State of the Science for Quantifying Carcinogenic Potency of Hexavalent Chromium: Considerations for Developing Airborne Guidelines in California

JULY 2017

ToxStrategies

Innovative solutions
Sound science

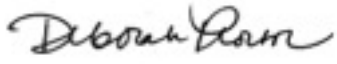
© 2008 ToxStrategies, Inc. All rights reserved.

State of the Science for Quantifying Carcinogenic Potency of Hexavalent Chromium: Considerations for Developing Airborne Guidelines in California

JULY 2017

PREPARED FOR:
Metal Finishers Association of Southern California

PREPARED BY:
ToxStrategies, Inc.
20532 El Toro Road
Suite 206
Mission Viejo, CA 92692



Deborah M. Proctor
Managing Principal Health Scientist

Table of Contents

List of Figures

List of Tables

Executive Summary

In 2017, the South Coast Air Quality Management District (SCAQMD) initiated discussions regarding Proposed Amended Rule 1469, Hexavalent Chromium Emissions from Chromium Electroplating and Chromic Acid Anodizing Operations, and the Proposed Amended Rule 1426, Emissions from Metal Finishing Operations (SCAQMD, 2017). As part of these discussions, ambient monitoring and ambient thresholds have been described for hexavalent chromium [Cr(VI)]. Specifically, for Paramount, a fenceline threshold of 1.0 ng/m^3 for Cr(VI) has been applied for two facilities. SCAQMD has indicated that this threshold is based on a scenario in which residential exposure to 0.2 ng/m^3 is associated with a theoretical increased cancer risk of 100 in one million and roughly five-fold dilution is expected between the facilities and the closest residence. The 0.2-ng/m^3 value is based on modeling cancer risk using the Hotspots Analysis and Reporting Program Version 2 (HARP2) model developed by the Office of Environmental Health Hazard Assessment (OEHHA). HARP2 assumes that Cr(VI) poses a cancer risk by multiple exposure pathways, including:

- inhalation
- oral pathways of homegrown crop consumption and incidental ingestion of soil and dust
- dermal contact.

The majority of the total estimated risk comes from the inhalation pathway (63%), while homegrown crop consumption contributes 36% of the total risk.

These cancer risks are calculated using the cancer potency estimates developed by OEHHA for oral and inhalation exposure pathways. The oral potency estimate is based on a drinking water study in rodents wherein high concentrations (>20,000 ppb) of Cr(VI) caused intestinal tumors in mice (NTP 2008), and the inhalation cancer potency estimate is based on cancer risks occurring at extremely high airborne concentrations (average concentrations estimated at 1,000,000 ng/m^3 [or 1 mg/m^3]) experienced by workers employed in the a chromate production plant in Painesville, Ohio, starting in the 1930s (Mancuso 1975). These exposure conditions are not representative of exposure to Cr(VI) in ambient air, and using these data and the OEHHA models greatly exaggerates the potential cancer risk.

OEHHA's approaches significantly overestimate risk for several reasons. HARP2 does not consider chromium chemistry or that Cr(VI) is readily reduced in most conditions to non-toxic trivalent chromium [Cr(III)]. As such, Cr(VI) will not exist in fruit and vegetables, which are organic and typically acidic, and provide conditions in which Cr(VI) is not stable. Several studies have shown that in plants grown in Cr(VI)-containing water, 100% of the chromium in produce exists in the non-toxic trivalent state (e.g., Zayet et al., 1998). The generic approach used in HARP2 for assessing risk from homegrown crop ingestion should not be used for Cr(VI) because it is not stable in crops. All chromium in crops will be in trivalent form. As such, 36% of the total risk to

residents from Cr(VI) that is estimated using the OEHHA model comes from a pathway that does not exist for Cr(VI).

Furthermore, Cr(VI) is rapidly reduced to Cr(III) by stomach fluid, and this is well recognized to be a detoxification process (ATSDR, 2012; De Flora et al., 2016; IARC, 2012; Kirman et al., 2016; NIOSH, 2013). As such, upon ingestion, Cr(VI) poses a cancer hazard only at high doses that allow for sufficiently high concentrations of Cr(VI) to avoid reduction in the stomach. A reference dose (RfD), which is level of exposure below which there is no increased cancer risk even for sensitive subpopulations, has been calculated in a recent study (Thompson et al. 2017). The dose from all ingestion pathways in the OEHHA HARP2 at 1 ng/m^3 is only one-tenth of this reference dose. Thus, the dose that HARP2 projects for ingestion is well below the level that could pose a cancer hazard by this pathway. As such, any ambient thresholds for Cr(VI) should be based solely on the potential cancer risk from inhalation exposure because exposure by ingestion will not pose an increased cancer risk.

Cr(VI) has been shown to be an inhalation carcinogen from historical high-level occupational exposures in certain industries (ATSDR, 2012; NIOSH, 2013), and cancer potency estimates are specific to historical studies of workers in the chromate production industry, which produced pure Cr(VI) chemicals by roasting chromite ore and processing the leachate to make chromium chemicals.

The inhalation cancer potency estimates used in HARP2 are outdated. Specifically, OEHHA's inhalation risk assessment was conducted in 1985[1] and is based on the Mancuso (1975) study of 332 workers, who started working in the Painesville, Ohio chromate production plant from 1931-1937. This 40-year old assessment is highly outdated, and today far improved and updated data are available for inhalation risk assessment. Most agencies in the US and abroad use these new data, but OEHHA has not updated its risk assessment. More importantly, all inhalation cancer potency estimates for Cr(VI) developed by US and European regulatory agencies are markedly lower than that used by OEHHA. Thus, the inhalation cancer risks estimated by other regulatory agencies (other than those in California) are markedly lower for a given concentration of Cr(VI) than those estimated by OEHHA for that same concentration.

The exposure data in Mancuso (1975) are of extremely poor quality and are severely limited by the manner in which the exposure assessment was conducted. First, only total chromium was measured (i.e., no Cr(VI) exposure data were collected); exposure data were collected in only a single survey in 1949, conducted 18 years after exposure began in 1931, and no data on smoking were available.

---

[1] In 1985, California Department of Health Services developed the inhalation risk assessment, and that division of CDHS later became OEHHA. In the 2011 Drinking Water Public Health Goal document, OEHHA evaluated the epidemiology data of the Gibb et al. (2000) study for the purposes of updating the cancer potency value, but chose to continue to rely on the original assessment from 1985.

Two updates of a larger, newer, and better characterized Painesville worker cohort have been published since (Luippold et al., 2003; Proctor et al., 2016), and these studies have been used to quantitatively estimate lung cancer risk in association with Cr(VI) exposure in several studies (Crump et al. 2003; OSHA 2006; Haney et al. 2014; Proctor et al. 2016). Other agencies, including the U.S. Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH) and the Texas Commission on Environmental Quality (TCEQ) have also quantified risk from a much larger cohort—workers at a chromate production plant in Baltimore—in addition to the more current and highly improved studies of the Painesville cohort. The TCEQ and the Scientific Committee on Occupational Exposure Limits (SCOEL) for the European Union (EU) have further used studies of workers in Europe with lower exposure levels, in addition to the two newer US studies (workers of Baltimore and Painesville) (Haney et al. 2012, 2014; SCOEL, 2017; TCEQ, 2014). None of these US and European organizations has developed or recommended inhalation unit risk estimates for Cr(VI) that are as high as those used by OEHHA.

This report summarizes the currently available science for Cr(VI), in support of improved risk assessment approaches. Details of HARP2's and OEHHA's assumptions of multi-pathway exposures via homegrown crop consumption for Cr(VI) are also quantified. The current epidemiologic data used for inhalation risk assessments, as used by several government agencies in the U.S. and abroad, are presented and discussed.

1 Background

Chromium is a naturally occurring element found ubiquitously in rocks and soil. It is a transition metal and as such exists in several valence states. In the environment, its most common valence states are the trivalent [Cr(III)] and hexavalent [Cr(VI)] forms (ATSDR, 2012). Cr(III) is used as a dietary supplement and is thought to be relatively inert; in comparison, Cr(VI) is toxic at high exposures and is classified as a known human carcinogen based on studies of workers in which it was shown that inhalation exposure at very high concentrations of Cr(VI) in certain industries is associated with increased lung cancer risk (IARC, 1990, 2012). In recent animal studies by the National Toxicology Program (NTP), mice and rats drinking high concentrations of Cr(VI) throughout their lifetimes had increased rates of small-intestine cancers (only mice at greater than or equal to 20,000 ppb) and oral-cavity cancers (only rats at 180,000 ppb) (NTP, 2008). Increased oral or small-intestine cancer risks have not been observed in studies of workers exposed to Cr(VI) (Gatto et al., 2010).

The California Office of Environmental Health Hazard Assessment (OEHHA) has developed toxicity criteria and health-based exposure guidelines for Cr(VI) **(Table 1**).

Table 1. OEHHA toxicity criteria and guideline values for Cr(VI)

Exposure Route	Type	Value
Inhalation	Inhalation unit risk (IUR)	0.15 $(\mu g/m^3)^{-1}$
	Inhalation cancer slope factor	510 $(mg/kg\text{-}day)^{-1}$
	Chronic reference exposure level (REL)[a]	200 ng/m^3 for particulates 2 ng/m^3 as chromic acid mists
Ingestion	Oral cancer slope factor	0.5 $(mg/kg\text{-}day)^{-1}$
	Public health goal (PHG)	0.2 ppb

Sources: CDHS (1985), OEHHA (2008, 2011, 2016)

[a] For noncancer effects, including nasal, throat, and respiratory irritation and allergies

The basis for the Cr(VI) inhalation unit risk (IUR) in California is a study of chromate production workers from Painesville, Ohio, published more than 40 years ago (Mancuso, 1975). Based on the same data, the U.S. Environmental Protection Agency (U.S. EPA) developed an IUR of 1.2×10^{-2} $(\mu g/m^3)^{-1}$—more than 10-times lower than that developed by OEHHA.

OEHHA also developed an oral cancer slope factor based on the 2-year NTP carcinogenicity bioassays. Using very conservative default approaches, which are currently being reassessed, OEHHA developed a public health goal (PHG) for Cr(VI) in drinking water of 0.02 ppb (OEHHA, 2011)—which is more than 100,000-times lower than the lowest dose that caused cancer in mice. This same approach is being applied in HARP2 to assess exposure from ingestion of crops and incidental ingestion of soil and dust from deposition of airborne particles and results in highly exaggerated risk estimates.

With regard to the OEHHA ingestion cancer risk assessment, it is important to recognize that OEHHA is currently reconsidering the public health goal based on recently published science supporting a more mechanistic approach to risk assessment. Since the NTP (2008) study, an extensive research effort has been underway to investigate the limited tumor outcomes observed in rats and mice. More than two dozen studies have been published that delineate the carcinogenic mode of action (MOA) for Cr(VI) since 2010, and risk assessments have been conducted in consideration of the MOA data (see Attachment A).

For inhalation cancer risk assessment of Cr(VI), there are newer studies of workers, including those of the Painesville cohort, that have been used by various agencies in the

U.S. and abroad (including the U.S. Occupational Safety and Health Administration [OSHA], the National Institute for Occupational Safety and Health [NIOSH], the European Commission's Scientific Committee on Occupational Exposure Limits [SCOEL], and Texas Commission on Environmental Quality) to develop occupational and environmental inhalation IURs for Cr(VI). These data sets are of far higher quality than that relied on by OEHHA to develop an IUR. Specifically:

- The more current studies[2] are based on speciated Cr(VI) exposure data, whereas the older study used by OEHHA (CDHS 1985) is based on total chromium monitoring data.
- The current studies use monitoring data collected at the same time as the workers were exposed, whereas the older study used by OEHHA relied on a single monitoring event conducted in 1949, up to 18 years after exposures began for the workers in 1931–1937.
- The current studies reconstructed the entire exposure duration of employees, whereas the older study used by OEHHA did not reconstruct exposures of employees after 1949, even though the plant continued to operate until 1972 and exposures of long-term workers were underestimated.
- The current studies have far greater statistical power, with more workers evaluated and more lung cancer deaths captured than the older study, which allows for a more robust analysis of risk and greater precision around the risk estimates.
- The current studies include data on smoking and thus can assess multiple extraneous variables, such that smoking-related lung cancer risk as a co-variate in the model in a quantitative manner.

The quality of the newer studies, as compared to that used by OEHHA to develop the inhalation cancer potency estimates, is remarkably improved, and clearly, new and better science should be used to set cancer potency estimates for California.

In 2017, the South Coast Air Quality Management District (SCAQMD) released the Proposed Amended Rule 1469, Hexavalent Chromium Emissions from Chromium Electroplating and Chromic Acid Anodizing Operations, and the Proposed Amended Rule 1426, Emissions from Metal Finishing Operations (SCAQMD, 2017). In the City of Paramount, SCAQMD has used an ambient threshold of 1.0 ng/m^3 for monitoring conducted in proximity to a facility, assuming that, through dilution in air, this airborne concentration approximately equates to an airborne concentration of 0.2 ng/m^3 at nearby residential locations. However, the risk-based value of 0.2 ng/m^3 was derived based on assumptions that oral exposures by pathways such as vegetable consumption contribute to an increased cancer risk. Additionally, SCAQMD is using outdated risk assessments from OEHHA to assess risk by inhalation. The objectives of this report are to review the

---

[2] Gibb et al., 2000; 2015; Park et al., 2004; Park and Stayner, 2006; Luippold et al., 2003; Crump et al., 2003; Proctor et al., 2003; 2004; 2016; Haney et al., 2012, 2014.

state of the science regarding the potential for Cr(VI) to pose a cancer hazard from ingestion of deposited particulates on soil, dust, and homegrown crops, and to review the current inhalation epidemiology data and risk assessment models, as compared to that developed by OEHHA and used in the HARP2 model for Cr(VI).

2 Inhalation Cancer Risk Assessment of Cr(VI)

OEHHA's inhalation cancer risk assessment is far outdated, is not based on the best science currently available, and overestimates risk compared to risk assessments developed by other regulators from updated and improved data sets. The IUR [0.15 $(\mu g/m^3)^{-1}$] developed by OEHHA is based on a 40+-year-old study of Painesville chromate production workers. Specifically, the Mancuso (1975) study of chromate production workers, who started working during 1931–1937 in Painesville, Ohio, is the basis of OEHHA's current value. Further by comparison with today's practice, OEHHA (CDHS in 1985) conducted the risk assessment using crude modeling approaches.

In the 2011 OEHHA Drinking Water Public Health Goal document, OEHHA considered an update of its inhalation cancer risk assessment using the published results from the Gibb et al. (2000) study to calculated alternative cancer potency estimates. Gibb et al. (2000) conducted a very robust study but the actual publication provided only limited information as compared to that typically used for modeling and quantitative risk assessment. OEHHA presented multiple attempts to fit a linear model to the Gibb et al. published data. Although OEHHA recognized the superior nature of the Gibb et al. (2000) data set, because of difficulties with model fit, it selected to continue using the previously determined inhalation unit risk developed in 1985 from the Mancuso (1975) study reasoning that the results form that work were within the range of values that could be developed from the models of Gibb's study. Other researchers (OSHA 2006; Park et al. 2004; Haney et al. 2014) have obtained the original Gibb et al. (2000) data, rather than relying on the published summary, in order to perform cancer risk assessment from these data. Those results are presented in comparison with the OEHHA unit risk below.

There are several limitations to the approach used by OEHHA to determine its IUR value. First, OEHHA relies on outdated information from Painesville chromate production workers. Newer studies and risk assessments of Painesville workers have been published since 1985 (Crump et al., 2003; Luippold et al., 2003; Proctor et al., 2016). Second, additional studies regarding the Baltimore chromate production worker cohort and risk assessments of that data exist in the published literature (Gibb et al., 2000; Park et al., 2004; Park and Stayner, 2006; Gibb et al., 2015). Both Painesville and Baltimore chromate production worker cohorts are recognized internationally as the key cohorts for evaluating Cr(VI) risk from inhalation exposures (Seidler et al. 2013; TCEQ 2014; OSHA 2006). Updated data from these cohorts have been used by OSHA, NIOSH, and TCEQ, as well as abroad by the Scientific Committee on Occupational Exposure Limits (SCOEL) and the European Chemicals Agency (ECHA), as the basis for Cr(VI) inhalation risk assessments. Third, the exposure information from the Mancuso (1975) study is not reliable and is not relevant for current exposure conditions, especially for the residential scenario.

The Mancuso (1975) study evaluated chromate production workers who started in the 1931–1937 period, and the only airborne measures of chromium collected for this study were done in 1949, and only measured total chromium (soluble and insoluble). Because there were no measurements of Cr(VI), assumptions were made regarding how much of the total chromium concentration was attributable to Cr(VI) to use this study in risk assessment. Recent updates of the Painesville and Baltimore cohorts are based on exposure assessments with industrial hygiene monitoring data specifically of Cr(VI). Further, Proctor et al. (2003), which presented Cr(VI)-specific measures of exposure from the Painesville plant in the 1940s, showed that the OEHHA assumptions regarding the fraction of total chromium that was Cr(VI) was not accurate. The Painesville plant was a Cr(VI) chemical production facility, and in many areas of the plant, exposures were exclusively to Cr(VI). Clearly, use of these outdated data and incomplete information renders the current OEHHA IUR unreliable and inadequate for rule-making.

Attachment B provides the complete citations for all recent studies of the Painesville and Baltimore cohorts, as well as the risk assessments that have been conducted by several government agencies and researchers. Below is a brief discussion of the recent inhalation risk assessments of Cr(VI) (both environmental and occupational) that have been conducted to date.

2.1 Environmental Risk Assessments

An increase in lung cancer risk among environmentally exposed populations has never been reported, and regulatory agencies use the risk observed in historical occupational studies as the basis for assessing potential lung cancer risk from airborne exposures in the environment using IUR values. Historically Cr(VI) exposed workers in the chromate production industry, which is the basis for the IUR values were exposed to extremely high concentrations. For example, the average concentration of Cr(VI) in the Painesville Ohio plant in the 1940s was reported to be 720,000 ng/m^3 (Proctor et al. 2003).

In 1984, U.S. EPA conducted an inhalation risk assessment using the same data as OEHHA used—from the Mancuso (1975) study (U.S. EPA, 1998). In fact, the OEHHA 1985 assessment relies upon the analyses of the U.S. EPA from 1984. The US EPA's IUR is 0.012 ($\mu g/m^3$)$^{-1}$; the California value is 12.5-times that of U.S. EPA. In Mancuso (1975) lung cancer deaths were observed to increase along with increases in cumulative total chromium exposures.[3] Hexavalent chromium was not measured in that survey, but soluble and insoluble chromium were reported. Proctor et al. (2003) evaluated assumptions regarding the fraction of Cr(VI) in total chromium measures using 3 surveys of monitoring data performed in the 1940s in the Painesville plant, wherein Cr(VI) was specifically measured. Mancuso's measures of exposure in 1949 underestimated early Cr(VI) exposures in most departments.

---

[3] Cumulative exposure is calculated as airborne concentration multiplied by years of exposure by job title.

In deriving the IUR, originally in 1984, U.S. EPA considered that 14% of the total chromium was Cr(VI). The Agency considered three factors that would contribute to an overestimation or under estimation of risk:

1. Industrial hygiene data may have underestimated exposure given that exposures started in the 1930s and exposure measures were not collected till 1949. This factor would result in an overestimation of risk because exposure is underestimated.
2. Chromate production workers were likely to have higher smoking rates than the general population, which is the source of the reference lung cancer rates. This factor would overestimate risk attributed to Cr(VI) because smoking risk is not accounted for.
3. Lung cancer risk was only quantified for total chromium, and if those results were used without any correction for the fraction of total chromium that was Cr(VI), risk would be underestimated because exposure would be overestimated.

After quantitative assessment of each of these factors, U.S. EPA in 1984 concluded that the underestimation of risk due to use of total chromium data, balanced the overestimation of risk due to non-concurrent exposure measures and lack of smoking data. Because the data were for humans rather than from animal studies, U.S. EPA, consistent with policy, used the maximum likelihood estimate of the relative risk to derive the IUR from the competing risk model. The competing risk model is consistent with the current state of the science in cancer risk assessment and accounts for competing causes of death in the determination of an IUR. As recognized by USEPA when the IUR was calculated and upon the most recent update in 1998, there is considerable uncertainty associated with the Cr(VI) IUR (U.S. EPA, 1998). As discussed herein, new data has been published since which allows for improved risk assessment of airborne Cr(VI) from occupational epidemiological studies. U.S. EPA is currently in the process of evaluating the new data for the purposes of updating its inhalation risk assessment.

In 1985, California DHS, which later became OEHHA, developed an IUR using the same data as U.S. EPA but selected more conservative approaches. CDHS indicated that there may be possible underestimation of Cr(VI) exposure with the Mancuso (1975) study data, and recommended use the 95% upper bound of the best estimate of the risk to derive the IUR (OEHHA, 1995). The California Air Resource Board's Scientific Review Panel accepted this decision. CDHS also assumed that one-sixth (14%) of total chromium exposure was to Cr(VI). Further, CDHS also chose to use the risk estimates from the "crude model" rather than the competing risk model, which gave 20% higher risk estimates, but is not now, nor was it in 1985, the most technically appropriate way to assess cancer potency. As a result of these assumptions and approaches, the OEHHA IUR is far more conservative than that developed by U.S. EPA using the same data. Reevaluations since the 1985 IUR, have not resulted in improved IUR values (OEHHA, 1995; 2011). In 1995, OEHHA noted that "there is considerable uncertainty in both unit risk values. Fortunately, a new study is currently underway between Johns Hopkins University and the U.S. EPA that is evaluating a much larger worker population with

better exposure data. The results of this study may help to resolve some of the differences and uncertainties in the unit risk values" (p. B-16, OEHHA, 1995). That study was published more than 15 years ago (Gibb et al. 2000), and TCEQ (2014), OSHA (2006) and NIOSH (2013) have all used the data for quantitative risk assessment.

OEHHA (2011) also attempted to model those data, but worked from the summary findings in the published paper rather than the original data, which are publically available. OSHA, NIOSH and TCEQ all worked from the original data, rather than the published summaries, and were able to model the exposure-response. Although recognizing the superior nature of the Gibb et al. (2000) study for risk assessment, as compared to the work of Mancuso, OEHHA retained the older value from 1985 because it was within the range of values determined from OEHHA's model of the Gibb et al. (2000) study. The mortality assessment of the Gibb et al. (2000) study was also updated in 2015, and relative risks for lung cancer were reduced. To our knowledge, those updated data have not been used to quantify an IUR.

The Baltimore study (Gibb et al. 2000; 2015), along with updates of the Painesville cohort, provide the best available science upon which to base IURs, and IURs from these data exist in the peer-reviewed scientific literature (Crump et al. 2004; Park et al. 2004; Haney et al. 2015; Proctor et al. 2016) as well as in regulatory documents. Importantly, in all cases, the IRUs are lower than that developed by OEHHA. The newer and much improved data of the Baltimore and Painesville cohorts should be used for cancer risk assessment rather than the outdated OEHHA value.

2.1.1 Environmental IUR values

IUR values can be calculated for occupational exposure scenarios, workers with exposure starting at age 18 for 45 year working lifetime, or environmental exposures, continuous exposure from birth throughout a lifetime. Further, there are differences in the competing causes of death throughout a lifetime for the general population, as compared to a worker population, IURs are calculated separately for each using life-table analyses (See Proctor et al. 2016 as an example). Thus, IURs for occupational exposures differ from that for an environmental continuous exposure scenario, and IURs for environmental exposures are discussed in this section.

The most recent update of the Painesville cohort was published last year by Proctor et al. (2016). Lung cancer mortality information for 714 workers was updated through 2011; Poisson and Cox regression models were applied, as well as life-table analysis (Proctor et al., 2016). Cox models accounted for age at hire and smoking, which were both statistically significant. Furthermore, this study used an exposure reconstruction based on measured exposures for Cr(VI) that were collected at the same time that the workers were exposed (Proctor et al., 2004). From this updated study, an environmental unit risk factor of 0.0083 $(\mu g/m^3)^{-1}$ was calculated, which is 18-times lower than the current IUR used by OEHHA. The upper confidence limit on the IUR [0.0174 $(\mu g/m^3)^{-1}$], is 8-times lower than the OEHHA value. This study used the industrial hygiene data specific to Cr(VI) and did not require any adjustment for estimating the fraction of Cr(VI) to total chromium (Proctor et al., 2016).

TCEQ recently developed an IUR for Cr(VI), and the assessment was based on the data from both the Painesville and Baltimore cohorts (Haney et al., 2014; TCEQ, 2014). TCEQ used Poisson regression for the Painesville cohort data set (Crump et al., 2003), and Cox proportional hazards modeling for the Baltimore cohort data set (Gibb et al., 2000). Life-table analyses were also performed. Supporting assessment was conducted from a cohort of four low-dose chromate plants (Leverkusen and Uerdingen, Germany; Corpus Christi, Texas; Castle Haynes, North Carolina). Occupational concentrations were converted to environmental concentrations to account for occupational ventilation rate for an 8-hour day, the non-occupational ventilation rate for a 24-hour day, and the number of working days per week. Preferred IURs from Painesville [Crump et al. (2003)] and Baltimore [Gibb et al. (2000)] cohorts were identified as 0.00194 and 0.00256 $(\mu g/m^3)^{-1}$, respectively. The final IUR was derived as 0.0023 $(\mu g/m^3)^{-1}$, considering overall weighting factors of 44.4% for Crump et al. (2003) and 55.6% for Gibb et al. (2000). This IUR is 63-times lower than that used by OEHHA in the HARP2 model.

All of these IUR-based approaches assume that the risk observed at very high exposures (e.g., >>50,000 ng/m^3) can be extrapolated to very low exposures—in the case of SCAQMD's proposed rule (0.2 ng/m^3), a >100,000 difference in concentrations, using a linear model. This assumption is extremely uncertain and known to be highly conservative.

2.2 Occupational Risk Assessment

The risk assessments by NIOSH and OSHA were based on the newer data sets from the Painesville and Baltimore cohorts. OSHA's permissible exposure limit (PEL) was promulgated in 2006, and NIOSH published the recommended exposure limit (REL) in 2013 (NIOSH, 2013; OSHA, 2006). The promulgated OSHA PEL is 5,000 ng/m^3 and the NIOSH REL is 200 ng/m^3. While the OSHA PEL considers technical feasibility, the NIOSH REL is based solely on health risk assessment data. OSHA evaluated six epidemiologic studies of Cr(VI)-exposed workers for cancer risk assessment including Mancuso (1975). OSHA selected studies of Baltimore and Painesville cohorts as the focus studies, indicating the Painesville and Baltimore cohorts as key cohorts upon which to base risk estimates. The OSHA and NIOSH risk assessments rely on potency estimates that are approximately 3- to 15-fold lower (when estimated for environmental as compared to occupational exposures) to that used by OEHHA.

In Europe, SCOEL indicated 1,000 ng/m^3, as an 8-hour TWA, to be the occupational exposure limit (SCOEL, 2017). Likewise, risk assessment calculations were based on the Painesville and Baltimore cohort data from Crump et al. (2003) and Park et al. (2004) with life-table analyses.

The substantial elevation of lung cancer risk among workers in the historical chromate production industry has been recognized for more than 50 years, and the association has been observed very consistently. However, the carcinogenicity of Cr(VI) by inhalation has been observed only in certain industries (chromate production, pigment production, ferrochromium production, and plating) in which workers are exposed to the most potent forms of Cr(VI) and at very high concentrations. Other industries with significant Cr(VI)

exposures and considerable epidemiological data, including data from stainless-steel welding, the aerospace industry, and ferrochromium production, have not observed an increased lung cancer risk from Cr(VI) exposures (IARC, 1990; IARC, 2012; NIOSH, 2013). It is also important to note that the inhalation risk assessments for Cr(VI) are based on chromate production workers, and thus, whether and to what degree risks observed in this industry can be directly extrapolated to the residential populations should be considered. Workers in the chromate production industry are exposed to Cr(VI) concentrations that are several orders of magnitude higher than those measured in the ambient environment. For example, in the Painesville plant, the average Cr(VI) concentrations is reported up to 720,000 ng/m^3 in the 1940 to 1949 period (Proctor et al. 2003). By comparison, the current average ambient exposure of Cr(VI) is reported in the SCAQMD Multiple Air Toxics Exposure Study in the South Coast Air Basin (MATES IV) as 0.11 ng/m^3 at the fixed monitoring site at Compton, California (SCAQMD, 2015). Not surprisingly, evidence of an increased lung cancer risk from environmental exposures to Cr(VI) has not been demonstrated.

2.3 Inhalation MOA

It is notable that U.S. EPA Cancer Risk Assessment Guidelines (2005a) recommend evaluating the MOA, or how a chemical causes cancer at high doses, to determine whether the same mechanisms are expected to be active at very low exposures. A recent published assessment of the inhalation cancer MOA for Cr(VI) (Proctor et al., 2014), concluded that the mechanisms involved in Cr(VI) carcinogenicity support a sublinear extrapolation of risk. Figure 1 is a schema of the MOA for Cr(VI)-induced lung cancer, and the key events include exceedance of lung reductive capacity and pulmonary clearance mechanisms, cytotoxicity, and inflammation, which ultimately results in chromosomal instability and lung tumorigenesis.

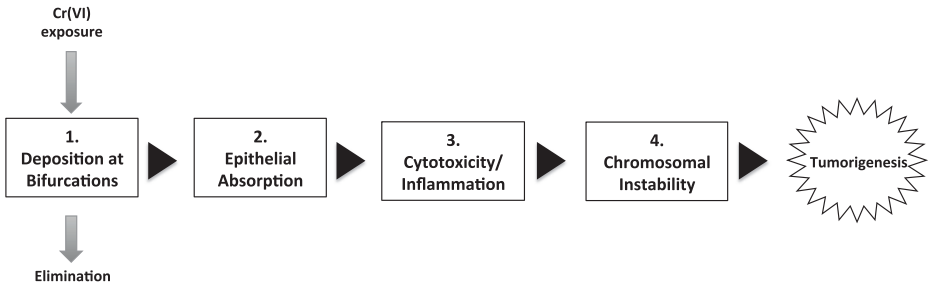


Figure 1. MOA for Cr(VI)-induced lung cancer, as published in Proctor et al. (2014). Note that the elimination process indicates extracellular reduction of Cr(VI) to Cr(III) and particle clearance from the lung.

The first step in the carcinogenic MOA for inhalation exposures is overwhelming the reductive ability of the extracellular lung fluids. Similar to the gastrointestinal tract, the lung has natural defenses, anti-oxidants, that reduce Cr(VI) to Cr(III), which is a detoxification process occurring prior to absorption (Proctor et al. 2014; Haney et al.

2012; De Flora et al. 1997). A schematic showing reductive capacity of the lung components and biochemistry of Cr(VI) from Proctor et al. (2014) is provided as Figure 2.

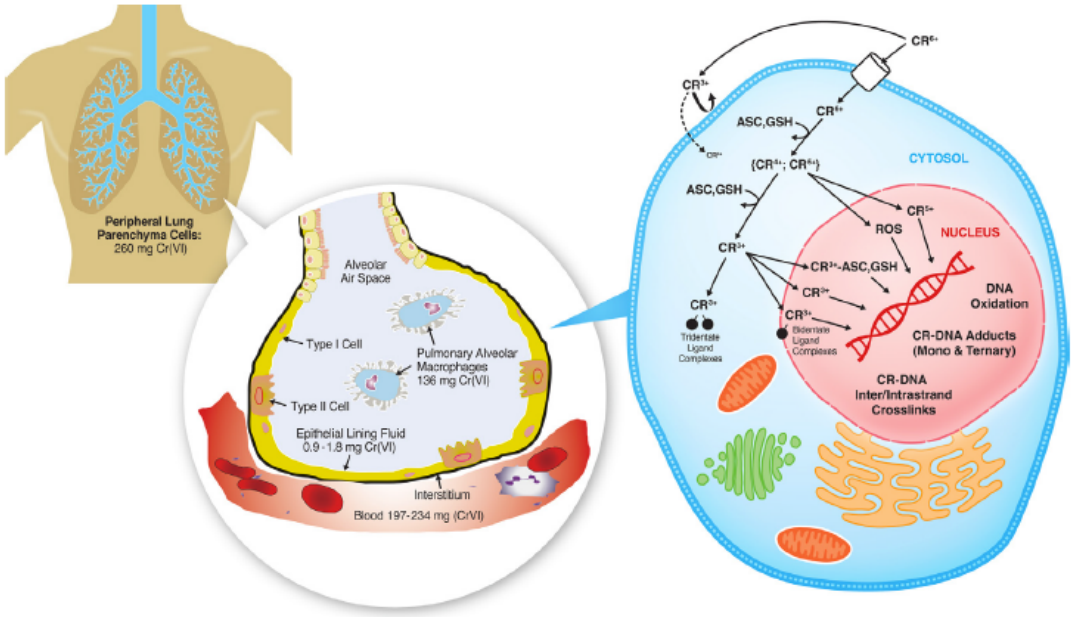


Figure 2. Estimates of the overall Cr(VI) reducing capacity per individual (de Flora et al., 1997) and hypothesized Cr(VI) biochemistry in the lung (from Proctor et al., 2014)

TCEQ considered the MOA of Cr(VI) and quantified the reduction of Cr(VI) to Cr(III) to develop a chronic inhalation reference value, which is a threshold for carcinogenicity and was developed to be protective of lung cancer for the general population (Haney et al., 2012; TCEQ, 2014). Several data sets, including those of the Baltimore and Painesville cohorts, were used in this quantitative assessment, and TCEQ identified a chronic inhalation reference value of 240 ng/m^3 Cr(VI). Far more certainty and confidence are accorded to the results of TCEQ's assessments, because information from the Painesville and Baltimore cohorts was used, and mechanistic considerations of Cr(VI) carcinogenicity were incorporated.

2.4 Summary of IURs for Cr(VI)

Table 2 provides a summary of the IURs (specifically, environmental unit risk factors) and the airborne concentrations at the 10^{-4} (100 in one million) risk level. It should be noted that 0.2 ng/m^3, as calculated using HARP2 by SCAQMD, assumes that Cr(VI) is carcinogenic by ingestion, including ingestion of fruits and vegetables. All values in Table 2 are based on inhalation exposures alone. As discussed in Section 3, the

assumption of multi-pathway exposure is not supported by the current state of the science, and the comprehensive MOA research and Cr(VI) reduction kinetics data demonstrate that the risk of cancer from ingestion exposure is likely to be *de minimis* at environmental levels. Furthermore, in HARP2, the inhalation unit risk is converted to a potency factor of 510 $(mg/kg\text{-}day)^{-1}$. Use of the IURs, over the cancer potency factors, is recommended by U.S. EPA inhalation risk assessment guidance (U.S. EPA 2009); thus IURs are used to calculate airborne concentrations for all values, other than the HARP2 values (top row), in Table 2. Finally, Age-Sensitivity Factors (ASFs) developed by OEHHA are used for the HARP2 model and as included in Table 2.

Table 2. Summary of inhalation unit risk (IUR) values for Cr(VI) and concentrations at 10^{-4} (100 in one million) target risk for residential exposures

Agency/ Citation	Cohort/Data Source	IUR $(\mu g/m^3)^{-1}$	Exposure Route	Cr(VI) Concentration at 10^{-4} Target Risk Level $(ng/m^3)^*$
OEHHA HARP2	Painesville/Mancuso (1975)	Uses Cancer Slope Factor 510 $(mg/kg\text{-}day)^{-1}$	Inhalation (within the HARP2 model for residential scenario including ASF)	0.3
OEHHA	Painesville/Mancuso (1975)	0.15	Inhalation	1.6
EPA	Painesville/Mancuso (1975)	0.012	Inhalation	19
Haney et al. 2014	Baltimore Gibb et al. (2000) & Painesville Luippold et al. (2003)	0.0023	Inhalation	100
Proctor et al. (2016)	Update of the Painesville cohort (through 2011)	0.0083	Inhalation	28

* Calculation of concentration at 10^{-4} risk level = 0.0001 ÷ IUR; calculated for a 30-year residential exposure consistent with HARP2 assumptions (70-year lifetime/30-year residential exposure duration). HARP2 values include Age-Sensitivity Factors but they have not been included for any other Cr(VI) inhalation.

3 Limited Evidence for Cr(VI) Carcinogenicity from Ingestion Exposure

The US Environmental Protection Agency (EPA) *Cancer Risk Assessment Guidelines* (2005a) recommends that the carcinogenic Mode of Action (MOA) be used to assess the potential for a chemical to cause cancer at low doses. More simply put, it is important to understand how a chemical causes cancer and to determine whether those biological mechanisms, observed at high doses, are active at low doses. A wealth of MOA data for Cr(VI) has been published and generally supports that Cr(VI) is carcinogenic only at high doses that exceed the body's ability to naturally detoxify Cr(VI) (DeFlora, 2000; Haney, 2015; Nickens et al., 2010, Thompson et al., 2013, 2015a,b).

3.1 Oral Carcinogenicity of Cr(III) and Cr(VI)

NTP studied the oral ingestion of both Cr(III) and Cr(VI) in male and female mice and rats in 2-year cancer bioassays (NTP, 2008, 2010). Ingestion of high concentrations of bioavailable Cr(III) in the form of chromium-picolinate in dietary feed for 2 years was not carcinogenic to rats or mice (NTP, 2010). In fact, no histopathological lesions were reported in the Cr(III) study—indicating that ingested Cr(III) has very low toxicity and is essentially inert. These data demonstrate that, to pose a health hazard, chromium must be absorbed into cells as Cr(VI), and that if it is reduced to Cr(III) prior to absorption, it poses no hazard.

In contrast to Cr(III), ingestion of high concentrations of Cr(VI) in the form of the sodium salt sodium dichromate dihydrate (SDD) in drinking water for 2 years was associated with tumors in certain locations within the gastrointestinal tract (NTP, 2008). Specifically, rats in the 180-ppm group had significant elevations in oral-cavity tumors relative to the control rats. No other tumors were observed in rats. Mice exhibited elevations in tumors in the proximal small intestine beginning at ~20 ppm or 20,000 ppb Cr(VI). These tumors were mainly in the duodenum (which is the location of nutrient absorption in the small intestine and proximal to the stomach). No other tumors were observed in mice.

Additionally, epidemiologic studies have not found an increased risk of intestinal or oral cancers among workers exposed to Cr(VI). Several meta-analyses of Cr(VI)-exposed workers have been conducted (Cole and Rodu, 2005; Gatto et al., 2010; Welling et al., 2015; Suh et al., 2017). Three of these meta-analyses, including one which included rigorous systematic review and risk-of-bias evaluation (Suh et al., 2017), reported that Cr(VI) exposures did not significantly increase gastrointestinal cancers among workers. These occupational epidemiologic studies assessed workers with exposures that are orders of magnitude greater than those found in the environment, supporting that Cr(VI) is not expected to pose a significant cancer risk from oral exposures at environmentally-relevant exposure levels.

3.2 Carcinogenic Mode of Action for Cr(VI) from Ingestion Exposure

After publication of the NTP (2008) Cr(VI) bioassay, an extensive research effort was initiated to investigate the limited tumor outcomes observed in rats and mice. This research has led to ~26 peer-reviewed journal publications in some of the top journals in the field of toxicology (Attachment A). Recently, several scientists and regulators have reviewed the recent research and concluded that the data support (a) non-mutagenic MOAs for both tumor locations, and (b) threshold approaches for developing toxicity criteria (e.g., reference dose values) to be protective of cancer (Haney, 2015; Health Canada, 2015; TCEQ, 2016; Thompson et al., 2014, 2017). Other scientists/organizations, including OEHHA, are currently re-evaluating and assessing Cr(VI) in consideration of the large body of newly published data in highly relevant target tissues.

The proposed MOA for intestinal tumors is shown in **Figure 1** (below). There is evidence for a non-genotoxic MOA involving chronic damage to the intestinal villi, which results in regenerative hyperplasia (chronic wound and healing process) (**Figure 1**). Specifically, high concentrations of Cr(VI) induce regenerative hyperplasia after only one week of exposure (Thompson et al., 2011, 2015a), indicating that mice in the 2-year NTP (2008) cancer bioassay experienced continuous wounding and healing of the small intestinal tissues. Such a mechanism result in increased cell turnover rates and increased probability of spontaneous mutation. This is a well recognized mechanism of tumor formation, and only occurs at doses that can cause cell death and healing. Interestingly, the only other chemical to clearly induce small-intestine tumors in an NTP study is captan (NCI, 1977, 2008), which has been determined by some regulators to induce intestinal tumors through a similar MOA involving chronic wounding and regenerative hyperplasia (Cohen et al., 2010; Gordon, 2007; U.S. EPA, 2004).

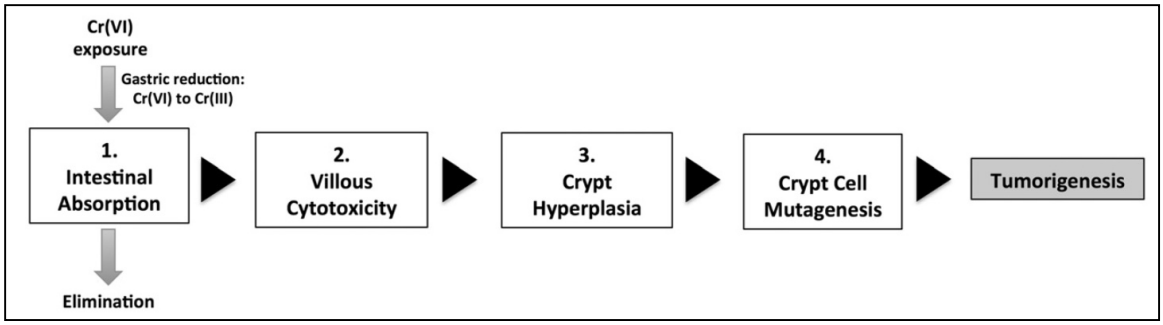


Figure 3. Depiction of mode of action for intestinal tumors in mice (source: Thompson et al., 2013)

In vivo genotoxicity data show an absence of effects. For example:

- No micronuclei induction in the duodenal crypts of mice exposed to ≤180 ppm Cr(VI) for 7 or 90 days (Thompson et al., 2015a)
- No increase in Kras codon 23 mutant frequency in the duodenum of mice exposed to ≤180 ppm Cr(VI) for 90 days (O'Brien et al., 2013)
- No increases in mutant frequency of the duodenum or oral cavity for transgenic Big Blue® rats exposed to 180 ppm for 27 days (Thompson et al., 2015b, 2017)

Regarding the oral tumors that were significantly elevated in rats at 180 ppm Cr(VI), several regulators have determined that protection against intestinal damage, hyperplasia, and tumors at lower concentrations is likely sufficient to also protect against the oral tumors observed at 180 ppm Cr(VI) (Health Canada, 2015; TCEQ, 2016). The relevance of these oral tumors at such high concentrations is questionable, because oral cavity tumors were not significantly elevated at lower concentrations or in mice at any concentration. Perhaps most compelling is the fact that transcriptomic analysis of oral tissue from mice and rats exposed to ≤180 ppm Cr(VI) for 7 or 90 days did not reveal significant changes in gene expression (Rager et al., 2017), indicating that the tissues were not responding to Cr(VI).

3.3 Toxicity Criteria for Cr(VI) for Oral Exposure

Shortly after the release of the NTP (2008) 2-year cancer bioassay, some regulatory agencies began drafting new toxicity values for oral exposure to Cr(VI):

- In 2009, the New Jersey Department of Environmental Protection (NJDEP) developed a cancer slope factor (NJDEP, 2009), which was used by U.S. EPA and OEHHA.
- In 2010, U.S. EPA released a draft assessment that contained a reference dose (RfD) for intestinal hyperplasia and a cancer slope factor based on intestinal tumors. Based on an assumed mutagenic MOA, U.S. EPA additionally applied age-dependent adjustment factors (ADAFs)[4] per U.S. EPA guidance (U.S. EPA, 2005a,b). That assessment is under revision to date and no oral cancer risk assessment has been developed by U.S. EPA.
- In 2011, OEHHA published its public health goal (PHG) based on a cancer slope factor for intestinal cancer (OEHHA, 2011).

As discussed in the previous sections, data published since the release of the NTP (2008) bioassay and the U.S. EPA and OEHHA assessments support a finding that Cr(VI) (a) does not induce genotoxicity in target tissues (intestine and oral mucosa), but (b) does

[4] ADAFs are also referred to as Age Sensitivity Factors (ASF) in OEHHA guidance.

induce villus toxicity and regenerative hyperplasia. There is no scientific basis for using either a slope factor alone, or a slope factor supplemented with ASFs, when deriving safety standards for oral exposure to Cr(VI). Indeed, more recent assessments that have evaluated the recent mechanistic research have used threshold approaches. For example, the draft assessment by Health Canada derived a total daily intake (TDI) value of 0.0044 mg/kg (equivalent to a water maximum acceptable concentration [MAC] of ~100 ppb) (Health Canada, 2015). Health Canada (2015) explains:

"The MOA analysis supports a progression from noncancer to cancer effects after exposure to Cr(VI) in drinking water. Thus, the assessment of chromium in drinking water, which is based on the health effects of Cr(VI), considers the cancer and noncancer effects together. The critical health effect on which to establish a guideline for chromium in drinking water is diffuse hyperplasia of the small intestine, as it is the most sensitive endpoint and a precursor of tumour formation."

Similarly, TCEQ derived an RfD of 0.003 mg/kg (equivalent to a water maximum contaminant level [MCL] of ~100 ppb) (TCEQ, 2016). TCEQ explains:

"In addition to the numerous studies published as part of the CrVI MOA research project, TCEQ staff have independently and critically evaluated the relevant published study data (and supplemental data) and its implications for the carcinogenic dose-response assessment of oral exposure to CrVI… The WOE indicates that cytotoxicity-induced regenerative hyperplasia is indubitably the most scientifically well-supported MOA."

As shown in Attachment A, many newly published studies on Cr(VI) are now available that are directly relevant to deriving toxicity criteria. Regulators who have reviewed these data have determined that low-dose linear extrapolation and development of cancer slope factors is not the most scientifically supportable approach for deriving toxicity values for oral exposure to Cr(VI). For more than a decade, the U.S. EPA has advocated for the use of MOA and physiologically based pharmacokinetic (PBPK) modeling in cancer risk assessment, as opposed to default approaches (U.S. EPA, 2005a, 2006), such as those used by OEHHA in its cancer potency estimates. The recent Cr(VI) assessments by Health Canada and TCEQ are examples of using such data for risk assessment. The carcinogenic MOA of Cr(VI) for gastrointestinal tumors in rodent bioassays strongly supports the existence of a threshold-type dose-response. Furthermore, the MOA and the data do not show increased risk of cancer from early life exposures, indicating that ASFs are not likely to be applicable for this pathway.

3.4 Overestimation of Risk from Ingestion of Cr(VI) in Homegrown Vegetables with HARP2

HARP2 is used to fulfill requirements of the Air Toxics "Hot Spots" Program in California (Assembly Bill 2588). However, HARP2 overestimates the risk posed by Cr(VI) due to homegrown crop ingestion. The model should be revised to remove this pathway from consideration for Cr(VI), and SCAQMD should not base risk estimates for Cr(VI) on this model, including ingestion pathways of exposure. The OEHHA model that is used to calculate risk within the HARP2 software package generically for all chemical

particulates considers potential exposure via ingestion of chemicals deposited on homegrown crops and taken up in food crops from soil and air (OEHHA, 2015). However, these approaches are not reliable for Cr(VI), which is not stable in organic media (such as fruit and vegetables).

For Cr(VI) emissions, this model estimates that, for a default deposition rate of 0.02 m/s applied in HARP2, homegrown crop consumption and soil ingestion contribute 36% and 1% of the total cancer risk, respectively. With this, the ingestion pathway represents 37% of the total cancer risk, and crop ingestion (36%) represents 97% of the ingestion cancer risk. Homegrown crop ingestion is thus modeled as a major contributor to overall Cr(VI) cancer risk using HARP2. The exact parameters and steps used to calculate cancer risk associated with homegrown crop ingestion are summarized below, followed by a discussion of the applicability of the homegrown crop pathway in Cr(VI) risk assessment.

3.4.1 Calculating Risk Associated with Homegrown Crop Ingestion

In calculating the overall risk associated with exposure via homegrown crop ingestion, the OEHHA model implemented in HARP2 carries out three steps. First, the concentration of the specific substance in different types of homegrown produce is estimated based on the concentration in the air, which influences the chemical deposition and root uptake. Second, the dose of the specific substance is estimated based on the type of produce, as well as other factors (e.g., gastrointestinal absorption and bioavailability factors). Last, the cancer risk is calculated separately for different age groups and is then summed to yield an overall cancer risk. Details on these calculation steps are provided in this section.

3.4.1.1 Step One: Calculating Concentration

The average concentration of a substance in and on produce is a function of direct deposition of the substance onto the produce and of root translocation or uptake from soil (Equation 1).

Equation 1

$$C_v = C_{depv} + C_{trans}$$

where:

Cv = Concentration in a specific type of produce (i.e., exposed, leafy, protected, root) (µg/kg)
Cdepv = Concentration due to direct aerial deposition (µg/kg)
Ctrans = Concentration due to root translocation or uptake (µg/kg).

3.4.1.2 Step Two: Calculating Dose

The dose of substance to which a receptor is exposed via ingestion of homegrown crops is a function of the type of produce (i.e., exposed, leafy, protected, root), gastrointestinal relative absorption factor, bioavailability, and the fraction of plant ingested that is

homegrown (Equation 2). The calculation is carried out for each type of produce and then summed to result in a total dose (Equation 3).

Equation 2

$$DOSE_p = C_v \times IP \times GRAF \times L \times EF \times 10^{-6}$$

where:

DOSEp = Exposure dose through ingestion of homegrown produce (mg/kg/d)
Cv = Concentration in specific type of crop (i.e., exposed, leafy, protected, root [µg/kg])
IP = Consumption of specific type of crop (g/kg BW*day)
GRAF = Gastrointestinal relative absorption factor (unitless)
L = Fraction of plant type consumed that is homegrown or locally grown (unitless)
EF = Exposure frequency (unitless, days/365 days)
10-6 = Conversion factor (µg/kg to mg/g).

Equation 3

$$Total\ DOSE_p = DOSE_p(leafy) + DOSE_p(root) + DOSE_p(exposed) + DOSE_p(protected)$$

3.4.1.3 Step Three: Calculating Risk

The cancer risk for homegrown crops is calculated by multiplying the oral dose by the oral cancer potency factor, the age sensitivity factor, and the exposure duration divided by averaging time (Equation 4). Risk is calculated separately for each age grouping and then summed to yield cancer risk, representing a specific risk for a resident over a 30-year exposure duration (Equation 5). It is noteworthy that 97% of the dose and risk from the crop ingestion comes from the absorption of Cr(VI) from soil and translocation to the fruit, were as 3% occurs from deposition on leafy produce.

Equation 4

$$RISK_{noninh} = DOSE_{noninh} \times CPF_{oral} \times ASF \times {}^{ED}/_{AT}$$

where:

RISKnoninh = Non-inhalation pathway cancer risk
DOSEnoninh = Daily dose (mg/kg-day) for a specified non-inhalation pathway for each age group
CPForal = Oral cancer potency (slope) factor (mg/kg-day^{-1})
ASF = Age sensitivity factor for a specified age group (unitless)
ED = Exposure duration (in years) for a specified age group
AT = Averaging time for lifetime cancer risk (years).

To account for age-dependent adjustment factors **Equation 5** is applied[5]:

$$RISK_{noninh} = (DOSE_{noninh\_3rd\_trimester} \times CPF_{oral} \times 10\times {}^{0.25}/_{70}) + (DOSE_{noninh\_age\_0<2} \times CPF_{oral} \times 10\times {}^{2}/_{70}) + (DOSE_{noninh\_age\_2<16} \times CPF_{oral} \times 3\times {}^{14}/_{70}) + (DOSE_{noninh\_age\_16<30} \times CPF_{oral} \times 1\times {}^{14}/_{70})$$

3.4.2 Overestimation of Risk via Ingestion of Homegrown Crops

The HARP2 model fails to consider Cr(VI) reduction that occurs in plants, resulting in the conversion of Cr(VI) to Cr(III).

The reduction of Cr(VI) to Cr(III) in plants has been shown, for instance, by a study evaluating chromium species in the following crops: beet, broccoli, cabbage, cantaloupe, cauliflower, celery, chive, collard, cucumber, garden pea, kale, lettuce, onion, radish, spinach, strawberry, tomato, and turnip (Zayed et al., 1998). After all tested exposure conditions, lasting up to seven days of treatment, chromium speciation analysis indicated that all Cr(VI) was converted to Cr(III) in all plants (Zayed et al., 1998). An additional study found that Cr(VI) supplied in nutrient culture of wetland plants was fully reduced to Cr(III) within the root and shoot tissues (Lytle et al., 1998). The authors used these findings to advocate for the utility of plant-based Cr(VI) reduction in Cr(VI)-contaminated waste streams (Lytle et al., 1998).

Additional studies have specifically evaluated plants for Cr(VI) remediation purposes. For instance, Xu and Jaffe (2006) evaluated two wetland plants and found that the plants significantly removed aqueous Cr(VI) in sediments. Corroborating the aforementioned studies, speciation analysis identified Cr(III) as the dominant form of chromium in plant materials (Xu and Jaffe, 2006). Other plants, including tumbleweed (Gardea-Torresdey et al., 2005), fern (Su et al., 2005), weed plants (Sampanpanish et al., 2006), and certain tree species (Mangkoedihardjo et al., 2008), have also shown potential utility for phytoremediation of Cr(VI)-contaminated soil.

Together, these data show that Cr(VI) is efficiently reduced to Cr(III) in plants, including fruit and vegetable crops. Thus, the ingestion of Cr(VI) via homegrown crops is unlikely to occur and should not be considered in HARP2 for Cr(VI). The inclusion of homegrown crop ingestion when calculating risk associated with emitted Cr(VI), as is done using standard OEHHA models, results in a significant overestimation of risk and an invalid basis for setting a guidance value or criteria used in rule-making.

---

[5] Note that OEHHA's calculations include increased risk from exposure during the 3rd trimester; however a fetus does not breathe air or ingest soil, dust, or vegetables, and as such the age-sensitivity factor for this age is clearly not appropriate. This equation is generically applied to all chemical carcinogens including Cr(VI), but is not valid for Cr(VI).

3.5 Consideration of Chromium Reduction Kinetics: Extracellular Reduction of Cr(VI) to Cr(III) Following Ingestion

Chromium reduction kinetics, specifically related to the extracellular reduction of Cr(VI) to Cr(III) following ingestion, has been described in numerous publications and by government agencies ATSDR, U.S. EPA, NIOSH, and OEHHA. It is well recognized that Cr(VI) is reduced to Cr(III) in the stomach and other tissues, which reduces the toxicity of Cr(VI) (ATSDR, 2012; IARC, 2012; NIOSH, 2013). Cellular uptake of Cr(III) is limited by this extracellular reduction, and IARC indicates that "cell membrane is nearly impermeable barrier for Cr(III)" (IARC, 2012).

Absorption and reduction of Cr(VI) are competing kinetic processes delineated by PBPK models. Recent publications by Kirman, Proctor, and De Flora and colleagues have extensively characterized Cr(VI) reduction kinetics in human gastric fluid and developed PBPK models (Kirman, et al., 2016, 2017). In De Flora et al. (2016), human gastric fluid was effective in reducing Cr(VI) to Cr(III) and mitigating its mutagenicity. In 16 paired gastric fluid samples from eight healthy volunteers, the mean reducing ability was measured as 20.4 ± 2.6 μg Cr(VI)/mL gastric fluid in post-meal samples (De Flora et al., 2016). Moreover, at pH 2.0, gastric fluid reduction of Cr(VI) to Cr(III) was rapid, with greater than 70% of total reduction complete within 1 minute. Using highly sophisticated measurement instruments, Kirman and colleagues also showed that human gastric samples contained multiple pools of reducing agents that reduced Cr(VI) to Cr(III), and that low concentrations of Cr(VI) (<0.7 mg/L) are reduced rapidly to Cr(III) (Kirman et al., 2016).

The results of these studies indicate that, at daily exposures less than or equal to 0.003 mg/kg-day among sensitive subpopulations, Cr(VI) is reduced to Cr(III) prior to or upon systemic absorption (Thompson et al. 2017). The total oral dose that can be calculated in HARP2 at an airborne concentration of 1 ng/m^3 is an order of magnitude lower than this dose (0.0003 mg/kg-day). Thus, even if one were to presume that Cr(VI) could exist in crops and accumulate in dust and soil without been reduced to Cr(III), the theoretical dose is well below the dose at which Cr(VI) can be detoxified. As such, the best available science support that there is no increased cancer risk from ingestion exposures due to deposition of Cr(VI) particles on soil and uptake by homegrown crops.

4 Conclusions

The SCAQMD risk-based benchmark of 0.2 ng/m^3 and the related source monitoring benchmark of 1 ng/m^3 are not supported by the current state of the science for Cr(VI). The assumption of risk by ingestion of crops and by ingestion of particles of dust and soil is invalid. Correcting this incorrect assumption would result in changing airborne benchmarks of 0.2 ng/m^3 and 1 ng/m^3 to 0.32 ng/m^3 and 1.6 ng/m^3, respectively (a factor of 1.6 [1 ÷ 0.63)] because 37% of OEHHA and SCAQMD's calculated cancer risk comes from ingestion exposures. However, at these doses and by ingestion of fruits and vegetables, the evidence clearly supports that no cancer risk exists.

There is no evidence that Cr(VI) is associated with elevated lung cancer risk at environmental levels, and considerable data supporting that at the low levels encountered in the environment, the risk is *de minimis*. OEHHA, and most regulatory agencies, use risk assessment models that presume that the risk at very high exposures can be extrapolated to very low exposures using a linear model. Using the conservative linear model with more reliable and current assessments of the inhalation cancer potency of Cr(VI) would result in benchmarks that are substantially higher than that currently being developed from the outdated OEHHA assessment.

5 References

ATSDR. 2012. Toxicological profile for chromium. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Cohen SM, Gordon EB, Singh P, Arce GT, Nyska A. 2010. Carcinogenic mode of action of folpet in mice and evaluation of its relevance to humans. Crit Rev Toxicol 40(6):531-45, 10.3109/10408441003742903.

Cole P, Rodu B. 2005. Epidemiologic studies of chrome and cancer mortality: A series of meta-analyses. Regul Toxicol Pharmacol 43(3):225-31.

Crump C, Crump K, Hack E, Luippold R, Mundt K, et al. 2003. Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal 23(6):1147-63.

De Flora S. 2000. Threshold mechanisms and site specificity in chromium(VI) carcinogenesis. Carcinogenesis 21:533-41.

De Flora S, Camoirano A, Micale RT, La Maestra S, Savarino V, et al. 2016. Reduction of hexavalent chromium by fasted and fed human gastric fluid. I. Chemical reduction and mitigation of mutagenicity. Toxicol Appl Pharmacol 306:113-9, 10.1016/j.taap.2016.07.004.

Gardea-Torresdey JL, de la Rosa G, Peralta-Videa JR, Montes M, Cruz-Jimenez G, Cano-Aguilera I. 2005. Differential uptake and transport of trivalent and hexavalent chromium by tumbleweed (Salsola kali). Arch Environ Contam Toxicol 48(2):225-32.

Gatto NM, Kelsh MA, Mai DH, Suh M, Proctor DM. 2010. Occupational exposure to hexavalent chromium and cancers of the gastrointestinal tract: A meta-analysis. Cancer Epidemiol 34(4):388-99, 10.1016/j.canep.2010.03.013.

Gibb HJ, Lees PS, Pinsky PF, Rooney BC. 2000. Lung cancer among workers in chromium chemical production. Am J Indust Med 38(2):115-26.

Gibb HJ, Lees PS, Wang J, Grace O'Leary K. 2015. Extended followup of a cohort of chromium production workers. Am J Indust Med 58(8):905-13, 10.1002/ajim.22479.

Gordon E. 2007. Captan: transition from 'B2' to 'not likely'. How pesticide registrants affected the EPA Cancer Classification Update. J Appl Toxicol 27(5):519-26, 10.1002/jat.1265.

Haney JT, Erraguntla N, Sielken RL, Valdez-Flores C. 2012. Development of a cancer-based chronic inhalation reference value for hexavalent chromium based on a nonlinear-threshold carcinogenic assessment. Regul Toxicol Pharmacol 64(3):466-80, 10.1016/j.yrtph.2012.10.008.

Haney JT Jr, Erraguntla N, Sielken RL Jr, Valdez-Flores C. 2014. Development of an inhalation unit risk factor for hexavalent chromium. Regul Toxicol Pharmacol 68(2):201-11, 10.1016/j.yrtph.2013.12.005.

Haney J Jr. 2015. Consideration of non-linear, non-threshold and threshold approaches for assessing the carcinogenicity of oral exposure to hexavalent chromium. Regul Toxicol Pharmacol 73(3):834-52, 10.1016/j.yrtph.2015.10.011.

Health Canada. 2015. Chromium in drinking water: Document for public consultation.

IARC. 1990. Chromium, nickel, and welding. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans 49:1-648.

IARC. 2012. Chromium (VI) compounds. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100C, Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-9.pdf doi.

Kirman CR, Hays SM, Aylward LL, Suh M, Harris MA, et al. 2012. Physiologically based pharmacokinetic model for rats and mice orally exposed to chromium. Chem Biol Interact 200:45-64, 10.1016/j.cbi.2012.08.016.

Kirman CR, Suh M, Hays SM, Gurleyuk H, Gerads R, et al. 2016. Reduction of hexavalent chromium by fasted and fed human gastric fluid. II. Ex vivo gastric reduction modeling. Toxicol Appl Pharmacol 306:120-33, 10.1016/j.taap.2016.07.002.

Kirman CR, Suh M, Proctor DM, Hays SM. 2017. Improved physiologically based pharmacokinetic model for oral exposures to chromium in mice, rats, and humans to address temporal variation and sensitive populations. Toxicol Appl Pharmacol 325:9-17, 10.1016/j.taap.2017.03.023.

Luippold RS, Mundt KA, Austin RP, Liebig E, Panko J, et al. 2003. Lung cancer mortality among chromate production workers. Occup Environ Med 60(6):451-7.

Lytle CM, Lytle FW, Yang N, Qian J-H, Hansen D, Zayed A, Terry N. 1998. Reduction of Cr(VI) to Cr(III) by wetland plants: Potential for in situ heavy metal detoxification. Environ Sci Technol 32:3087-93.

Mancuso TF. 1975. Consideration of chromium as an industrial carcinogen. International Conference on Heavy Metals in the Environment, Toronto, Ontario, Canada, October 27-31. pp. 343-356.

Mangkoedihardjo S, Ratnawati R, Alfianti N. 2008. Phytoremediation of hexavalent chromium polluted soil using Pterocarpus indicus and Jatropha curcas L. Word Appl Sci J 4(3):338-42.

Nickens KP, Patierno SR, Ceryak S. 2010. Chromium genotoxicity: A double-edged sword. Chemico-Biol Interact 188:276-88.

NCI. 1977. Bioassay of captan for possible carcinogenicity, CAS No. 133-06-2. National Cancer Institute, Carcinogenesis Technical Report Series 15.

NIOSH. 2013. Criteria for a recommended standard. Occupational Exposure to Hexavalent Chromium. Department of Health and Human Services, National Institute for Occupational Safety and Health, Publication No. 2013-128.

NJDEP. 2009. Derivation of ingestion-based soil remediation criterion for Cr+6 based on the NTP chronic bioassay data for sodium dichromate dihydrate. New Jersey Department of Environmental Protection.

NTP. 2008. National Toxicology Program technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies), NTP TR 546. NIH Publication No. 08-5887.

NTP. 2010. National Toxicology Program technical report on the toxicology and carcinogenesis studies of chromium picolinate monohydrate (CAS NO. 27882-76-4) in F344/N rats and B6C3F1 mice (feed studies). NIH Publication No. 08-5897.

O'Brien TJ, Ding H, Suh M, Thompson C, Parsons BL, Harris MA, et al. 2013. Assessment of K-Ras mutant frequency and micronucleus incidence in the mouse duodenum following 90-days of exposure to Cr(VI) in drinking water. Mutat Res 754(1-2):15-21, 10.1016/j.mrgentox.2013.03.008.

OEHHA. 1995. Appendix B. Comparison of Cal/EPA and US EPA Toxicity Values. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, https://oehha.ca.gov/media/downloads/risk-assessment/report/appbraac.pdf doi.

OEHHA. 2008. Technical supporting document for noncancer RELS, Appendix D3. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, https://oehha.ca.gov/media/downloads/crnr/appendixd3final.pdf

OEHHA. 2011. Final technical support document on public health goal for hexavalent chromium in drinking water. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Pesticide and Environmental Toxicology Branch.

OEHHA. 2016. Chromium-hexavalent. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, https://oehha.ca.gov/chemicals/chromium-hexavalent.

OSHA. 2006. Occupational exposure to hexavalent chromium, final rule. Occupational Safety and Health Administration, 29 CFR Parts 1910, 1915, 1917, 1918, and 1926.

Park RM, Bena JF, Stayner L, Smith RJ, Gibb H, Lees PSJ. 2004. Hexavalent chromium and lung cancer in the chromate industry: A quantitative risk assessment. Risk Anal 24(5):1099-108, 10.1111/j.0272-4332.2004.00512.x.

Park RM, Stayner LT. 2006. A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. Risk Anal 26:79-88.

Proctor DM, Panko JP, Liebig EW, Scott PK, Mundt KA, et al. 2003. Workplace airborne hexavalent chromium concentrations for the Painesville, Ohio, chromate production plant (1943-1971). Appl Occup Environ Hyg 18:430-49.

Proctor DM, Panko JP, Liebig EW, Paustenbach DJ. 2004. Estimating historical occupational exposure to airborne hexavalent chromium in a chromate production plant: 1940–1972. J Occup Environ Hyg 1:752-67.

Proctor DM, Suh M, Aylward LL, Kirman CR, Harris MA, Thompson CM, et al. 2012. Hexavalent chromium reduction kinetics in rodent stomach contents. Chemosphere 89(5):487-93, 10.1016/j.chemosphere.2012.04.065.

Proctor DM, Suh M, Campleman SL, Thompson CM. 2014. Assessment of the mode of action for hexavalent chromium-induced lung cancer following inhalation exposures. Toxicology 325:160-179.

Proctor DM, Suh MS, Mittal L, Hirsch S, Valdes Salgado R, Bartlett C, et al. 2016. Inhalation cancer risk assessment of hexavalent chromium based on updated mortality for Painesville chromate production workers. J Expo Sci Environ Epidemiol 26(2):224-31, 10.1038/jes.2015.77.

Rager JE, Rager JE, Ring CL, Fry RC, Suh M, Proctor DM, Haws LC, et al. 2017. High-throughput screening data interpretation in the context of in vivo transcriptomic responses to oral Cr(VI) exposure. Toxicol Sci kfx085. doi: 10.1093/toxsci/kfx085.

Sampanpanish P, Pongsapich W, Khaodhiar S, Khan E. 2006. Chromium removal from soil by phytoremediation with weed plant species in Thailand. Water Air Soil Pollut: Focus 6(1):191-206.

SCAQMD. 2015. MATES IV. Final Report: Multiple Air Toxics Exposure Study in the South Coast Air Basin. May 2015. Appendix IV. Summaries for the MATES IV Fixed Monitoring Sites. South Coast Air Quality Management District, http://www.aqmd.gov/docs/default-source/air-quality/air-toxic-studies/mates-iv/d-appendix.pdf?sfvrsn=7

SCAQMD. 2017. Proposed rules and proposed amended rules. South Coast Air Quality Management District, http://www.aqmd.gov/home/regulations/rules/proposed-rules .

SCOEL. 2017. SCOEL/REC/386. Chromium VI compounds. Recommendation from the Scientific Committee on Occupational Exposure Limits. European Commission B-1049, Brussels.

Su Y, Han FX, Sridhar BB, Monts DL. 2005. Phytotoxicity and phytoaccumulation of trivalent and hexavalent chromium in brake fern. Environ Toxicol Chem 24(8):2019-26.

Suh M, Harvey S, Wikoff D, Mittal L, Ring C, Goodmanson A, Proctor D. Meta-analysis of hexavalent chromium and stomach cancer. Poster presented at Society of Toxicology Annual Meeting. March 13, 2017. Baltimore, MD.

TCEQ. 2014. Development Support Document, Final. Hexavalent Chromium (Particulate Compounds). Texas Commission on Environmental Quality. https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/final/august2014/hexavalent_chromium.pdf.

TCEQ. 2016. Hexavalent chromium oral reference dose: Development Support Document (Final). Texas Commission on Environmental Quality.

Thompson CM, Proctor DM, Haws LC, Hebert CD, Grimes SD, Shertzer HG, et al. 2011. Investigation of the mode of action underlying the tumorigenic response induced in B6C3F1 mice exposed orally to hexavalent chromium. Toxicol Sci 123(1):58-70, 10.1093/toxsci/kfr164.

Thompson CM, Hixon JG, Proctor DM, Haws LC, Suh M, Urban JD, Harris MA. 2012. Assessment of genotoxic potential of Cr(VI) in the mouse duodenum: An in silico comparison with mutagenic and nonmutagenic carcinogens across tissues. Regul Toxicol Pharmacol 64(1):68-76, 10.1016/j.yrtph.2012.05.019.

Thompson CM, Proctor DM, Suh M, Haws LC, Kirman CR, et al. 2013. Assessment of the mode of action underlying development of rodent small intestinal tumors following oral exposure to hexavalent chromium and relevance to humans. Crit Rev Toxicol 43:244-74.

Thompson CM, Kirman CR, Proctor DM, Haws LC, Suh M, Hays SM, et al. 2014. A chronic oral reference dose for hexavalent chromium-induced intestinal cancer. J Appl Toxicol 34(5):525-36, 10.1002/jat.2907.

Thompson CM, Wolf JC, Elbekai RH, Paranjpe MG, Seiter JM, Chappell MA, et al. (2015a). Duodenal crypt health following exposure to Cr(VI): Micronucleus scoring, gamma-H2AX immunostaining, and synchrotron X-ray fluorescence microscopy. Mutat Res. 789-790:61-6, 10.1016/j.mrgentox.2015.05.004.

Thompson CM, Young RR, Suh M, Dinesdurage HR, Elbekai RH, Harris MA, et al. 2015b. Assessment of the mutagenic potential of Cr(VI) in the oral mucosa of Big Blue((R)) transgenic F344 rats. Environ Mol Mutagen 56(7):621-8, 10.1002/em.21952.

Thompson CM, Young RR, Dinesdurage H, Suh M, Harris MA,Rohr AC, Proctor DM. 2017. Assessment of the mutagenic potential of hexavalent chromium in the duodenum of Big Blue® rats. Toxicol Appl Pharmacol 330(1):48-52.

Thompson CM, Kirman, CR, Hays, SM, Suh M, Harvey SE, Proctor DM, Rager JE, Haws LC, and Harris MA. 2017 In Press. Integration of Mechanistic and Pharmacokinetic Information to Derive Oral Reference Dose and Margin-of-Exposure Values for Hexavalent Chromium. Journal of Applied Toxicology, Accepted.

U.S. EPA. 1998. Toxicological review of hexavalent chromium in support of summary information on the integrated risk information system (IRIS). U.S. Environmental Protection Agency, Washington, D.C.

U.S. EPA. 2004. Captan; Cancer Reclassification; Amendment of Reregistration Eligibility Decision; Notice of Availability. U.S. Environmental Protection Agency, Federal Register 69:68357-68360.

U.S. EPA. 2005a. Guidelines for carcinogen risk assessment. EPA/630/P-03/001F. U.S. Environmental Protection Agency, Risk Assessment Forum Washington, D.C.

U.S. EPA. 2005b. Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. EPA/630/R-03/003F.U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, D.C.

U.S. EPA. 2006. Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment. EPA/600/R-05/043F. U.S. Environmental Protection Agency, Washington, D.C.

U.S. EPA. 2009. Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part F, Supplemental Guidance for Inhalation Risk Assessment). EPA-540-R-070-002 OSWER 9285.7-82. U.S. Environmental Protection Agency, Washington, D.C.

U.S. EPA. 2017a. Chromium (VI). CASRN 18540-29. File First On-Line March 31, 1987. U.S. Environmental Protection Agency, Washington, D.C. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0144_summary.pdf -nameddest=cancerinhal.

U.S. EPA. 2017b. Data summary of the Third Unregulated Contaminant Monitoring Rule (UCMR3). EPA 815-S-17-001. U.S. Environmental Protection Agency, Washington, D.C.(data accessed January 15, 2017).

Welling R, Beaumont JJ, Petersen SJ, Alexeeff GV, Steinmaus C. 2015. Chromium VI and stomach cancer: A meta-analysis of the current epidemiological evidence. Occup Environ Med 72(2):151-9, 10.1136/oemed-2014-102178.

Xu S, Jaffe PR. 2006. Effects of plants on the removal of hexavalent chromium in wetland sediments. J Environ Qual 35(1):334-341.

Zayed A, Lytle M, Qian J-H, Terry N. 1998. Chromium accumulation, translocation and chemical speciation in vegetable crops. Planta 206:293-299.

APPENDIX A

Recent Peer-Reviewed Publications Related to Cr(VI) Oral Carcinogenicity

Publications are listed in chronological order, from current to oldest. Hyperlinks to the publication are available for each paper.

Thompson CM, Young RR, Dinesdurage H, Suh M, Harris MA, Rohr AC, Proctor DM. 2017. Assessment of the mutagenic potential of hexavalent chromium in the duodenum of Big Blue® rats. Toxicol Appl Pharmacol 330(1):48-52.

Rager JE, Rager JE, Ring CL, Fry RC, Suh M, Proctor DM, Haws LC, et al. 2017. High-throughput screening data interpretation in the context of in vivo transcriptomic responses to oral Cr(VI) exposure. Toxicol Sci 158(1):199–212.

Thompson CM, Rager JE, Suh M, Ring CL, Proctor DM, Haws LC, Fry RC, Harris MA. 2016. Transcriptomic Responses in the oral cavity of F344 rats and B6C3F1 mice following exposure to Cr(VI): implications for risk assessment. Env Mol Mut. 57: 706-716.

De Flora S, Camoirano A, Micale RT, La Maestra S, Savarino V, Zentilin P, Marabotto E, Suh M, Proctor DM. 2016. Reduction of hexavalent chromium by fasted and fed human gastric fluid. I. Chemical reduction and mitigation of mutagenicity. Toxicol Appl Pharmacol. 306: 113-119.

Kirman CR, Suh M, Hays SM, Gürleyük H, Gerads R, De Flora S, Parker W, Lin S, Haws LC, Harris MA, Proctor DM. 2016. Reduction of hexavalent chromium by fasted and fed human gastric fluid. II. Ex vivo gastric reduction modeling. Toxicol Appl Pharmacol. 306: 120-133.

Thompson CM, Bichteler A, Rager JE, Suh M, Proctor DM, Haws LC, Harris MA. 2016. Comparison of in vivo genotoxic and carcinogenic potency to augment mode of action analysis: case study with hexavalent chromium. Mutat Res-Gen Tox En. 800-801: 28-34.

Thompson CM, Seiter J, Chappell MA, Tappero RV, Proctor DM, Suh M, Wolf JC, Haws LC, Vitale R, Mittal L, Kirman CR, Hays SM, Harris MA. 2015. Synchrotron-based imaging of chromium and γ-H2AX immunostaining in the duodenum following repeated exposure to Cr(VI) in drinking water. Toxicol Sci. 143(1): 16-25.

Thompson CM, Wolf JC, Elbekai RH, Paranjpe MG, Seiter JM, Chappell MA, Tappero RV, Suh M, Proctor DM, Bichteler A, Haws LC, Harris MA. 2015. Duodenal crypt health following exposure to Cr(VI): Micronucleus scoring γ-H2AX immunostaining, and synchrotron X-ray fluorescence microscopy. Mutat Res. 789-790: 61-66.

Thompson CM, Young RR, Suh M, Dinesdurage HR, Elbekai RH, Harris MA, Rohr AC, Proctor DM. 2015. Assessment of the Mutagenic Potential of Cr(VI) in the Oral Mucosa of Big Blue Transgenic F344 Rats. Environ Mol Mutagen. 56: 621-628.

Suh M, Thompson CM, Kirman CR, Carakostas M, Haws LC, Harris M, Proctor D. 2014. High concentrations of hexavalent chromium in drinking water alter iron homeostasis in F344 rats and B6C3F1 mice. Food Chem Toxicol. 65: 381-388.

Thompson CM, Kirman CR, Proctor DM, Haws LC, Suh M, Hays S, Hixon JG, Harris MA. 2014. A chronic oral reference dose for hexavalent chromium-induced intestinal cancer. J Appl Toxicol. 34: 525-536.

O'Brien T, Ding H, Suh M, Thompson C, Parsons BL, Harris MA, Winkelman WA, Wolf JC, Hixon JG, Schwartz AM, Myers MB, Haws LC, Proctor DM. 2013. Assessment of K-Ras mutant frequency and micronucleus incidence in the mouse duodenum following 90-days of exposure to Cr(VI) in drinking water. Mutat Res. 754(1-2): 15-21.

Thompson CM, Proctor DM, Suh M, Haws LC, Kirman CR, Harris MA. 2013. Assessment of the mode of action underlying development of rodent small intestinal tumors following oral exposure to hexavalent chromium and relevance to humans. Crit Rev Toxicol. 43(3): 244-274.

Kirman CR, Hays SM, Aylward LL, Suh M, Harris MA, Thompson CM, Haws LC, Proctor DM. 2012. Physiologically based pharmacokinetic model for rats and mice orally exposed to chromium. Chem-Biol Interact. 200(1): 45-64.

Kopec AK, Thompson CM, Kim S, Forgacs AL, Zacharewski TR. 2012. Comparative Toxicogenomic Analysis of Oral Cr(VI) Exposure Effects in Rat and Mouse Small Intestinal Epithelium. Toxicol Appl Pharmacol. 262(2): 124-38.

Kopec AK, Kim S, Forgacs AL, Zacharewski TR, Proctor DM, Harris MA, Haws LC, Thompson CM. 2012. Genome-wide gene expression effects in B6C3F1 mouse intestinal epithelia following 7 and 90 days of exposure to hexavalent chromium in drinking water. Toxicol Appl Pharmacol. 259(1): 13-26.

Proctor DM, Suh M, Aylward LL, Kirman CR, Harris MA, Thompson CM, Gürleyük H, Gerads R, Haws LC, Hays SM. 2012. Hexavalent chromium reduction kinetics in rodent stomach contents. Chemosphere. 89(5): 487-93.

Thompson CM, Fedorov Y, Brown DD, Suh M, Proctor DM, Kuriakose L, Haws LC, Harris MA. 2012. Assessment of Cr(VI)-Induced Cytotoxicity and Genotoxicity Using High Content Analysis. PLoS ONE. 7(8): e42720.

Thompson CM, Hixon JG, Proctor DM, Haws LC, Suh M, Urban JD, Harris MA. 2012. Assessment of Genotoxic Potential of Cr(VI) in the Mouse Duodenum: An In Silico Comparison with Mutagenic and Nonmutagenic Carcinogens Across Tissues. Regul Toxicol Pharmacol. 64(1): 68-76.

Thompson CM, Proctor DM, Suh M, Haws LC, Hebert CD, Mann JF, Shertzer HG, Hixon JG, Harris MA. 2012. Comparison of the Effects of Hexavalent Chromium in the Alimentary Canal of F344 Rats and B6C3F1 Mice Following Exposure in Drinking Water: Implications for Carcinogenic Modes of Action. Toxicol Sci. 125(1):79-90.

Thompson CM, Proctor DM, Harris MA. 2012. Duodenal GSH/GSSG Ratios in Mice Following Oral Exposure to Cr(VI). Toxicol Sci. 126(1): 287-288.

Thompson CM, Proctor DM, Haws LC, Hebert CD, Grimes SD, Shertzer HG, Kopec AK, Hixon JG, Zacharewski TR, Harris MA. 2011. Investigation of the Mode of Action Underlying the Tumorigenic Response Induced in B6C3F1 Mice Exposed Orally to Hexavalent Chromium. Toxicol Sci. 123(1): 58-70.

Thompson CM, Haws LC, Harris MA, Gatto NM, Proctor DM. 2011. Application of the U.S. EPA Mode of Action Framework for Purposes of Guiding Future Research: A Case Study Involving the Oral Carcinogenicity of Hexavalent Chromium. Toxicol Sci. 119(1): 20-40.

APPENDIX B

Recent Publications and Reports Related to Cr(VI) Epidemiology and Inhalation Risk Assessment

Publications are listed in alphabetical order.

Crump C, Crump K, Hack E, Luippold R, Mundt K, et al. 2003. Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal 23(6):1147-63. https://www.ncbi.nlm.nih.gov/pubmed/14641890

Haney JT, Erraguntla N, Sielken RL, Valdez-Flores C. 2012. Development of a cancer-based chronic inhalation reference value for hexavalent chromium based on a nonlinear-threshold carcinogenic assessment. Regul Toxicol Pharmacol 64:466-80. http://www.sciencedirect.com/science/article/pii/S0273230012001948

Haney JT Jr, Erraguntla N, Sielken RL Jr. Valdez-Flores C. 2014. Development of an inhalation unit risk factor for hexavalent chromium. Regul Toxicol Pharmacol 68:201-11. http://www.sciencedirect.com/science/article/pii/S0273230013002201?via%3Dihub

NIOSH. 2013. Criteria for a recommended standard. Occupational Exposure to Hexavalent Chromium. Department of Health and Human Services, National Institute for Occupational Safety and Health, Publication No. 2013-128. https://www.cdc.gov/niosh/docs/2013-128/pdfs/2013_128.pdf

OSHA. 2006. Occupational exposure to hexavalent chromium, final rule. Occupational Safety and Health Administration, 29 CFR Parts 1910, 1915, 1917, 1918, and 1926. https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=18599&p_table=federal_register

Park RM, Bena JF, Stayner LT, Smith RJ, Gibb HJ, et al. 2004. Hexavalent chromium and lung cancer in the chromate industry: A quantitative risk assessment. Risk Anal 24:1099-108. https://www.ncbi.nlm.nih.gov/pubmed/15563281

Park, RM and Stayner, LT. A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. Risk Anal. 26(1):79-88. https://www.ncbi.nlm.nih.gov/pubmed/16492182

Proctor D, Panko J, Liebig E, Mundt K, Buczynski M, Barnhart R, Harris MA, Morgan R, Finley B, and Paustenbach D. 2003. Workplace concentrations of airborne hexavalent chromium for the Painesville, Ohio chromate production plant. Appl Occ Environ Hyg J. 18(6):430-449.

Proctor DM, Panko JP, Liebig EW, Paustenbach, DJ. 2004. Estimating historical occupational exposure to airborne hexavalent chromium in a chromate production plant: 1940–1972. Occup Environ Hyg. 1:752–767.

Proctor DM, Suh M, Campleman SL, Thompson CM. 2014. Assessment of the mode of action for hexavalent chromium-induced lung cancer following inhalation exposures. Toxicology 325:160-179. https://www.ncbi.nlm.nih.gov/pubmed/25174529

Proctor DM, Suh M, Mittal L, Hirsch S, Valdes Salgado R, et al. 2016. Inhalation cancer risk assessment of hexavalent chromium based on updated mortality for Painesville chromate production workers. J Expo Sci Environ Epidemiol 26:224-31. https://www.ncbi.nlm.nih.gov/pubmed/26669850

SCOEL. 2017. SCOEL/REC/386. Chromium VI compounds. Recommendation from the Scientific Committee on Occupational Exposure Limits. European Commission B-1049, Brussels.

Seidler, A, Jahnichen, S, Hegewald, J et al. 2013. Systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium. Int. Arch. Occup Envion Health. 86(8): 943-99. https://www.ncbi.nlm.nih.gov/pubmed/23079792