Tox Strategies

Comments:
Docket ID No. EPA-HQ-ORD-2014-0313 for the Hexavalent Chromium IRIS Inhalation Cancer Risk Assessment

December 19, 2022

We appreciate the update that EPA has conducted for the hexavalent chromium [Cr(VI)] inhalation cancer risk assessment, and recognize that the use of new data from Gibb et al. (2015) has substantially improved the information available, relative to that used for the current IRIS assessment, which was conducted originally in 1984, to evaluate increased cancer risk associated with current environmental exposures. However, several significant limitations exist with the epidemiological data used for this assessment that should be clearly recognized. Based on these limitations, it is questionable whether the studies of the Baltimore cohort of chromate production workers should be considered of "high" confidence for assessing environmental exposures for several reasons. Importantly, the margin of exposure (MOE) between current environmental exposures to Cr(VI) (upper bound of ~0.1 ng/m^3) and exposures that induce lung cancer in animal and human studies, including the study of Baltimore chromate production workers used for the IRIS update, is approximately 500,000 (Proctor et al., 2021). Therefore, low-dose extrapolation includes a high degree of uncertainty, and better data are needed to understand the lung cancer risk (if any) at exposures that are more representative of current environmental exposures.

Specific concerns that should be recognized and discussed in the IRIS document include the following.

1. Extrapolation from short-term, high-concentration occupational exposures to long-term, low-level exposure introduces significant uncertainties, especially considering that cumulative dose is the dose metric used in all assessments, and that a dose-rate effect has been observed for lung cancer with Cr(VI) in both animals and humans (Steinhoff et al., 1986; Gibb et al., 2011).
2. Clinical symptoms of tissue damage (ulcerated, perforated nasal septum) have been associated with increased lung cancer risk in epidemiologic studies of the Baltimore cohort (Gibb et al., 2015, 2020). Although tissue damage may be a marker of exposure, it is arguably a causal factor in the mode of action (Proctor et al. 2014, 2021). The currently available epidemiologic data does not inform whether respiratory tissue damage is an intermediate marker of high-intensity exposure, or a causal factor, and this uncertainty should be considered as a potential basis for environmental risk assessment.

3. The Baltimore chromate production plant used lime in chromate production kilns, creating sparingly soluble calcium chromate compounds, which are known from animal studies to have greater carcinogenic potency than chromate salts (Steinhoff et al., 1986; Levy et al., 1986). Additionally, workers in the Baltimore chromate production industry were exposed to concentrated forms of chromic acid, because the plant operated a chromic acid production process. The Baltimore plant also produced chromate pigments, which have been shown in animal studies to be, by far, the most carcinogenic forms of Cr(VI). Different chemical forms of Cr(VI) have highly varied carcinogenic potency in animal studies (Levy et al., 1986), and the particular chemical forms of Cr(VI) are of questionable relevance to current environmental exposures.
4. The exposure reconstructions for the Baltimore cohorts quantified exposure to soluble forms of Cr(VI) (Gibb et al., 2000b), and the extent to which insoluble or slightly soluble forms of Cr(VI) were captured in the exposure reconstructions is not known.
5. The Baltimore cohort included only males and is of limited racial diversity.
6. The Baltimore cohort includes a significant fraction who worked in the plant for only a short time. Median tenure was only 4 months, and a large fraction of the person years at risk were associated with very short-term workers (60% of person years at risk were derived from workers with less than 1 year of exposure). Exposure misclassifications, particularly among those leaving employment early, possibly for health-related reasons, were noted to have unpredictable effects on the low end of the estimated exposure-response curve (Park and Stayner, 2006).
7. Detailed information regarding exposure concentrations in the Baltimore plant has not been reported, with the exception of summaries published by Braver et al. (1985). However, the fraction of workers with irritated or ulcerated nasal septum was >60%, and mean and median exposures associated with those effects were 24–27 Cr(VI)/m^3 and 10 µg Cr(VI)/m^3, respectively (Gibb et al., 2000a). Because these exposure concentrations were reported based on annual mean concentrations by job title, it is expected that peak exposures far exceeded these average values, and shorter-term variations, including peak concentrations that are more likely to be associated with acute respiratory tissue damage, were not quantified or captured in the exposure reconstruction. The high rates of irritated or ulcerated nasal septum at relatively low exposures may call into question whether the exposures were underestimated or whether the forms of Cr(VI) to which the Baltimore workers were exposed were highly toxic. Regardless, there is a general lack of transparency on airborne concentrations to which workers were exposed.
8. An extensive body of smoking prevalence data is available, with current status at start of employment available for 91% of workers. The fraction of smokers was approximately 80%, and the vast majority of lung cancers also occurred among smokers, with only 4 of 217 lung cancer deaths occurring among non-smokers (Gibb et al., 2015). The authors indicate that an association between smoking and Cr(VI) exposure may exist, but due to the small number of lung cancer deaths among non-smokers, it is not possible to quantify the association. Gibb et al. (2000a) states that the lung cancer relative risk associated with smoking greatly exceeds that from Cr(VI) among these workers [1.6 from Cr(VI) compared to approximately 6 from smoking

(Table VIII of Gibb et al., 2000a)]. This observation calls into question the representativeness of the Baltimore cohort, which had very high rates of smoking, to current environmentally exposed populations.

9. Sixty percent of employees in the Baltimore cohort experienced acute chromium irritation (chrome sores, nasal ulcers, nasal perforations, etc.), most within the first months of employment (Park and Stayner, 2006). A significant association was found between the number of medical treatments for irritated, ulcerated, and perforated nasal septum and increased lung cancer risk (Gibb et al., 2015). Environmental exposures do not cause nasal tissue irritation, thus it is unlikely that the intense exposures that occurred at the Baltimore facility can be extrapolated to low-level environmental exposures.
10. It is highly improbable that not a single case of mesothelioma occurred among the more than 2000 workers of the Baltimore cohort, most of whom had very short-term tenure at the facility, and certainly held other blue-collar jobs in the Baltimore Harbor shipyards (where the facility was located) and worked during the peak of asbestos usage. Rather, the available information indicates that mesothelioma deaths were likely misclassified and misreported as lung cancers. There is clear potential for misclassification given that coding of lung cancer and mesothelioma deaths is not discussed in Gibb et al. (2015), but rather, it is simply stated only that coding by ICD[1] 8, 9, and 10 occurred by date of death. Coding in Gibb et al. (2000b) was performed by ICD 8, and no clinical code for malignant mesothelioma existed until ICD 10 (Tai et al. 2021). The Gibb et al. authors should have addressed this uncertainty, and EPA reviewers should have understood that the lack of mesothelioma cases most likely reflects a lack of clear differentiation between mesothelioma and lung cancer in Baltimore mortality assessment. In fact, neither paper even addresses the potential for mesothelioma deaths, or how mesotheliomas were differentiated from lung cancers.
11. Finally, the de-identified individual-level data from Gibb et al. (2015) are not publicly available, and the risk assessment used by EPA is not in the published literature. ToxStrategies requested that the Agency provide this data set on July 15, 2021, via Freedom of Information Act Request EPA-2022-005463; however, the Agency responded that they do not have possession of the data (Letter from John Steenback, July 18, 2021). The Agency should correct this glaring lack of transparency in the development of the IRIS inhalation unit risk (IUR) by providing the original de-identified data, so that the analysis can be reproduced and independently evaluated by external scientific peer reviewers and the public.

Need for New Risk Assessment Data

Uncertainties and limitations of the studies currently available for inhalation cancer risk assessment of Cr(VI) are well recognized in the scientific community (Proctor et al. 2021), but alternative data sources are not readily available. Thus, to improve the information

[1] International Classification of Disease.

available for risk assessment, new worker epidemiology data for Cr(VI) are needed. In particular, there is a need to specifically study longer term and lower intensity exposure conditions to improve statistical power in the low range of exposure. Additionally, a need for greater diversity of gender and race/ethnicity, and epidemiological data from outside the historical chromate production industry. Such data are likely to be more applicable to current exposure conditions and would greatly inform risk assessment at environmentally relevant exposures.

Given the importance of improved inhalation cancer risk assessment to regulatory decision making and allocation of resources for public health protection, the California Metals Coalition, a non-profit 501C (6) trade association, has provided funding to develop the exposure and cancer mortality data from the Lockheed Martin Burbank Aircraft Manufacturing cohort, which includes more than 3,000 men and women who were routinely exposure to Cr(VI), and had a minimum of 1 year of occupational exposure in metal finishing, painting, sanding, blasting, and related occupations (Lipworth et al 2021, attached). The cohort was limited to those exposed after 1959, through plant closure in 1996. Very importantly, exposure intensities were far below those of the Baltimore and other available cohorts, and historical medical records indicate no evidence of nasal tissue damage due to excessive Cr(VI) exposure. This project builds on previous studies of the Lockheed Martin aircraft manufacturing cohort (Boice et al., 1999; Marano et al., 2000; Lipworth et al., 2011), focusing specifically on those workers identified as being exposed to Cr(VI) in previous studies. Because of the long tenure of workers at the plant (averaging 19 years), and the relatively low levels of Cr(VI) to which workers were exposed (Marano et al., 2000), this data set was identified as a much more robust foundation for developing a cancer risk assessment that is relevant to environmental exposures.

The project team is being directed by Co-Principal Investigators, Dr. Loren Lipworth and Mr. Bruce Allen. Dr. Lipworth, Professor of Medicine at Vanderbilt University Medical Center (VUMC), is the lead author of the previous cohort mortality study update for this cohort (Lipworth et al., 2011). Mr. Allen, who is conducting the quantitative risk assessment, worked with OSHA to develop the occupational cancer risk estimates associated with Cr(VI) exposure for the 2006 Cr(VI) Occupational Exposure Rule. ToxStrategies is providing industrial hygiene, biostatistics, and epidemiology support for the project.

While the mortality follow-up and exposure reconstruction are complete for the Burbank cohort, the project has been expanded to include a combined analysis for lung cancer risk assessment, using the individual data from both the Painesville and Baltimore[2] cohorts, excluding workers with less than one year of occupational exposure consistent with the Burbank cohort. The advantage of this approach is that it will no longer necessary to rely on only one cohort to develop an IUR, and combining all of the available individual-level data will help overcome the many uncertainties noted above in interpreting the Baltimore cohort data in isolation. The approach is statistically robust. It includes data for workers

[2] For the Baltimore cohort the publicly available data from Gibb et al. (2000b) is being used.

with lower levels of exposure—which are more environmentally relevant—and for longer duration exposures, which are less likely to be confounded by exposures to inhalation carcinogens outside the work environment. Finally, the assessment is not specific to one historical industry, with questionable relevance to environmental exposures to Cr(VI).

This project is ongoing but is expected to be completed and published in the peer-reviewed literature in 2023, during the review of USEPA's updated draft IRIS assessment. We believe that this study will provide a data set with the highest confidence of any currently available, allowing for a refined risk assessment that is more relevant to environmental exposures.

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Improving the Inhalation Cancer Risk Assessment for Hexavalent Chromium: Lung Cancer Mortality and Exposure Reconstruction of Aircraft Manufacturing Workers with Long-term Low-level Exposures

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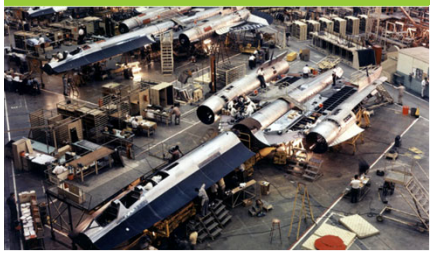


Lockheed Martin Factory Floor Skunkworks, 1965

Introduction

For decades, lung cancer risk assessment for hexavalent chromium [Cr(VI)] has been based on occupational epidemiology studies of male chromate production workers, exposed for relatively short durations to extremely high concentrations, and particularly toxic forms, of Cr(VI). Uncertainties related to using these data to assess cancer risk from low level environmental and occupational exposures are numerous, and improved epidemiologic data and robust risk assessment methods are needed to better quantify risk associated with chronic exposures at low concentrations.

Objective

To reconstruct the Cr(VI) exposures and update the mortality experience of 7,233 aircraft manufacturing workers, in order to provide improved data for cancer risk assessment of airborne Cr(VI) that may be used for regulatory programs

Methods

1. **Mortality Assessment**— The vital status of the chromate exposed members of the Lockheed Martin (LM) aircraft manufacturing cohort was updated through 2019. 7,458 factory workers had the potential for routine daily or intermittent exposure to Cr(VI). Of these, 225 workers had missing job history files and were excluded; thus, 7,233 factory workers, including 715 women, were evaluated.
2. **Exposure Reconstruction**—The workers' exposures to Cr(VI) are quantified using a job exposure matrix and available industrial hygiene data from the historical records, including both short- and long-term samples, consisting of area and personal samples. Facility records were supplemented with data from literature sources.
3. **Cancer Risk Assessment**—The individual level exposure estimates and lung cancer mortality experience will be combined to quantify lung cancer risk associated with cumulative exposure.
4. **Independent external scientific advisory panel (ESAP),** organized by SciPinion, reviewed study protocols and preliminary results and provided guidance to improve methods and regulatory acceptance.

Results

Cohort Description and Mortality Assessment

We previously conducted a large-scale epidemiologic mortality study of workers from the LM aircraft manufacturing facilities in Burbank, California (Boice et al., 1999; Marano et al., 2000; Lipworth et al., 2011).

In our update, as shown in **Figure 1**, a total of 4,892 (68%) workers in the study cohort were found to have died by December 31, 2019 (the end of follow-up) with cause of death known for 99% of them. Only 4 were lost to follow-up.

Figure 1. Cohort vital status tracing flow diagram

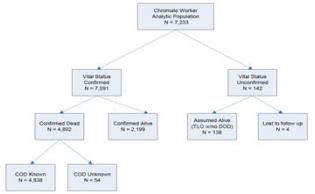


Table 1 shows characteristics of the study cohort, including race, sex, age, calendar year of hire and cumulative duration of employment, as well as duration of follow-up.

Table 1. Characteristics of the chromate-exposed members of the LM Burbank aircraft manufacturers worker cohort with available job histories (N=7,233)

Characteristic	N	%
Sex		
Male	6518	90.1%
Female	715	9.9%
Race		
White	5981	82.7%
Non-White	1252	17.3%
Year of Hire		
Before 1950	1624	22.5%
1950–1959	1993	27.6%
1960–1969	1282	17.7%
1970–1979	1398	19.3%
1980 or after	936	12.9%
Categorical duration of employment (years)		
1–4	1185	16.4%
5–9	1185	16.4%
10–19	1638	22.7%
20–29	1501	20.8%
30–39	1400	19.4%
40+	324	4.5%
Mean Duration of employment (years)	18.8	
Mean Follow-up (years)	36.3	

Table 2. SMRs for lung cancer among chromate-exposed members of the LM Burbank aircraft manufacturers worker cohort

	N workers	Person-years	Obs	Exp [1]	SMR
Cancer, overall	7,233	262,716	1196	1156.2	1.03
Lung cancer, overall	7,233	262,716	347	336.1	1.03
Lung cancer, by decade of hire					
Before 1950	1,624	50,801	89	117.3	0.76*
1950–1959	1,993	75,335	122	124.6	0.98
1960–1969	1,282	52,154	69	54.9	1.26
1970–1979	1,398	52,260	45	28.4	1.58*
1980 or after	936	32,168	22	10.8	2.03*
Lung Cancer, by duration of employment (years)[2]					
Less than 5 years	4,192	54,899	36	28.3	1.27
5-9 years	4,425	50,827	48	31.4	1.53*
10-19 years	4,720	65,209	81	69.3	1.17
20-29 years	3,225	50,382	105	89.8	1.17
> 30 years	1,725	41,400	77	117.3	0.66*

[1] Expected numbers were computed based on race, age, calendar year and sex-specific rates in the general population of California for white workers. For nonwhite workers, US general population rates were used because the racial composition of nonwhites was more similar to that of the US than California.

[2] Duration of employment (DOI) is calculated as the length of time (in years) since the first hire date and is calculated continuously over their time at risk. Therefore, a participant can contribute time at risk over multiple DOE categories.

SMR = Standardized mortality ratio; Obs = Observed; Exp = Expected; * p<0.05 for SMR difference from 1.0

Note: ICD codes for lung cancer include bronchus, trachea, and lung (ICD9: 0478-0479; ICD9: 161-163; ICD7: 161-163; ICD8: 162; ICD9: 162; ICD10: C33-C34)

Observed deaths were counted by race, sex, age and calendar year for workers overall and by subgroups. Standardized Mortality Ratios (SMRs) for cancer overall and for lung cancer were computed for the worker cohort with available job histories and evaluated by decade of hire and years of occupational tenure (**Table 2**). Note that occupational tenure in **Table 2** is not specific to work in the Cr(VI)-exposed jobs but overall tenure in the facility.

Exposure Reconstruction

The exposures by job activity for relevant short-term and full-shift measures are summarized in **Table 3**. Measured air concentration data were not available for every year that cohort members held Cr(VI)-related job titles. Generally, the earliest date for which measured data for most job activities were available was in the 1970s. For this reason, extrapolation was used to estimate air concentrations from time periods preceding 1970, using the distribution of means for the metal processing data set, whose earliest sample dates were 1925 and 1965. We conducted Bayesian statistical analysis to estimate air concentrations for years where measured data were missing.

Table 3. Summary of full-shift and short-term Cr(VI) air concentrations and job activities

Job Activity	Air Concentration (µg/m³) Number of samples	Minimum	Median	Maximum
Metal Processing				
Full-Shift	79	<0.02	2.1	2.912
Short-Term	26	<0.52	0.78	624
Aircraft Painting				
Full-Shift	471	<0.02	6.6	2,900
Short-Term	78	<1.0	24	3,703
Surface Preparation — Sanding[1]				
Full-Shift	200	<0.02	0.74	290.2
Surface Preparation — Abrasive Blasting[1]				
Full-Shift	57	<0.02	2.3	302.4
Aircraft Assembly and non-routine exposures				
Full-Shift	22	<0.1	0.29	5.72
Short-Term	4	<0.2	1.2	4.5

[1] No short-term samples identified.

We assumed that the lognormal probability distribution would adequately model the workers' exposure levels (Lavoué et al., 2019) and log-transformed the data. The goal of Bayesian linear regression was to estimate the distribution of the model parameters (intercept, slope, and standard deviation of the residue), and to simulate new exposure "observations" (i.e., samples from the posterior predictive distribution). We used 50,001 iterations to specify the estimated air concentrations for each job activity. Examples are provided for metal processing (electroplating) (**Figure 2A**) and sanding (**Figure 2B**).

Figure 2A. Bayes regression analysis of detected airborne concentrations for full shift metal processing

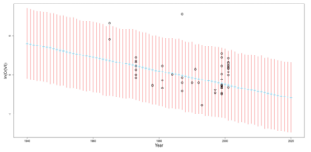
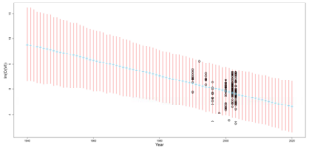


Figure 2B. Bayes regression analysis of detected airborne concentrations for full shift sanding



Cancer Risk Assessment Methods

Combining the results of lung cancer risk with cohort member-specific cumulative exposures, the dose-response analysis will employ Bayesian modeling approaches. The risk assessment will consider various dose metrics that allow varied dose computation approaches. The candidate data-generating processes will consist of dose-response models that define the functional relationship between the independent variables and lung-cancer risk. Three dose-response models will be evaluated:

1. Logistic Model
2. Externally-Standardized Relative Risk Model
3. Poisson Regressions

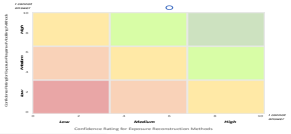
A Markov chain Monte Carlo (MCMC) procedure will be used to generate a sample from the joint posterior for the parameter and predictions of interest.

This approach allows for many modeling options including definition of dose from the exposure data and with the dose-response models, including the possibility to use other Cr(VI) dose-response data to help define priors for the model parameters.

External Scientific Advisory Panel

SciPinion was independently retained to organize an ESAP. The ESAP includes 12 experts with a range of experience including exposure reconstruction, quantitative risk assessment, including Bayesian modeling, and regulatory policy regarding cancer risk assessment. The ESAP has reviewed the protocol and provided comments. ESAP members gave high confidence scores to the exposure-response and exposure reconstruction study methods (**Figure 3**). The ESAP will also review and comment on the study findings and risk assessment in 2021.

Figure 3. ESAP Protocol Review Confidence Scores



Conclusions

This project offers the opportunity to develop a new lung cancer risk assessment for Cr(VI) exposure using state of the science methods and data that are more representative of low intensity, chronic exposures than has been available to date for regulatory risk assessment. The study data address current uncertainties related to how risk varies by gender, exposure intensity, and industry.

Acknowledgments

This study has been funded by the California Metals Coalition. Lockheed Martin has provided records under terms of a data use agreement with ToxStrategies. The independent Institutional Review Board (IRB) IntegReview issued an Exemption Determination and approved the protocol on June 25, 2020.

References available upon request.