Development Support Document
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Hexavalent Chromium and Compounds

CAS Registry Numbers:
Hexavalent chromium 18540-29-9
Ammonium dichromate 7789-09-5
Calcium chromate 13765-19-0
Chromic acid 7738-94-5
Chromium trioxide 1333-82-0
Sodium chromate 7775-11-3
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

Prepared by
Joseph T. Haney, Jr., M.S.
Neeraja K. Erraguntla, Ph.D.
Toxicology Division

Office of Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

The following Section 3.1.2 is from the acute noncarcinogenic assessment section, although it may be considered supplemental information to the carcinogenic MOA section in Section 4.2…

3.1.2 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.
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> *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.

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.

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 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 intermediates (CrV, CrIV) from rapid reduction to CrIII generate oxygen radical species believed to be responsible for many of the deleterious effects of chromium on cells. 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.

As with many chemicals, a complete and clear picture of the underlying mechanisms and/or MOA(s) producing the adverse effects of CrVI is yet to be fully elucidated.

4.2 Carcinogenic Potential

USEPA (1984) derived a unit risk factor (URF) of 1.2E-02 per $\mu g/m^3$ 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.

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), appear to be more potent lung carcinogens, with extracellular dissolution of the CrVI compound critical to activity (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 aerosols/mists 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 brief summary 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).

Various MOAs have been proposed for CrVI-induced carcinogenicity. 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, indicates that the weight of evidence supports the plausibility that CrVI may act through a mutagenic MOA. However, TCEQ (2012) indicates 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).

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. Experimental data support the reduction of CrVI to CrIII as an important detoxification mechanism, which may represent a hurdle to CrVI-induced carcinogenicity in some instances (e.g., low exposure well within lung CrVI reductive capacity extracellular to target tissue). This may be viewed as consistent with key epidemiology and animal studies that have shown no excess lung cancer risk at low cumulative doses and/or concentrations (e.g., Crump et al. 2003, Glaser et al. 1986, 1988). These facts are relevant to the carcinogenic MOA and consistent with an MOA wherein the first key event is exceeding the body's capacity to effectively reduce and carcinogenically detoxify CrVI, extracellularly in particular (i.e., prior to CrVI having the opportunity to enter cells and produce intracellular reduction products). 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. These MOA concepts are consistent with ATSDR (2012) indicating that CrVI absorption into tissues may be a function of doses high enough to overwhelm CrVI reduction mechanisms and the results of a recent oral carcinogenic MOA analysis (Thompson et al. 2011).

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, 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 (e.g., nonlinearity).

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 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 a paper (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 for comparison to default linear low-dose extrapolation approaches. More specifically, 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 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 ReV of 0.24 µg CrVI/m^3 following dosimetric adjustments and application of appropriate UFs (total UF of 30). However, while data relevant to the carcinogenic MOA and the epidemiological analyses conducted support consideration of nonlinear-threshold assessments for CrVI inhalation carcinogenicity, 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 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 (90% confidence interval (CI) of 0.401-0.920) and the slope for the analogous model with additive background as 0.00164 (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 1. 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.

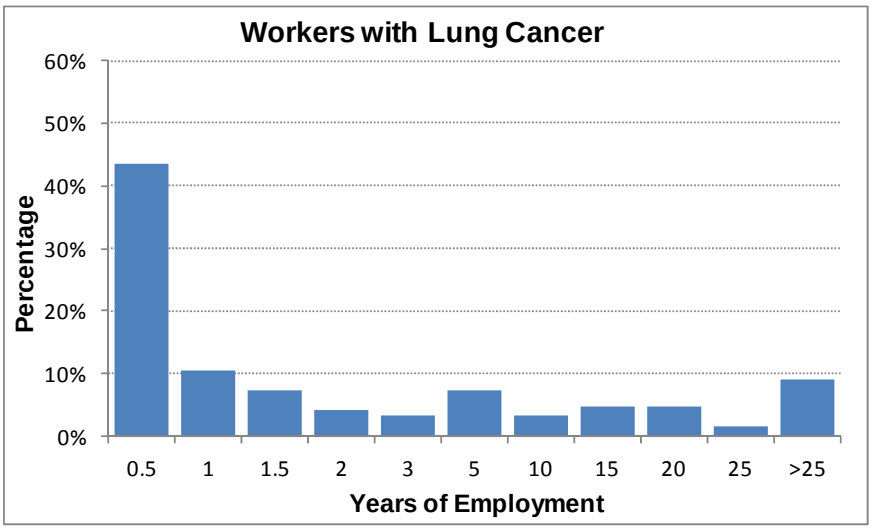
4.2.3.1.3.2 Baltimore, Maryland Key Cohort

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. 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 for the Baltimore cohort). 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 to increase SMRs for respiratory and other cancers (Boffetta et al. 1997), their risk factors may differ from long-term workers (important when short-term, low-dose workers are used as the referent) and the general population (important when the general population is the referent as in Gibb et al. 2000). Additionally, the exposure scenario they 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 have been discussed by other authors, such as not controlling for smoking (e.g., Exponent 2002a,b).

Figure 1. **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: Leverkusen and Uerdingen, Germany, Corpus Christi, Texas, and Castle Hayne, North Carolina

In addition to use of 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 worker studies, 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 2. 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
α = 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
β = 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 were 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 3. 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 μg/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 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).

Table 4. **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	823	767	601	413	56	55	29

Duration ≥ 1.0 Years			(73.03)	(50.18)		(98.21)	(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 establish 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 statistical 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 5. **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 6. 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 7. 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:

$$Concentration_{HEC} = Concentration_{OC} \times (VE_{ho}/VE_h) \times (\text{days per week}_{oc}/\text{days per week}_{res})$$

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 day (10 m^3/day)
VE_h = non-occupational/environmental ventilation rate for a 24-h day (20 m^3/day)
$\text{days per week}_{oc}$ = occupational weekly exposure frequency (5 days per week)
$\text{days per week}_{res}$ = residential weekly exposure frequency (7 days per week)

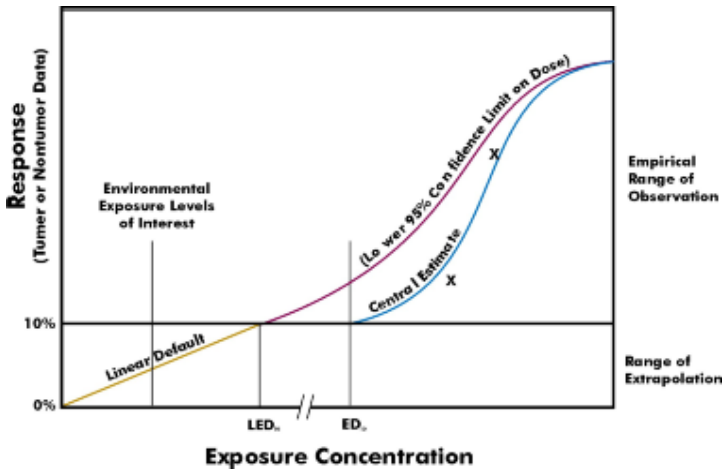
4.2.3.1.6 Unit Risk Factors (URFs) and Air Concentrations at 1 in 100,000 Excess Lung Cancer Risk

URFs express cancer potency in units of risk per air concentration (e.g., risk per $\mu g/m^3$) assuming continuous lifetime exposure. They are calculated using linear low-dose extrapolation when the carcinogenic MOA is 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 2. 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, a URF estimated using a lower POD within the range of the epidemiological data (e.g., 0.001) is approximately equal to a URF estimated using a high POD (as with animal data).

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 8. 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	1.34E-02 per

				µg/m^3 2.32E-03 µg/m^3	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 9. 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 candidate 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).

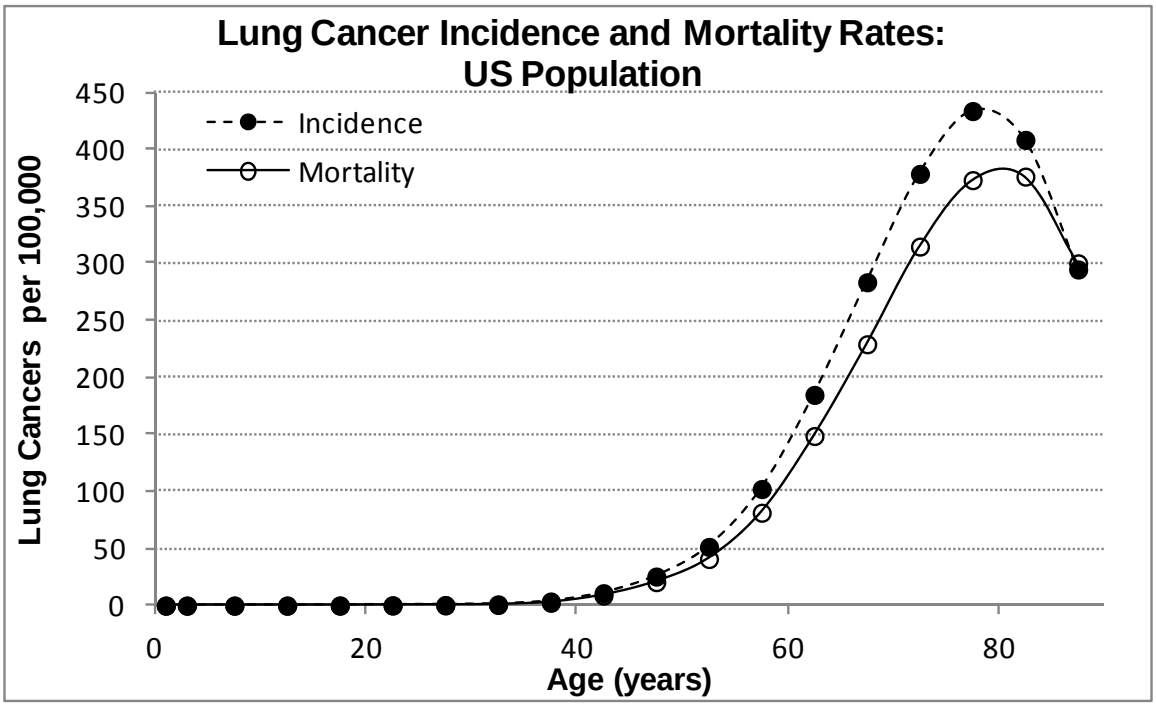
For Gibb et al. (2000), URFs based on Cox proportional hazards modeling for workers employed at least one year are preferred given: (1) the superiority of the Cox model over Poisson regression, (2) TCEQ's reservations about inclusion of very short-term workers in Gibb et al. (2000) to assess the excess 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%). 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 3. 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. 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.

CrVI has not been demonstrated to have a mutagenic MOA for lung carcinogenicity considering the reasonably scientifically-rigorous standard set under TCEQ guidelines (Section 5.7.4 of TCEQ 2012). For example, merely demonstrating plausibility is certainly not tantamount to an adequately robust demonstration that mutagenicity is in fact THE initiating event in target tissues. 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.

4.2.3.1.9 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 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 10. 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

$$= 2.28E\text{-}03 \text{ per } \mu g \text{ CrVI}/m^3$$

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 risk mortality of 1 in 100,000, rounded to two significant figures, is 0.0043 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).

4.2.3.1.9.1 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 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 derivation of the URF.

Chapter 5 References

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Appendix A. Modeled Data and Results for Studies Not Included in the Primary TCEQ Carcinogenic Analyses for Derivation of a 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 24 and 25, respectively, at the end of this appendix.

Table 11. 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 19, 20, and 21-22 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 24 and 25, respectively, at the end of this appendix.

Table 12. 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 13. 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 14. 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 15. 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 23 below. Beta (β) values and life-table analysis URF estimates with corresponding 1 in 100,000 excess risk air concentrations are given in Tables 24 and 25, respectively, at the end of this appendix.

Table 16. 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 24 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 17. 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 25 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 18. 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 $\mu g/m^3$ 5.87E-02 $\mu g/m^3$	7.05E-04 per $\mu g/m^3$ 1.42E-02 $\mu g/m^3$	1.24E-03 per $\mu g/m^3$ 8.06E-03 $\mu g/m^3$
		US	1.83E-04 per $\mu g/m^3$ 5.47E-02 $\mu g/m^3$	7.57E-04 per $\mu g/m^3$ 1.32E-02 $\mu g/m^3$	1.33E-03 per $\mu g/m^3$ 7.51E-03 $\mu g/m^3$
Gibb et al. (2000) Baltimore, MD	5-yr	TX	2.93E-03 per $\mu g/m^3$ 3.42E-03 $\mu g/m^3$	1.09E-02 per $\mu g/m^3$ 9.17E-04	1.89E-02 per $\mu g/m^3$ 5.30E-04

				µg/m^3	µg/m^3
		US	3.14E-03 per µg/m^3 3.18E-03 µg/m^3	1.17E-02 per µg/m^3 8.54E-04 µg/m^3	2.03E-02 per µg/m^3 4.93E-04 µg/m^3
Park et al. (2004) Baltimore, MD	5-yr	TX	2.02E-03 per µg/m^3 4.95E-03 µg/m^3	5.60E-03 per µg/m^3 1.79E-03 µg/m^3	9.21E-03 per µg/m^3 1.09E-03 µg/m^3
		US	2.17E-03 per µg/m^3 4.61E-03 µg/m^3	6.01E-03 per µg/m^3 1.66E-03 µg/m^3	9.89E-03 per µg/m^3 1.01E-03 µg/m^3
Environ (2003) [b] Baltimore, MD	5-yr	TX	3.34E-03 per µg/m^3 3.00E-03 µg/m^3	8.84E-03 per µg/m^3 1.13E-03 µg/m^3	1.44E-02 per µg/m^3 6.97E-04 µg/m^3
		US	3.58E-03 per µg/m^3 2.79E-03 µg/m^3	9.49E-03 per µg/m^3 1.05E-03 µg/m^3	1.54E-02 per µg/m^3 6.49E-04 µg/m^3
Birk et al. (2006) Leverkusen and Uerdingen, Germany	None	TX	NA	2.57E-02 per µg/m^3 3.89E-04 µg/m^3	7.38E-02 per µg/m^3 1.35E-04 µg/m^3
		US	NA	2.76E-02per µg/m^3 3.62E-04 µg/m^3	7.93E-02per µg/m^3 1.26E-04 µg/m^3
	10-yr	TX	NA	8.66E-03 per µg/m^3 1.15E-03 µg/m^3	2.27E-02 per µg/m^3 4.40E-04 µg/m^3
		US	NA	9.29E-03 per µg/m^3 1.08E-03 µg/m^3	2.44E-02 per µg/m^3 4.10E-04 µg/m^3
	20-yr	TX	NA	6.38E-03 per µg/m^3 1.57E-03 µg/m^3	1.79E-02 per µg/m^3 5.58E-04 µg/m^3
		US	NA	6.84E-03 per µg/m^3 1.46E-03 µg/m^3	1.92E-02 per µg/m^3 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)

Robert L. Sielken Jr., Ph.D.
Ciriaco Valdez-Flores, Ph.D., P.E.
Sielken & Associates Consulting Inc
3833 Texas Avenue, Suite, 230, Bryan, TX 77802
Tel: 979-846-5175; Fax: 979-846-2671; Email: SielkenAssoc@aol.com
TCEQ, Austin, TX

December 17, 2007

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 α 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;

β = multiplicative factor by which background risk increases with cumulative exposure;

d_j = cumulative exposure for exposure group j;

α = 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 α and β 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 λ 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 λ_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 α and β can then be obtained by selecting the values of α and β that maximize the value of L. Finding the values of α and β 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 α and β.

The parameters α and β 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 α and β, and hence, the values of α and β 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 α and β can also be obtained by solving for α and β 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 α and β, 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 α and β. The variance-covariance matrix of the parameters α and β 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 α, $\partial^2 LL/\partial\beta^2$ is the second partial derivative of the logarithm of the likelihood with respect to β, and $\partial^2 LL/\partial\alpha\partial\beta$ is the partial derivative of the logarithm of the likelihood with respect to α and β. 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 α and β 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 α 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 β 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

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

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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 19. 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	US	3.45E-04 per µg/m^3 2.90E-02 µg/m^3	**2.08E-03 per µg/m^3** **4.80E-03 µg/m^3**	3.81E-03per µg/m^3 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 1.23E-03 µg/m^3	2.33E-02 per µg/m^3 4.30E-04 µg/m^3
	10-yr	US	NA	**4.65E-03 per µg/m^3** **2.15E-03 µg/m^3**	1.41E-02 per µg/m^3 7.11E-04 µg/m^3
	20-yr	US	NA	4.61E-03 per µg/m^3 2.17E-03 µg/m^3	1.44E-02 per µg/m^3 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 20. 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 4.2.3.1.9, 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).