Hexavalent Chromium Carcinogenicity: Use of a Nonlinear-Threshold Assessment to Develop a Cancer-Based Chronic Inhalation Reference Value

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Abstract

It is important to conduct up-to-date chemical assessments for known human lung carcinogens such as hexavalent chromium (CrVI). An updated carcinogenic assessment has been conducted for CrVI, the carcinogenicity of which has been the subject of recent scientific debate (e.g., gastrointestinal reductive capacity, mode of action). In addition to default linear low-dose extrapolation methods used to calculate an inhalation unit risk factor (URF), the study authors believe epidemiological data supported by data relevant to the mode of action (MOA) are sufficient to justify considering the results of a nonlinear-threshold carcinogenic assessment for comparison to URF-based *de minimis* excess risk (e.g., 1 in 100,000) air concentrations. The intent of the current study is not to perform an exhaustive weight of evidence evaluation of all data potentially relevant to the MOA (or MOAs), but rather to present available summary MOA information and statistical evidence interpreted as supporting a potential practical threshold for CrVI-induced carcinogenicity and the results of the consequential nonlinear-threshold carcinogenic assessment. Epidemiological studies available in the scientific literature were reviewed and additional statistical dose-response analyses conducted to identify potential carcinogenic thresholds and points of departure (PODs). Occupational-to-environmental dosimetric adjustment of the "sub-threshold" cumulative exposure POD selected (0.195 mg CrVI/m^3-yr) resulted in a POD_{HEC} of 7.1 µg CrVI/m^3. Uncertainty factors (total UF of 30) were then applied to derive a cancer-based chronic inhalation reference value (ReV) of 0.24 µg CrVI/m^3. The margin of exposure (MOE) is approximately 16,000-475,000 between the "sub-threshold" cumulative exposure POD and cumulative exposures estimated based on long-term average CrVI ambient air concentrations measured at various sites in Texas (5.9E-06 to 1.7E-04 µg CrVI/m^3), which are 1,400-41,000 times lower than the calculated cancer-based chronic Reference Value (ReV).

Introduction

CrVI is an environmental contaminant that is generated primarily by industrial processes. Toxics Release Inventory (TRI 2009) data indicate there are at least approximately 4,900 facilities that produce or process chromium in the US, including around 200-300 facilities in Texas (Tables 5-1 and 5-2 in ATSDR 2012). Major manufacturers of chromium compounds in Texas appear to include Elementis Chromium of Corpus Christi (chromic hydrate, chromium hydroxide, chromium(III) hydroxide, chromium oxide) and Elementis LTP of Amarillo (chromic sulfate, chromium(III) sulfate) (Table 5-3 of ATSDR 2012). Long-term CrVI average ambient concentrations (total suspended particulate or PM_{10}) measured at various sites in Texas range from approximately 5.9E-06 to 1.7E-04 µg CrVI/m^3 (Karnack: 0.00017 µg/m^3, Deer Park: 0.00014 µg/m^3, Midlothian: 5.9E-06 to 6.0E-05 µg/m^3).

The Texas Commission on Environmental Quality (TCEQ), USEPA, International Agency for Research on Cancer (IARC), and National Toxicology Program (NTP) consider CrVI as a known human carcinogen by the inhalation route of exposure (USEPA, 1998; IARC, 2012; NTP, 2011). USEPA (1984) is the latest final USEPA toxicity assessment to derive an inhalation unit risk factor (URF) for CrVI (a URF of 1.2E-02 per µg/m^3 was estimated for environmental exposure to CrVI using linear low-dose extrapolation). The TCEQ is currently performing an updated inhalation carcinogenic assessment for CrVI. In doing so, the TCEQ is exploring the differences between health-protective air concentrations derived using default linear low-dose extrapolation (i.e., URF) versus nonlinear-threshold approaches. A nonlinear-threshold inhalation carcinogenic assessment was conducted for CrVI considering relevant MOA information, available scientific evidence for potential practical thresholds, and other relevant data. Appropriate dosimetric adjustments and uncertainty factors were applied to the ultimate POD to derive a cancer-based chronic inhalation ReV.

Carcinogenic Mode-of-Action (MOA)

Various MOAs have been proposed for CrVI-induced carcinogenicity. Some examples include: genomic instability due to DNA double strand break-induced G2 arrest ultimately resulting in neoplastic transformation (Holmes et al. 2008), cellular resistance to CrVI-induced death through dysregulated DNA repair and/or survival signaling and transcriptional repatterning (Nickens et al. 2010), mutagenicity as the initiating step (McCarroll et al. 2009), and other MOAs and mechanisms (e.g., Zuo et al. 2012; Xie et al. 2008; Thompson et al. 2011). Although the carcinogenic MOA(s) is yet to be fully elucidated (particularly at low doses), as the earliest key events what the proposed MOAs have in common 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.

Based on available MOA-relevant information:

- the bioavailability and carcinogenic/toxic potential of chromium compounds are dependent on the oxidation state of chromium, 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., CrIV, CrV, oxygen radicals) generated during the rapid intracellular reduction of CrVI to CrIII, which is the final product of intracellular CrVI reduction and forms deleterious complexes with (or causes other deleterious effects on) target macromolecules (e.g., Cr-DNA adducts, strand breaks, DNA–DNA and DNA–protein crosslinks); and
- the human body has a significant ability to reduce CrVI to CrIII, extracellular to target tissue as well as intracellularly (ATSDR 2012; De Flora et al. 1997).

The significant ability of the body to reduce CrVI to CrIII (extracellular to target tissue in particular) is an important detoxification mechanism that: (1) appears to restrict the targets of carcinogenicity (e.g., lung, GI tract); (2) could impart a nonlinear or threshold character to CrVI-induced carcinogenicity at sufficiently low exposure levels; (3) is consistent with key epidemiology and animal studies showing no excess lung cancer risk at low cumulative doses and/or concentrations; and (4) is relevant to the carcinogenic MOA and consistent with a possible MOA wherein the first key event is exceeding the body's capacity to effectively reduce and detoxify CrVI, extracellularly in particular (i.e., prior to CrVI having significant opportunity to enter target tissues and the intracellular reduction products having any opportunity to potentially interact with DNA). It also provides a biologically-plausible basis for at least considering a nonlinear-threshold assessment for inhalation CrVI carcinogenicity. That is, preventing the overwhelming of reductive capacity at the target tissue (lung) may be a biologically-plausible basis supporting consideration of a nonlinear-threshold assessment to complement a linear low-dose extrapolation.

Consequently, a nonlinear-threshold carcinogenic assessment was conducted to derive a cancer-based chronic inhalation ReV as it is plausible that CrVI carcinogenesis may have a practical biological threshold which may not be exceeded at some occupational air exposure levels and/or environmentally-relevant, long-term doses.

Nonlinear-Threshold Approach

In considering a nonlinear-threshold approach, while other studies have statistically evaluated the epidemiological data for thresholds or other nonlinearities (e.g., Crump et al. 2003; Park and Stayner 2006), this study conducted such analyses more fully taking into account MOA-relevant information such as lung CrVI reductive capacity estimates. Statistical results from key epidemiological studies on the Painesville, Ohio (Crump et al. 2003; Luippold et al. 2003), Baltimore, Maryland (Gibb et al. 2000; Park and Stayner 2006; Park et al. 2004), and other cohorts (Birk et al. 2006, Applied Epidemiology 2002) were reviewed and additional statistical analyses performed to identify potential carcinogenic thresholds and points of departure (PODs) .

Potential thresholds were identified based on worker exposures associated with statistically significant elevated lung cancer risk or trends. Sub-threshold candidate PODs were generally identified based on exposures below those associated with excess risk. Then, estimated inhalation doses associated with sub-threshold candidate PODs were compared to estimates of lung CrVI reductive capacity (e.g., extracellular to target lung tissue) to help frame the reasonableness of a possible threshold (i.e., the lack of an apparent carcinogenic response).

Potential Sub-Threshold PODs

Potential sub-threshold candidate PODs not associated with statistically increased risk were identified based on statistical analyses of epidemiological study dose-response data (e.g., Crump et al. 2003; Luippold et al. 2003; Gibb et al. 2000; Park et al. 2004; Park and Stayner 2006; Birk et al. 2006, Applied Epi. 2002). More specifically, possible carcinogenic thresholds were identified as the first cumulative dose associated with excess risk and/or the cumulative dose group causing the trend across exposure groups to become statistically significant based on standard mortality rate (SMR) analyses. The midpoint of the cumulative exposure group just below a possible carcinogenic threshold generally served as a candidate sub-threshold POD.

The candidate sub-threshold PODs of 0.195, 0.26, and 0.817 mg CrVI/m^3 yr from Birk et al./Applied Epi. (German & US low-dose cohorts), Park and Stayner (Baltimore cohort), and Crump et al. (Painesville cohort) were based on :

- the midpoint of the highest exposure group without excess lung cancer risk (Birk et al., Applied Epi.);
- the cumulative exposure with the most improved threshold model fit (Park and Stayner, although not statistically significantly better), as it was a lower value than the midpoint of the highest exposure group (0.381 mg CrVI/m^3 yr) which did not cause the trend to become significant (Park et al.) and below the range of 95% UCLs for possible thresholds (0.660-0.775 mg CrVI/m^3 yr) based on TCEQ Cox hazards proportional hazards modeling (workers > 1 yr, smoking covariate, 0-6.5 yr exposure lags); and
- the average for the highest exposure group without excess lung cancer risk or causing causing the trend to become statistically significant (Crump et al.).

With mean exposure durations of 9.8 , 3.1, and 9.2 years, these candidate cumulative exposure PODs correspond to estimated average occupational air concentration (POD_{OC}) values of 19.9, 83.9, and 88.8 µg CrVI/m^3, respectively. Animal data support use of these POD_{OC} values for the nonlinear-threshold assessment as they are lower than the lowest laboratory animal LOAELs identified for a CrVI-induced carcinogenic response (e.g., weak lung tumor response in Wistar rats at 100 µg/m^3 in Glaser et al. 1986, 1988; increased incidence of lung tumors in mice at 4,300 µg CrVI/m^3 in Nettesheim et al. 1971), with or without dosimetric model extrapolation to human equivalent concentrations, and lower than NOAELs of 1,600–15,500 µg CrVI/m^3 for carcinogenic effects in rats, rabbits, and guinea pigs (Lee et al. 1989; Baetjer et al.1959; Steffee and Baetjer 1965).

These PODs are those best supported by the epidemiological analyses and animal data as not being associated with excess lung cancer risk for use in a nonlinear-threshold inhalation assessment. The daily and 3-month doses (total CrVI mass) associated with the candidate PODs were compared to estimates of total lung CrVI reductive capacity (ELF + PAM + PLP)* and lung reductive capacity extracellular (ELF + PAM) to the target lung tissue.

Table 1: Comparison of inhalation doses from candidate PODs to crude lung total CrVI reductive capacity and extracellular reductive capacity estimates

Candidate POD (mg/m^3-yr)	At-Work Daily Average (µg/m^3) [a]	Worker Daily Dose (mg) [b]	Worker 3-Month Dose (mg) [c]
0.195	19.9	0.199	12.44
% of Estimated Total Reductive Capacity [d] (% of mean reduction-SD)		0.08 (0.4)	3.1 (22)
% of Extracellular Reductive Capacity [d] (% of mean reduction-SD)		0.15 (1.7)	4.6 (53)
Candidate POD (mg/m^3-yr)	**At-Work Daily Average (µg/m^3) [a]**	**Worker Daily Dose (mg) [b]**	**Worker 3-Month Dose (mg) [c]**
0.26	83.9	0.839	52.4
% of Estimated Total Reductive Capacity [d] (% of mean reduction-SD)		0.32 (1.9)	13 (94) [e]
% of Extracellular Reductive Capacity [d] (% of mean reduction-SD)		0.61 (7.0)	19 (223) [e]
Candidate POD (mg/m^3-yr)	**At-Work Daily Average (µg/m^3) [a]**	**Worker Daily Dose (mg) [b]**	**Worker 3-Month Dose (mg) [c]**
0.817	88.8	0.888	55.5
% of Estimated Total Reductive Capacity [d] (% of mean reduction-SD)		0.34 (2.0)	14 (99) [e]
% of Extracellular Reductive Capacity [d] (% of mean reduction-SD)		0.65 (7.4)	20 (236) [e]

[a] Equal to the POD (mg/m^3-yr) divided by the estimated average work duration (yr). [b] Equal to the at-work daily average (µg/m^3) x daily occupational inhalation rate of 10m^3/day x 1 mg/1,000 µg. [c] Equal to the worker daily dose (mg) x 250 work days/yr divided by 4.
[d] Total: reductive capacity of ELF + PAM + peripheral lung parenchyma; Extracellular to target lung tissue: reductive capacity of ELF + PAM; 3-month reductive capacity includes replenishment of PAM (Table 1 of De Flora 1997). [e] Essentially ≥ 100% of the associated reductive capacity.
*ELF: epithelial lining fluid ; PAM; Pulmonary alveolar macrophage, and PLP: Peripheral lung parenchyma.

Considering potential intraspecies variability, the protective role of CrVI reduction prior to absorption, and the uncertainties associated with the crude lung CrVI reduction capacity estimates, the two higher PODs exceeding the 3-month (mean-SD) extracellular reduction estimate is considered of concern and not supportive. On the other hand, worker doses associated with the lower candidate POD (0.195 mg CrVI/m^3 yr) being below estimates of lung CrVI reductive capacity (extracellular in particular) may be viewed as consistent with the lack of a carcinogenic response in these workers, and thereby lends support to this POD to be carried forward in the nonlinear-threshold carcinogenic assessment.

Dosimetric Adjustments

Cumulative exposure (mg CrVI/m^3-yr) is the dose metric available for the POD (0.195 mg CrVI/m^3-yr) based on Birk et al. 2006/Applied Epidemiology 2002). As footnoted in Table 1, this was converted to an air concentration POD_{OC} by dividing by average exposure duration (9.8 yr):

POD_{OC} = 0.195 mg/m^3-yr / 9.8 yr = 0.0199 mg/m^3 = 19.9 µg CrVI/m^3

This POD_{OC} of 19.9 µg CrVI/m^3 was then adjusted to an environmental POD applicable to the general population (POD_{HEC}) using the following dosimetric adjustment (TCEQ 2012):

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

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)
days per week$_{oc}$ = occupational weekly exposure frequency (5 days per week)
days per week$_{res}$ = residential weekly exposure frequency (7 days per week)

POD_{HEC} = 19.9 µg/m^3 x (10/20) x (5/7) = 7.1 µg CrVI/m^3

Cancer-Based Chronic ReV & MOE

To derive a cancer-based chronic ReV for lung cancer, the POD_{HEC} is divided by applicable uncertainty factors (UFs):

- A full intra-human variability UF_H of 10 is justified because:
  - Inter-individual differences in reductive capacity have been shown, and
  - The key study population did not include potentially sensitive subpopulations of concern such as the elderly, those with significant pre-existing health/respiratory conditions (e.g., lung reductive capacity could be affected), or children, and may have had increased PAM reductive capacity due to the high prevalence of smokers (e.g., cigarette smokers have 3-5 times as many PAMs as nonsmokers; Green et al. 1977).
- A database UF_D of 3 is justified because:
  - The limited statistical power of epidemiological studies to detect increased risk at low exposure levels (as is common with epidemiology studies), and
  - A lack of accurate lung CrVI reductive capacity rates which would better enable comparisons to potential PODs for a nonlinear-threshold assessment.

Cancer-based chronic ReV = POD_{HEC} / (UF_H x UF_D) = 7.1 µg/m^3 / (10 x 3) = 0.24 µg CrVI/m^3

Various sites in Texas have long-term ambient air concentrations of CrVI that range from approximately 5.9E-06 to 1.7E-04 µg CrVI/m^3 (Karnack: 0.00017 µg/m^3, Deer Park: 0.00014 µg/m^3, Midlothian: 5.9E-06 to 6.0E-05 µg/m^3). The margin of exposure (MOE) is approximately 16,000-475,000 between the "sub-threshold" cumulative exposure POD and cumulative exposures estimated based on long-term average CrVI ambient air concentrations measured at various sites in Texas, which are 1,400-41,000 times lower than the calculated cancer-based chronic ReV.

Conclusions

- A cancer-based chronic inhalation ReV has been developed based on preventing excess lung cancer risk.
  - The most conservative POD (0.195 mg CrVI/m^3-yr) was selected of the candidate PODs considered based on statistical analyses of epidemiological data to identify possible cumulative exposure thresholds for lung cancer.
- The lack of significantly increased lung cancer risk associated with the POD used for derivation of the cancer-based chronic ReV is supported by other epidemiological data/analyses.
- Additionally, the lack of a carcinogenic response at the estimated POD_{OC} (19.9 µg CrVI/m^3) is supported by laboratory animal cancer bioassay data, and qualitatively by comparisons of the associated inhalation doses to crude estimates of lung CrVI reductive capacity.
- The MOE between the chronic ReV and long-term Texas air concentrations is 1,400-41,000.

Uncertainties

The primary uncertainties are those associated with:

- estimating potential thresholds or risks for the general population from occupational worker data,
- potential worker exposure estimation error and co-exposures to other compounds,
- key events of the carcinogenic MOA,
- evaluating dose-response data for potential thresholds,
- lung CrVI reductive capacity estimates.

Ultimately, these and other uncertainties associated with this assessment (e.g., limited statistical power of epidemiological studies, lack of a statistically better fitting threshold model, lack of data on competing rates of reduction and absorption) appear to preclude deviation from the default linear low-dose extrapolation for regulatory purposes.

References

Please see attached sheet.