVI compounds as a group to be "Carcinogenic to Humans" and is necessary as available data for the Baltimore and Painesville cohorts do not allow separate dose-response analyses of soluble and insoluble CrVI compounds, reported results indicate that there are likely differences among CrVI compounds in regard to carcinogenic potency (i.e., sparingly soluble CrVI compounds are likely more potent).

URFs calculated with slope β parameter estimates for the 95% LCL, MLE, and 95% UCL were reported for each analysis in order to provide information on uncertainty in the risk estimates based on the different cohorts. Regarding the preferred URFs from each study:

- For the Crump et al. (2003) study, URF estimates ranged from 3.21E-04 per $\mu g/m^3$ (95% LCL) to 3.55E-03 per $\mu g/m^3$ (95% UCL), a ratio of around 11, with the preferred URF of 1.94E-03 per $\mu g/m^3$ (MLE) being within a factor of 2 of the 95% UCL URF; and
- For the Gibb et al. (2000) study, URF estimates for workers employed at least a year with optimum lag and smoking as a covariate (the preferred analysis) ranged from 1.14E-03 per $\mu g/m^3$ (95% LCL) to 4.00E-03 per $\mu g/m^3$ (95% UCL), a ratio of around 3.5, with the preferred URF of 2.56E-03 per $\mu g/m^3$ (MLE) being within a factor of 1.6 of the 95% UCL URF. For comparison, URF estimates for all workers with optimum lag and smoking as a covariate ranged from 1.96E-03 per $\mu g/m^3$ (95% LCL) to 4.30E-03 per $\mu g/m^3$ (95% UCL), a ratio of around 2.2, with the MLE URF of 3.13E-03 per $\mu g/m^3$ for all workers being a factor of 1.2 apart from the preferred MLE URF for workers employed at least one year.

For the preferred analyses of the two key studies, the ratio of the URF (95% UCL) to the preferred URF (MLE) ranged from 1.56 for Gibb et al. (2000) to 1.83 for Crump et al. (2003), which indicates the precision of the estimates. Additionally, across the studies the ratio of the highest preferred URF (MLE) of 2.56E-03 per $\mu g/m^3$ (from Gibb et al. 2000) to the lowest preferred URF (MLE) of 1.94E-03 per $\mu g/m^3$ (from Crump et al. 2003) was 1.3, which indicates good agreement between dose-response modeling from the different cohort studies.

## *E.2 Estimating Risks for the General Population from Occupational Workers*

Human studies are preferred over animal studies to develop toxicity factors for chemicals to avoid uncertainty due to interspecies differences. However, as in the current case, human carcinogenic studies are usually epidemiological occupational studies, which themselves are subject to the following inherent uncertainties:

- The relationship between lung cancer mortality and exposure to CrVI was evaluated based on healthy male workers employed in chromate production plants (i.e., only 4 women were in the Painesville cohort and none were included in the Baltimore cohort). The

model may underestimate excess risks for subpopulations that are particularly more sensitive than chromate workers to CrVI exposures. Although workers are often healthier than the general population, the approach used by the TCEQ estimates how the risk of lung cancer changes with exposure to CrVI while adjusting for the differences between the workers and the general population background lung cancer rates (i.e., Texas general population lung cancer incidence and mortality background rates were used as opposed to those for the workers). The estimates of excess risks based on the derived models apply to the target population (e.g., Texas all sexes and all races) whose background lung cancer rates and survival probabilities are used in the estimation of the extra risks. The assumption being made in the calculation of the URFs is that the increase in the relative risk per unit increase in the dose metric (cumulative exposure) is the same for the workers and for the target population. Subpopulations with higher background lung cancer mortality rates will have higher estimated URFs.

- The general population does not have the same exposure levels as occupational workers, who are generally exposed to significantly higher concentrations. For example, the estimated average exposure (138 µg CrVI/$m^3$ = 1.27 mg CrVI/$m^3$-yr / estimated 9.2 yr average exposure duration x 1,000 µg/mg) for the lowest exposure group with significantly elevated lung cancer risk in Crump et al. (2003) is approximately 800,000-23,000,000 times higher than long-term average CrVI ambient air concentrations measured at various sites in Texas (5.9E-06 to 1.7E-04 µg CrVI/$m^3$). Lung cancer risk in chromate workers exposed to high concentrations of CrVI is elevated based on high occupational exposure, which is an important consideration if dose rate plays an important role in overwhelming protective mechanisms (e.g., lung CrVI extracellular reductive capacity) and producing excess risk.
- In addition, occupational workers may be exposed to a different CrVI species profile (e.g., more sparingly soluble and carcinogenically potent forms in both absolute and relative amounts) and/or particle size distribution than the general population.

## *E.3 Uncertainty Due to Potential Exposure Estimation Error*

Results from epidemiology studies have uncertainties because of potential exposure estimation error or insufficient characterization of exposure data (e.g., range, peak, mean exposure levels). For example, while daily measurements from personal air samples for each cohort member would be ideal, epidemiologists must estimate exposure based on professional judgment and whatever exposure data are available (e.g., area measurements). The airborne CrVI concentration data from the Painesville plant span nearly 30 years and provide more than 800 data points from 23 surveys for evaluating historical exposure of the 482 worker cohort. However, as is common for epidemiology studies the exposure data have various limitations (e.g., lack of personal monitoring data) as discussed elsewhere (e.g., Proctor et al. 2003). Although the Baltimore cohort has tens of thousands of CrVI air measurements from which to estimate job title-based exposure, there are limitations for this study as well such as the potential for low bias in the exposure estimates, which has been discussed elsewhere (e.g., Exponent 2002a,b). If historical

exposures were of greater magnitude than concentration estimates used to derive URFs for this study, risk due to CrVI exposure would tend to be overestimated. Lastly, CrVI carcinogenicity is most pronounced in the chromate production and chromate pigment production industries, where workers are exposed to sparingly soluble chromates, including calcium, zinc, strontium, and lead chromates (ToxStrategies 2012). However, human data are not available from which to calculate separate risk estimates for all the various species of CrVI, which differ in solubility and are expected to exhibit some differences in carcinogenic potency. The TCEQ recognizes that use of CrVI as the dose metric without regard to the particular species has associated uncertainty as it inherently assumes that CrVI compounds may be considered approximately equivalent for carcinogenic potential on a CrVI content basis, or alternatively, that total CrVI sufficiently represents the total carcinogenic potential of the CrVI compounds to which the workers were exposed. Ultimately, dose metrics (e.g., cumulative exposure) based on CrVI are the only ones of interest (e.g., total Cr is not) and available for dose-response assessment for the key epidemiological studies.

## *E.4 Uncertainty Due to Co-Exposures to other Compounds*

The excess lung cancer risk estimates for CrVI can be confounded by smoking, which is common in epidemiological studies. Many of the workers were smokers. In Gibb et al. (2000), smoking status at the start of employment was available for 93% of the cohort. Eighty-two percent were cigarette smokers and 86% were cigarette, cigar, and/or pipe smokers. However, smoking was not controlled for in the calculation of SMRs, which could serve as the basis quantitative cancer risk assessment. The model preferred by the TCEQ for analysis of the Gibb et al. data (i.e., the Cox proportional hazards model) utilized smoking as a covariate. For the Crump et al. (2003) study, smoking status was available for 41% of cohort, with 78% being identified as smokers. However, Crump et al. evaluated confounding of smoking with exposure to CrVI through several Cox modeling analyses and testing for nonhomogeneity of smoking prevalence in the 10 cumulative exposure groups and did not find that smoking had an appreciable effect on CrVI carcinogenic potency estimates for the Painesville cohort. Regardless, residual confounding by smoking could have influenced results for both cohorts since neither study had data regarding the intensity and duration of smoking (i.e., pack-years), as is common with epidemiology studies (Seidler et al. 2012).