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Development of an inhalation unit risk factor for hexavalent chromium

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ABSTRACT

A unit risk factor (URF) was developed for hexavalent chromium (CrVI). The URF is based on excess lung cancer mortality in two key epidemiological studies of chromate production workers. The Crump et al. (2003) study concerns the Painesville, OH worker cohort, while Gibb et al. (2000) regards the Baltimore, MD cohort. A supporting assessment was also performed for a cohort from four low-dose chromate plants (Leverkusen and Uerdingen, Germany, Corpus Christi, TX, Castle Hayne, NC). For the Crump et al. (2003) study, grouped observed and expected number of lung cancer mortalities along with cumulative CrVI exposures were used to obtain the maximum likelihood estimate and asymptotic variance of the slope (β) for the linear multiplicative relative risk model using Poisson regression modeling. For the Gibb et al. (2000) study, Cox proportional hazards modeling was performed with optimal exposure lag and adjusting for the effect of covariates (e.g., smoking) to estimate β values. Life-table analyses were used to develop URFs for each of the two key studies, as well as for supporting and related studies. The two key study URFs were combined using weighting factors relevant to confidence to derive the final URF for CrVI of 2.3E-03 per μg CrVI/m^3.

1. Introduction

Human and animal studies have shown that hexavalent chromium (CrVI) has the ability to induce carcinogenicity. That is, 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

2009). Particulate forms of CrVI, relatively water insoluble compounds more specifically, appear to be more potent lung carcinogens, with prolonged extracellular dissolution of the CrVI compound critical to potency (O'Brien et al., 2003; Holmes et al., 2008; ATSDR, 2012; Nickens et al., 2010). ATSDR (2012) indicates that epidemiology studies (e.g., chromate worker studies) show a strong association between occupational CrVI exposure and lung cancer, which has been used as the cancer endpoint and corroborated in numerous studies.

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 (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

pounds as a group to be carcinogenic to humans via inhalation.

The United States Environmental Protection Agency (USEPA) completed health assessments of chromium and CrVI in 1984 and 1998, respectively (USEPA, 1984, 1998). However, there are studies more recent than those available for evaluation at that time, including more recent studies for dose–response assessment of lung cancer mortality in chromate workers (e.g., Gibb et al. (2000) and Crump et al. (2003)). Additionally, CrVI has been detected in ambient air in Texas. Thus, it is important for the TCEQ to conduct an inhalation carcinogenic assessment of CrVI based on the latest scientific data and analyses in order to develop a unit risk factor (URF) to help ensure the protection of public health.

A URF for CrVI has been developed based on new dose–response analyses of lung cancer mortality data in the key epidemiological studies of Crump et al. (2003) and Gibb et al. (2000). The Crump et al. (2003) study, which is an update of the Mancuso (1975)

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study, and the Gibb et al. (2000) study were not available for the USEPA health assessments of chromium and CrVI (USEPA, 1984, 1998). Neither were various supporting or related studies (e.g., Applied Epidemiology (2002), Luippold et al. (2003), Park et al. (2004)). The cancer assessment section of TCEQ's *Hexavalent Chromium and Compounds Development Support Document Draft* (DSD, referenced as TCEQ (2013)) underwent an external scientific peer review organized by Toxicology Excellence for Risk Assessment (TERA, 2013) and a public comment period. That document is the source of the assessment presented herein. None of the comments affected the final inhalation URF value. The purpose of this paper is to present the procedures used in the carcinogenic assessment of CrVI, the derived URFs, and the final weighted URF. The final URF will be used to calculate the associated air concentrations at various *de minimis* extra lung cancer risk levels.

2. Materials and methods

The TCEQ (2012) guidelines for carcinogenic assessment employ the four-step risk assessment process formalized by the NRC (1983, 1994) and the procedures recommended in the most recent USEPA cancer guidelines (USEPA, 2005a,b) and scientific literature. For chronic adverse effects determined or assumed to be associated with linear dose–response relationships in the low-dose region, which is the case for CrVI-induced lung cancer, the TCEQ adopts or derives URFs. That is, for adverse effects associated with or assumed to have a linear dose–response at low doses (typically cancer), it is assumed that an effects threshold does not exist. In such cases, a linear extrapolation is performed to estimate excess lifetime risk at lower doses, for example, through use of the calculation of a point of departure using BEIR IV methodology (NRC, 1988) if data have been fit to a dose–response model. The slope of the line from zero excess risk at zero exposure to this point of departure is the inhalation URF, which may be described as the excess risk estimated to result from continuous lifetime exposure to an agent on a per $\mu g/m^3$ in air basis (i.e., excess risk per $\mu g/m^3$ assuming continuous lifetime exposure).

Human studies are preferred for URF derivation per the TCEQ (2012) guidelines, and in addition to reviewing the epidemiological studies previously considered and/or utilized by other agencies (e.g., USEPA, OSHA, NIOSH) for URF development, the TCEQ conducted a scientific literature search (through February 2013) for more recent CrVI inhalation epidemiological studies with adequate data for URF derivation. As with all chemicals for which TCEQ is developing toxicity factors, external interested parties had ample opportunity to submit relevant information (e.g., published, unpublished studies). See Section 3.3.2 of TCEQ (2012) for additional information on the procedures and sources used to identify essential data such as that from the key studies discussed herein.

The URF is based on excess lung cancer mortality in two key epidemiological studies of chromate production workers which are adequate to define dose–response relationships. The Crump et al. (2003) study concerns the Painesville, OH worker cohort of 482 workers, while Gibb et al. (2000) regards the Baltimore, MD cohort of 2357 workers. These cohorts have extensive follow-up and their respective studies provide standard mortality ratio (SMR) analyses for lung cancer mortality by cumulative CrVI exposure level (individual worker data are also available for Gibb et al. (2000)). Additional details on these key epidemiological studies are provided below.

3. Carcinogenic assessment

The following sections discuss key steps in the carcinogenic assessment of CrVI and development of URFs. Consistent with Figs. 1 and 2a of TCEQ (2012), the key steps are generally as follows:

- Conduct literature review and solicit information from interested parties.
- Perform carcinogenic weight of evidence and mode of action analyses (linear low-dose extrapolation is the default for a mutagenic or unknown mode of action).
- Identify key studies with sufficient information to conduct dose–response analyses (human study data are preferred and available for CrVI).
- Conduct dose–response modeling with the best methods available to derive slope parameter (β) estimates (linear multiplicative relative risk model using Poisson regression modeling, Cox proportional hazards modeling).
- Develop URFs using the best available method (life-table analyses were used in this case).
- Combine key study preferred URFs using weighting factors relevant to confidence to derive the final URF (inverse variance of the β estimates was used).

The first two steps shown above (i.e., literature search, carcinogenic weight of evidence and mode of action analyses) are inherently part of the process but need not be addressed in detail here since the focus of this paper is on documentation of the dose–response analyses and methods used in the URF derivation process. The first step was briefly discussed generally in the previous section. Additionally, carcinogenic weight of evidence analyses have already been conducted by many agencies (e.g., USEPA, ATSDR, IARC, NTP) and agree that CrVI is carcinogenic to humans via inhalation, and a mode of action analysis would not result in a departure from the linear, low-dose extrapolation approach employed in this study. Consequently, the following sections focus on the last four steps shown above.

3.1. Key studies

Human epidemiological studies are available and preferable over animal studies for the development of a URF. Not all epidemiological studies are adequate to define dose–response relationships, although numerous studies have investigated the association of CrVI exposure and lung cancer. The Painesville, OH (e.g., Crump et al. (2003)) and Baltimore, MD (e.g., Gibb et al. (2000)) chromate production worker cohorts have been used for quantitative risk assessment of lung cancer previously (e.g., 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, TX, Castle Hayne, NC) is the subject of various studies (e.g., Applied Epidemiology (2002), Birk et al. (2006)) and has been identified for a supporting quantitative dose–response assessment. Summary information for this supporting epidemiological study is also provided below.

3.1.1. Key cohorts: Painesville, OH and Baltimore, MD

3.1.1.1. Painesville, OH. Several studies have found increased lung cancer mortality (standard mortality ratios or SMRs) among workers at the chromate production plant in Painesville, OH (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 1 year from 1940 to 1972 and followed

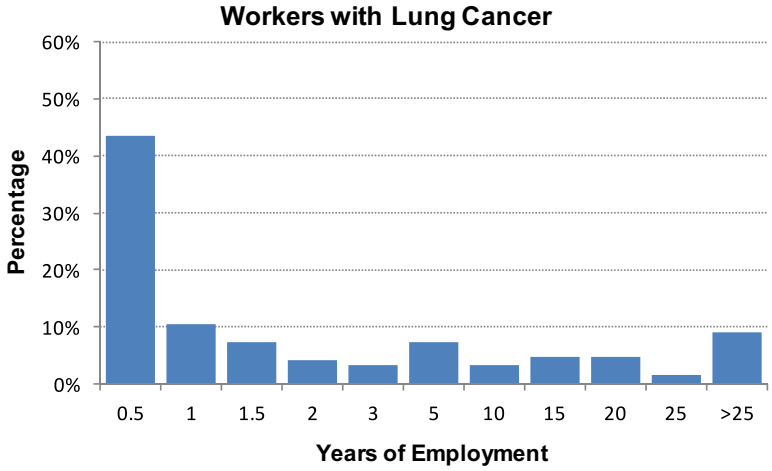

Fig. 1. Percentage of Baltimore chromate workers with lung cancer mortality by work duration (Tipton, 2007).

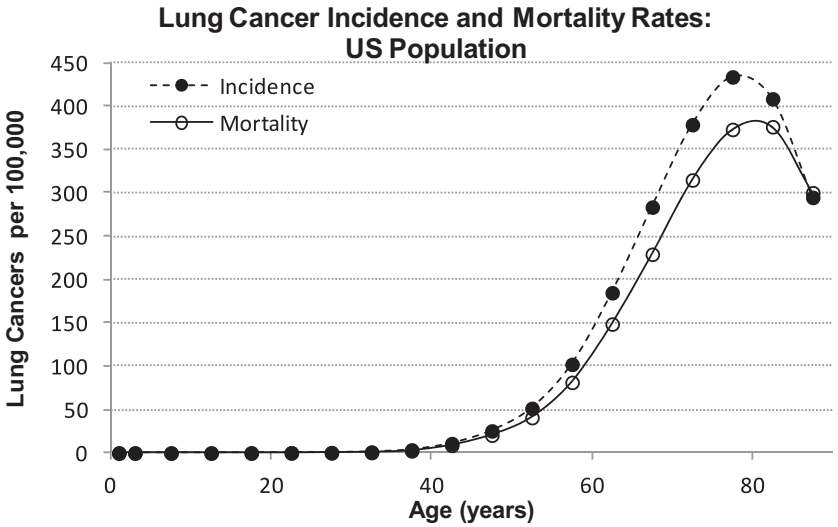

Fig. 2. Lung cancer incidence versus mortality (SEER, 2008).

through 1997 (14,443 person-years). Cumulative exposure to CrVI was significantly associated with increased lung cancer risk. Additionally, 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. The cumulative exposure and SMR data which will be used to calculate the slope parameter (β) estimates based on Crump et al. (2003) are given in Table 1 below.

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. 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, OH cohort and is used for the assessment of this cohort. Modeled data and results for Luippold et al. (2003) may be found in TCEQ (2013).

3.1.1.2. Baltimore, MD. Gibb et al. (2000) evaluated lung cancer mortality in a cohort of 2357 male chromate production workers in Baltimore, MD hired during 1950–1974, 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 (note that the cumulative CrO_3 exposure levels reported by Gibb et al. (2000) were converted to their CrVI equivalents based on molecular weight for this assessment). As a group, the lung cancer SMR was 1.80 (95% CI of 1.49–2.14). Other studies have also reanalyzed the data (e.g., Park et al. (2004), Environ (2003), Park and Stayner (2006)).

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 $\geqslant$5 years. By contrast, the median tenure for the Painesville workers was about 16 times longer at $\approx$6 years, with 17% working more than 20 years (as opposed to 15% working $\geqslant$5 years in the Baltimore co-

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)
0–0.06	0.00976	0	2.09	0
0.06–0.18	0.115	3	2.19	1.4
0.18–0.30	0.233	3	2.19	1.4
0.30–0.46	0.386	5	2.13	2.3
0.46–0.67	0.563	0	2.20	0
0.67–1.00	0.817	4	2.22	1.8
1.00–1.63	1.27	12	2.23	5.4
1.63–2.60	2.09	3	2.18	1.4
2.60–4.45	3.37	10	2.18	4.6
4.45–29.0	7.55	11	2.12	5.2

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

hort). Moreover, as can be seen from Fig. 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 and 12 months, respectively. Because short-term workers (e.g., <1 year) have been found more likely to lead an unhealthy lifestyle (e.g., abuse alcohol) and have a chronic disease such as cancer (Kolstad and Olsen, 1999), have increased mortality (Kolstad and Olsen, 1999; Steenland et al., 1996), and have increased SMRs for respiratory and other cancers (Bonfetta et al., 1997), their risk factors may differ from long-term workers and the general population (e.g., perhaps biasing low-dose risk high when the general population is the referent as in Gibb et al. (2000)). Additionally, the exposure scenario the Baltimore cohort experienced is most dissimilar to the lifetime, environmental exposure scenario of interest and therefore least relevant and likely most uncertain for occupational-to-lifetime, low level environmental extrapolation. Consequently, the TCEQ and others (e.g., Kolstad and Olsen (1999), Steenland et al. (1996)) consider inclusion of short-term workers as potentially problematic for assessing risk from long-term, low-dose exposure (although this was the reason these workers were included in Gibb et al.). Thus, the analysis for the Baltimore cohort will include a subset of workers exposed at least 1 year, which was also the worker inclusion criterion for the other cohorts evaluated herein. Other concerns about the Baltimore cohort, such as not controlling for smoking, have been discussed by other authors (e.g., Exponent (2002a,b)).

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 comparison to less refined modeling, modeled data and results for Gibb et al. (2000), Park et al. (2004) and , and Environ (2003) using maximum likelihood estimation procedures and Poisson regression modeling may be found in TCEQ (2013).

3.1.2. Low-dose supporting cohorts: Leverkusen and Uerdingen, Germany, Corpus Christi, TX, and Castle Hayne, NC

In addition to using the Painesville (Crump et al., 2003) and Baltimore (Gibb et al., 2000) cohorts for URF calculations, supporting dose–response data will be utilized from 1518 workers employed for at least 1 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, TX (187 workers), and Castle Hayne, NC (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 to 12.4 years and an overall mean exposure duration for the 4-plant study of 9.8 years.

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

$$\text{mg CrVI/m}^3 - \text{yr} = \mu\text{g Cr/L urine} - \text{yr}/[0.77\ \mu\text{g/L in urine per 1 } \mu\text{g CrVI/m}^3 \text{ in the air} \times 1000\ \mu\text{g/mg}]$$

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), 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 ($\geqslant$200 μg Cr/L-yr) based on SMR analyses. Logistic regression analyses found increased odds ratios for the intermediate and/or high exposure groups after adjusting for smoking (Applied Epidemiology, 2002; 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) at these lower exposures (e.g., $\leqslant$0.67 mg CrVI/m^3-yr) as the Painesville cohort study (8076). 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 more environmentally-relevant CrVI air concentrations (e.g., at a 1 in 100,000 excess risk level). 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, use of the Applied Epidemiology (2002) 4-plant study is being limited to that of a supporting study due to the relatively short, mean follow-up time of 17.2 years compared to the latency for CrVI-induced lung cancer deaths (e.g., 86% of lung cancer deaths occurred $\geqslant$20 years after first exposure in the Painesville cohort, Luippold et al. (2003)). Additionally, only 10.3% of the cohort was deceased. 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 2 below. Modeled data and results for the smaller 2-plant, low-dose study of Birk et al. (2006) may be found in TCEQ (2013).

3.2. Dose metric

The key chromate production plant epidemiological studies discussed above 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 commonly used for dose–response modeling based on epidemiological studies. Application of the URF (derived using cumulative exposure to CrVI as the dose metric) to all CrVI compounds inherently treats all CrVI compounds as toxicologically equivalent based on CrVI content, consistent with the TCEQ considering CrVI compounds as a group to be "Carcinogenic to Humans."

3.3. Dose–response assessment: slope parameter (β) estimates

3.3.1. Poisson regression modeling – Crump et al. (2003) and Applied Epidemiology (2002)

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. 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)), 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. Incorporation of the α term into the relative risk model equation from USEPA (1986, pp. 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 Crump et al. (2003) and Applied Epidemiology (2002), the mean or midpoint of each cumulative exposure group in units of μg CrVI/m^3-yr was used to estimate β values. Table 3 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.

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.

3.3.2. Cox proportional hazards modeling – Gibb et al. (2000)

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

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.

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,	None	0.88	2.58E-03	−1.97E-03	2.27E-03	6.51E-03
TX and Castle Hayne, NC	10-yr	1.07	1.91E-03	−1.60E-03	**1.55E-03**	4.69E-03
	20-yr	1.17	2.44E-03	−2.12E-03	1.90E-03	5.92E-03

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

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 1 year will be of primary interest and comparable to results based on the Painesville, OH cohort (Crump et al., 2003) and the supporting 4-plant, low-dose cohort (Applied Epidemiology, 2002), both of which utilized at least 1 year of employment as a criterion for the inclusion of workers in the cohort. For completeness, however, results for the Baltimore, MD cohort are also presented for all workers regardless of employment duration and those employed at least one-half year.

Cox modeling is superior than Poisson regression modeling in that Cox modeling uses individual exposure estimates for each worker (as opposed to the average or midpoint for each exposure group) as well as the actual age of the worker (as opposed to age interval groupings), and does not make any assumptions about the functional form of the background hazard rate. This method avoids dependence on the partitioning of cumulative exposure and optimally controls for the effect of age on lung cancer. (The Poisson model was used for the Painesville cohort discussed in the previous section because the Cox model requires more information than the summary data that were available for the Painesville study.) The effect of smoking and the effect of race on the model fit to the lung cancer mortality were assessed separately and concurrently. The data were split into three strata (non-smoker, smoker, unknown smoking) to adjust the model parameters for the effect of smoking and into two strata (white and non-white) to adjust the model parameters for the effect of race. The impact of these covariate effects were analyzed for the full cohort and the two subcohorts of workers employed at least one-half year and at least 1 year at the Baltimore plant (see Table 4 below).

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

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

where s_i is the effect of smoking for the i-th smoking group relative to the reference smoking group, r_j is the effect of race relative to the reference race group, and β is the change in the $\ln(RR_{ij})$ per unit change in the cumulative exposure (CumExp). The Cox-proportional hazards model was fit to the Baltimore epidemiological data using Version 9.2 of the SAS System for Windows SAS/STAT software (2002).

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 = $-2 \times$ log likelihood) when the covariate was included in the model versus the deviance when the covariate was not included in the model. The decrease in the deviance was compared to a chi-square distribution to evaluate the statistical significance of the improvement of the model fit to the data. Table 5 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 1 year, it does not result in a statistically significant reduction in the deviance for the full cohort and the subcohort of workers employed at least half a year. The deviance of the model adjusted for smoking and race is statistically significantly (p-value < 0.01) less than the deviance of the model not adjusted for any covariate for the full cohort and the two subcohorts analyzed. However, the statistically significant decreases of the deviance when both covariates are included in the model are driven by the effect of smoking and only marginally due to the effect of race.

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 6 lists the deviances ($-2 \times$ 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 1 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

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	2357	2235	1716 (76.78)	1134 (50.74)	122	118 (96.72)	71 (58.20)
Employment duration ⩾ 0.5 years	1086	1017	792 (77.88)	531 (52.21)	69	68 (98.55)	38 (55.07)
Employment duration ⩾ 1.0 years	823	767	601 (73.03)	413 (50.18)	56	55 (98.21)	29 (51.79)

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".

Table 6
Deviance for three subsets of the Baltimore cohort based on the Cox proportional hazards model with 0, 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".

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 7 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 3 and 7, 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-04–1.00E-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 1 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.

3.4. Dosimetric adjustments

Occupational concentrations ($\text{concentration}_{OC}$) were converted to environmental concentrations for the general population ($\text{concentration}_{HEC}$) using the following equation (TCEQ, 2012):

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

where: VE_{ho} = occupational ventilation rate for an 8 h day (10 m^3/day); VE_h = non-occupational ventilation rate for a 24 h day (20 m^3/day); $\text{days per week}_{oc}$ = occupational weekly exposure frequency (default of 5 days per week); $\text{days per week}_{res}$ = residential weekly exposure frequency (7 days per week).

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 μg/m^3-yr.
[b] 95% LCL = β − (1.645 × SE).
[c] 95% UCL = β + (1.645 × SE).

3.5. Extrapolation to lower exposures

3.5.1. Study-specific URFs

URFs express cancer potency in units of excess risk per air concentration (e.g., excess risk per μg/m^3) assuming continuous lifetime exposure. They are calculated using linear low-dose extrapolation when the carcinogenic MOA is mutagenic, unknown, or sufficient information to justify an alternative extrapolation approach is not available (TCEQ, 2012). Although there is not a consensus on the specific MOA for CrVI, significant information relevant to the carcinogenic MOA for CrVI is known and justifies at least the consideration of a nonlinear-threshold assessment in addition to the default linear low-dose extrapolation approach employed in this paper. The implementation of an exploratory nonlinear-threshold approach was published recently in Haney et al. (2012). However, 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 focus of the current study is use of the default linear low-dose extrapolation approach to derive URF estimates.

The BEIR IV methodology (NRC, 1988) was used to estimate CrVI URFs based on the β values calculated from human dose–response data (as discussed in Section 3.3). The BEIR IV life-table analyses were used to calculate separate URFs for the key studies of Crump et al. (2003) and Gibb et al. (2000) (as well as the supporting study of Applied Epidemiology (2002)) prior to combining the key study URF estimates through a weighting procedure for the final CrVI URF.

Table 8 shows URFs estimated for the key study of Crump et al. (2003), as well as the supporting study of Applied Epidemiology (2002). Additionally, Table 8 provides extrapolated air concentrations corresponding to a *de minimis* excess cancer risk of 1 in 100,000 based on β (MLE), β (95% LCLs), and β (95% UCLs) from Table 3, which were calculated 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 9 provides estimates of URFs as well as air concentrations at a *de minimis* 1 in 100,000 excess cancer risk based on β (MLE), β (95% LCLs), and β (95% UCLs) from Table 7. 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 analyses:

- Texas-specific lung cancer mortality rates for 2005–2009 and Texas-specific survival rates for 2010 are the latest available (TDSHS, 2010).

Although Texas background lung cancer mortality rates and survival probabilities are preferred by the TCEQ and were used for the results shown in Tables 8 and 9 below, similar results were obtained using US rates and are available in TCEQ (2013).

3.5.2. Selection of preferred lung cancer URFs

Based on the two key epidemiological studies (Crump et al., 2003; Gibb et al., 2000), two lung cancer URFs are selected in this section for combining into a final weighted URF. As indicated previously, Crump et al. (2003) provide one of the best summary SMR datasets for dose–response assessment due to a relatively high number of exposure groups (10) evaluated for excess lung cancer risk (14,443 person-years). Because exposure was not lagged and fewer cumulative exposure groups are provided by Luippold et al. (2003) for dose–response modeling, Crump et al. are considered to provide the best dose–response dataset for the Painesville, OH cohort. Thus, the preferred URF for the Painesville cohort (shaded in Table 8, associated β shaded in Table 3) 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 1 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 1 year of employment as a worker inclusion criterion). It is noted, however, that the URFs are fairly similar for the employment durations evaluated (e.g., the all worker 5 year lag MLE URF is only 22% higher than that for workers employed at least a year). Furthermore, use of the optimal exposure lag of 7.4 years is preferred as this lag maximizes the likelihood of the model fit to the data (although use of 5 year lag provides results within 4% and would result in an identical final weighted URF). The 7.4 year exposure lag is close to the 5 year lag results being used from Crump et al. (2003). Thus, the preferred URF for the Baltimore, MD cohort (shaded in Table 9, associated β shaded in Table 7) will be based on Cox modeling results for workers employed at least 1 year, 7.4 year exposure lagged data, and smoking as a covariate (see Section 3.3.2).

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

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 μg/m^3 2.32E-03 μg/m^{3}2.05E-03	1.34E-02 per μg/m^3 7.46E-04 μg/m^3

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

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 (Fig. 24 of Applied Epidemiology (2002)) as this would assume that on average, only the first 3 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 2) and produce a smaller β value variance (3.65E-06) than no lag (6.66E-06) (Table 3). 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 8, associated β lightly shaded in Table 3) will be based on the 10 year exposure lagged data from Applied Epidemiology (2002).

Lastly, as can be seen from Fig. 2, lung cancer mortality is reasonably predictive of lung cancer incidence (i.e., 5 year survival is only about 16% (American Cancer Society, 2005)). 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.

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 very similar (see TCEQ (2013)), 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 8 and 9). 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 to calculate a final URF.

3.6. Weighting preferred URFs for a final URF

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. However, in order to incorporate the available information from both key epidemiological studies, these two URFs are combined to derive a final URF using a weighting factor that reflects the relative statistical confidence in the URFs. Variance in the β values used to derive the preferred URFs reflects uncertainty in the β estimates and is used as a weighting factor. Since there is generally more confidence in β values with smaller variance, the reciprocal of the variance is used so that the resulting weighting factor is larger for the β value with the smallest variance (uncertainty). The URF based on a β with smaller variance receives greater weight as confidence is increased because a relatively lesser variance is an indication of a higher precision of the estimated parameter. 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) $\times$ 100 = overall weight% for a given URF). As shown in Table 10 below, the variances associated with the β (MLE) values for the two studies are similar (less than 12% apart), resulting in similar weighting factors.

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

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.

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 8.
[b] See Table 9.
[c] See Tables 3 and 7 for the values of the SE of β.
[d] Overall weight of URF (%) = (weighting factor/sum of weighting factors) × 100.

Final URF = Crump et al. (2003) URF × overall weight for Crump et al. (2003) + Gibb et al. (2000) URF × overall weight for Gibb et al. (2000)
= 1.94E-03 × 0.444 + 2.56E-03 × 0.556
= 2.28E-03 per μg CrVI/m^3

Thus, the final URF when rounded to two significant figures is 2.3E-03 per μg CrVI/m^3. Based on the final URF, the air concentration corresponding to a *de minimis* excess lung cancer mortality risk of 1 in 100,000 (rounded to two significant figures), for example, is 0.0043 μg CrVI/m^3 (i.e., 0.00001/2.3E-03 per μg CrVI/m^3). 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) (see TCEQ (2013)).

3.7. Uncertainty analysis

There are several uncertainties associated with the calculation of URFs in general and the URFs calculated herein. The primary uncertainties are those associated with dose–response modeling, estimating risks for the general population from occupational worker data, potential exposure estimation error, and co-exposures to other compounds. In regard to occupational worker data, use of a cumulative dose metric from high, less-than-lifetime occupational exposure for dose–response assessment results in some uncertainty when estimating risk for the general public based on much lower, lifetime average exposure levels. For example, if dose rate plays an important role in overwhelming protective mechanisms (e.g., lung CrVI extracellular reductive capacity) and producing excess lung cancer risk, a URF based on high, shorter duration occupational exposure may be conservative for estimating risk at low, lifetime environmental exposure levels. Regarding dose–response modeling, 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. One of the primary areas of interest in terms of uncertainty regards the similarities and/or differences in study URFs:

For the Crump et al. (2003) study:

- URF estimates range from 3.21E-04 per μg/m^3 (95% LCL) to 3.55E-03 per μg/m^3 (95% UCL), a ratio of around 11;
- The preferred URF of 1.94E-03 per μg/m^3 (MLE) is within a factor of 2 of the 95% UCL URF.

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) range from 1.14E-03 per μg/m^3 (95% LCL) to 4.00E-03 per μg/m^3 (95% UCL), a ratio of around 3.5;
- The preferred URF of 2.56E-03 per μg/m^3 (MLE) is within a factor of 1.6 of the 95% UCL URF;
- URF estimates for all workers (including those employed less than a year) with optimum lag and smoking as a covariate ranged from 1.96E-03 per μg/m^3 (95% LCL) to 4.30E-03 per μg/m^3 (95% UCL), a ratio of around 2.2;
- The MLE URF of 3.13E-03 per μg/m^3 for all workers is a factor of 1.2 apart from the preferred MLE URF for workers employed at least 1 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 μg/m^3 (from Gibb et al. (2000)) to the lowest preferred URF (MLE) of 1.94E-03 per μg/m^3 (from Crump et al. (2003)) was 1.3, which indicates good agreement between dose–response modeling from the different cohort studies. Refer to TCEQ (2013) for a more detailed uncertainty analysis.

4. Discussion and Conclusions

The URF was developed based on new dose–response analyses of extra lung cancer risk in two key epidemiological studies of chromate production workers (Crump et al., 2003; Gibb et al., 2000), with support provided by a dose–response assessment of a worker cohort from four low-dose chromate plants (Applied Epidemiology, 2002). For the key Crump et al. (2003) study and the supporting study, grouped observed and expected number of lung cancer mortalities along with the cumulative exposures to CrVI were used to ascertain the MLE and asymptotic variance of the slope (β) for the linear multiplicative relative risk model using Poisson regression modeling. For the key Gibb et al. (2000) study, Cox proportional hazards modeling was conducted with optimal exposure lag and adjusting for the effect of covariates (e.g., smoking) to estimate β values as more detailed, individual data were available. Life-table analyses were used to develop URFs for each of the two key studies, which were then combined using weighting factors pertinent to confidence to derive the final URF for CrVI of 2.3E-03 per μg CrVI/m^3. The corresponding 10^{-4}, 10^{-5}, and 10^{-6} excess risk air concentrations assuming continuous lifetime exposure are 0.042, 0.0042, and 0.00042 μg CrVI/m^3, respectively.

In conclusion, this new URF (2.3E-03 per μg CrVI/m^3) is based on current dose–response analyses and may be utilized in the evaluation of long-term (e.g., lifetime) air concentrations for all CrVI compounds and is considered sufficiently health-protective for use in protecting the general public against the potential carcinogenic effects of chronic exposure to CrVI in ambient air.

Conflict of interest

The authors declare that there are no conflicts of interest.

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