Lung Cancer Risk And Exposure to Hexavalent Chromium: Results Of Extended Mortality Study Of Workers with Low Level Exposures and Quantitative Risk Assessment Using Pooled Analysis of Three Cohorts

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Background

- Hexavalent chromium (CrVI) is known to cause lung cancer among workers exposed to high concentrations in certain historical industries.
- Past studies (e.g., Mancuso, 1975; Gibb et al., 2000; Proctor et al., 2016) have found a significantly elevated lung cancer risk associated with cumulative CrVI exposure and provide the basis for current regulatory risk assessments.
- However, very limited data currently exist to quantify risk at low-concentration occupational or environmental exposures, and studies are limited to male-only cohorts.

Objective

- Reconstruct individual-level exposures among 3,723 CrVI-exposed aerospace workers, including 440 women, with long-term low-level CrVI exposures and long-term mortality follow-up.
  - These data are more representative of current occupational and environmental exposure conditions.
- Combine this dose-response data with that of two cohorts of chromate production workers having much higher exposures and measurable dose-response relations.
  - This allows for derivation of an inhalation unit risk value (IUR) that includes all available individual level data and a wide range of exposures.
- Provide the most robust and inclusive data source for quantitative risk assessment (QRA) available to date.
  - This presentation focuses on the dose-response modeling options considered, how they were compared, and how the uncertainty represented in those options could be used in future Bayesian hierarchical analyses.

Methods

- Exposure reconstruction for the aerospace worker cohort was conducted by job title for CrVI exposed workers using industrial hygiene (IH) data from the plant and similar facilities, and using individual job histories and a job-exposure matrix (JEM). Bayesian methods were used to estimate exposure concentrations over time from 1960-1998. Respirator protection factors were applied based on detailed IH records.
- Standardized Mortality Ratios (SMR) for the aerospace worker cohort used California mortality rates, for men and women separately, and by exposure quartile.
- Individual-level data from the aerospace worker cohort was pooled with male chromate production workers with >1 year of exposure from previous studies of chromate production workers in Painesville (Proctor et al., 2016) and Baltimore (Gibb et al., 2000).
- Dose-response analyses were conducted by logistic regression of lung cancer deaths within individual person-years, with predictors including dose defined by variously weighted cumulative exposures, smoking data, and alternative functions of dose in the logistic framework.
- Sensitivity analyses included the addition of women from Burbank, short-term workers from Painesville and Baltimore, and removal of respiratory protection factors from Burbank cohort exposure estimates.

Results

Aerospace Worker Exposure Reconstruction

Mean and median cumulative exposures were 16 µg/m^3-yrs and 2.9 µg/m^3-yrs, respectively. Detailed data regarding the use of respiratory protection were included.

- Estimated exposures between 1960-1998 were relatively low (<20 ug/m^3) for assembly workers, electroplaters and aircraft assembly workers. Prior to 1978, airborne concentrations during painting activities were estimated to exceed the occupational exposure limit of 50 ug/m^3 (**Figure 1**).
- CrVI-exposed workers had 1 to 37 years of exposure (median: 8 years) and had mean and median cumulative exposures of 16 µg/m^3-yrs and 2.9 µg/m^3-yrs, respectively (**Figure 2**).

Figure 1

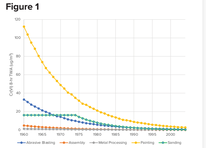
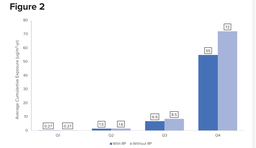


Figure 2



SMR Analyses of Aerospace Cohort

- With 147 total observed lung cancer deaths, including 24 among women, the lung cancer SMRs were significantly elevated at 1.39 (95% CI 1.17-1.63) overall and more highly elevated among women (SMR 2.61; 95% CI:1.66-3.92) (**Table 1**).
- No relation was observed between cumulative exposure and lung cancer SMR by quartile of exposure (**Table 2**), possibly due to elevated smoking rates.
- Smoking-related cancers were elevated for both males and females (**Table 1** and **2**) and smoking prevalence data, although limited, supported that the aerospace workers smoked more than the general population.
- No association between lung cancer risk and cumulative CrVI exposure was observed in internally referenced analyses.

Table 1. Standardized mortality ratios (SMRs) for male and female aerospace workers with CrVI exposure for >1 year (1960-1998)*

	Full Cohort			Male			Female		
Persons-at-risk	3,723			3,283			440		
Person-years	140,171			123,896			16,275		
Cause of Death (ICD9)	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All Causes of Death (001-999)	1,758	1.19*	1.14-1.25	1,583	1.18*	1.12-1.24	175	1.32*	1.13-1.53
All Malignant Neoplasms (140-208)	473	1.24*	1.13-1.36	418	1.22*	1.11-1.35	55	1.42*	1.07-1.84
Colon (153)	46	1.62*	1.19-2.17	43	1.69*	1.22-2.28	LT 10	1.04	0.21-3.03
Bronchus, Trachea, & Lung (162)	147	1.39*	1.17-1.63	124	1.28*	1.06-1.52	23	2.61*	1.66-3.92
Leukemia & Aleukemia (202.4, 204-208)	23	1.58*	1.00-2.38	22	1.65*	1.03-2.50	LT 10	0.85	0.01-4.74
Smoking Related Cancers (140-150, 157, 161-162, 188-189)	228	1.31*	1.15-1.49	201	1.25*	1.09-1.44	27	2.03*	1.34-2.96
Non-Smoking Related Cancers	245	1.19*	1.04-1.34	217	1.20*	1.04-1.37	28	1.09	0.73-1.58
All Heart Disease (390-398, 404, 410-429)	499	1.18*	1.08-1.29	452	1.16*	1.05-1.27	47	1.45*	1.06-1.93
Non-malignant Respiratory Disease (460-519)	157	1.27*	1.08-1.48	139	1.25*	1.05-1.47	18	1.44	0.86-2.28
Bronchitis, Emphysema, Asthma (490-493)	81	1.52*	1.21-1.89	68	1.44*	1.12-1.82	13	2.20*	1.17-3.76

*Results presented only for statistically significant increases relative to age and sex adjusted CA general population

Table 2. SMRs for aerospace workers with >1 year exposure by quartile of cumulative exposure

	Cumulative Exposure Q1			Cumulative Exposure Q2			Cumulative Exposure Q3			Cumulative Exposure Q4		
Persons-at-risk	930			931			931			931		
Person-years	35,290			34,776			34,432			35,672		
Cause of Death	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All Causes of Death (001-999)	335	1.10	0.98-1.22	426	1.25*	1.13-1.37	459	1.25*	1.14-1.37	538	1.18*	1.08-1.28
All Malignant Neoplasms (140-208)	87	1.11	0.89-1.37	111	1.26*	1.03-1.51	119	1.26*	1.04-1.51	156	1.31*	1.11-1.53
Colon (153)	LT 10	1.57	0.72-2.98	14	2.14*	1.17-3.59	LT 10	1.27	0.58-2.42	14	1.56	0.85-2.62
Bronchus, Trachea, & Lung (162)	29	1.42	0.95-2.04	35	1.45*	1.01-2.02	34	1.29	0.89-1.80	49	1.40*	1.04-1.85
All Lymphatic, Hematopoietic Tissue (200-208)	10	1.26	0.60-2.32	11	1.22	0.61-2.18	17	1.77*	1.03-2.83	12	0.98	0.51-1.72
Smoking Related Cancers (140-150, 157, 161-162, 188-189)	44	1.28	0.93-1.72	51	1.28	0.95-1.68	53	1.22	0.92-1.60	80	1.42*	1.13-1.77
Non-Smoking Related Cancers	43	0.98	0.71-1.32	60	1.23	0.94-1.59	66	1.29*	1.00-1.65	76	1.21	0.95-1.51
All Heart Disease (390-398, 404, 410-429)	91	1.11	0.89-1.36	115	1.2	0.99-1.43	124	1.16	0.96-1.38	169	1.22*	1.05-1.42
Non-malignant Respiratory Disease (460-519)	37	1.52*	1.07-2.10	39	1.39	0.99-1.90	38	1.22	0.87-1.68	43	1.06	0.77-1.43
Bronchitis, Emphysema, Asthma (490-493)	23	2.10*	1.33-3.15	17	1.38	0.80-2.21	25	1.91*	1.23-2.81	16	0.95	0.54-1.54

Pooled Cohort Characteristics

- Three cohorts were considered for the pooled analysis: Painesville, Baltimore and Burbank (aerospace workers). Baltimore and Painesville cohorts were only males and included workers with <1 year of exposure in the chromate production industry.
  - Burbank cohort included women, only workers with >1 year of exposure, and data on use of respirators.
- Pooling the data expands the included dose-response range, increases the sample size (both total included persons and person-years of follow-up), and allows for inclusion of women.
- Characteristics of the three cohorts, and average cumulative exposure estimates are shown in **Table 3**.

Dose-Response Modeling

- Basic unit of observation: a person-year (py)
  - For example: individual i worked (and was observed) for a full year in 1965. That year of observation contributes 1 py.
  - For example: individual j was observed until her death in the middle of 2011. That year of observation contributes 0.5 py.
- Response: presence or absence of a lung cancer death in the py under consideration. A 0/1 response variable, assumed to be Bernoulli distributed with underlying probability of response, p, depending on predictor variables, including dose, d, of CrVI (to be discussed further later)
- Used Logistic dose-response relationship:

$$ln\left(\frac{p}{1-p}\right) = \alpha + ln(fu) + \beta'[1{:}21] \cdot (cb, Site2, Site3, Smoke1, Smoke2, age, sex) + \beta[22] \cdot f(w)$$

- where the log-odds $[ln\left(\frac{p}{1-p}\right)]$ was related to a weighted cumulative exposure estimate ($f(w)$) and other explanatory variables, with intercept α and a vector of regression coefficients, β. An offset variable (fu) was added to adjust for the duration of follow-up.
- The function $f(w)$ is one of two forms:
  - Power model: $f(w) = w^p$ (note: when p = 1, the model is linear)
  - Hill model: $f(w) = \frac{w^p}{k + w^p}$ (note: when p = 1, the model is a Michaelis-Menten model)
- The evaluated exposure weighting functions (w) are shown in **Figure 3**.
- Cumulative exposure estimates were weighted to account for the timing and duration of exposure
- Five weighting schemes, including no weighting (W0), were evaluated (shown in **Figure 3**):
  - W0, where exposure in every year is given equal weight (equivalent to no lag)
  - W1-W4 are defined by lognormal distributions having log-scale means (and standard deviations) defined as follows. W1: 7 (2.08); W2: 3.1 (0.4); W3: 9.6 (2.5); W4: 2.47 (0.4).
- All weighting schemes were considered in the analysis
- There is a clear and consistent trend of increasing AIC with increasing power, across all weighting approaches and model types (see **Figure 4**). The model with the lowest AIC is clearly the Michalis-Menten (p =1) model with weighting approach 1 (**Figure 4b**). Exclusion of the dose parameter does not improve model predictivity (**Figure 5**).
- The coefficient for $f(w)$ and SE from the selected (Michaelis-Menten, W1) model were used in lifetable calculations to compute an IUR for selected hypothetical exposure scenarios (**Table 4**). The plateauing nature of the Michaelis-Menten dose-response function is evident in **Figure 6A**, displaying the extra lifetime risks associated with continuous lifetime exposures. The lower-dose region (i.e., exposures up to the defined IUR) is shown in **Figure 6B**.

Figure 3. Cumulative exposure weighting approaches evaluated for improving model predictivity

Table 3. Comparative cohort characteristics

		All Workers			Workers with Employment time > 1 yr			
Cohort	Calendar Years of Follow-up Observation	Cohort Size	P-Y of follow-up	# Lung Cancer Deaths	Cohort Size	P-Y of follow-up	# Lung Cancer Deaths	Average cumulative exposure (mg/m^3-yrs)
Painesville	1940-2013	714	24,438.0	77	499	17,263.8	61	1.55
Baltimore	1950-1992	2357	70,756.4	122	823	23,667.8	56	0.19
Burbank - males	1960-2019	3283	123,657.8	124	3283	123,657.8	124	0.023
Burbank - females	1960-2019	440	16,237.5	23	440	16,237.5	23	0.0046
Pooled Cohort*		6794 (6354)	235,089.7 (218,852.2)	346 (323)	5045 (4605)	180,826.9 (164,589.4)	264 (241)	

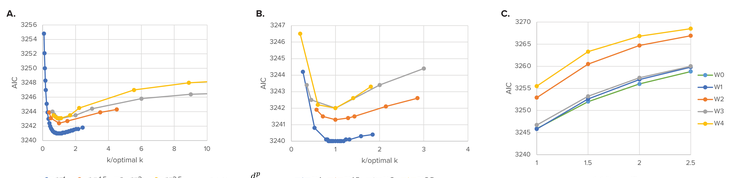
*Totals for only male workers are shown in parentheses. These are the numbers used in the primary analysis.

Table 4. Inhalation unit risk (risk per µg/m^3) for continuous lifetime exposure including sensitivity analyses

Analysis:	5th Percentile	Best Estimate	95th Percentile
Primary	0.0066	0.0096	0.0127
Sensitivity Analyses			
No adjustment for respirator use[a]	0.0058	0.0084	0.0111
Add short-term workers[c]	0.0079	0.0110	0.0143
Add females[d]	0.0190	0.0262	0.0343

Derived from selected model form: Michaelis-Menten function applied to weighting W1.
[a]This was done only for the Burbank cohort. Optimal value of k in the Michaelis-Menten equation was 0.0045 with coefficient value of 3.00.
[c]This added workers in the Baltimore and Painesville cohorts, see Table 1. Optimal value of k in the Michaelis-Menten equation was 0.003 with coefficient value of 2.63.
[d]This was done only for the Burbank cohort. Optimal value of k in the Michaelis-Menten equation was 0.0015 with coefficient value of 3.02.

Figure 4.
Model comparisons: Hill model (A & B) vs Power model (C). The Hill model with weighting W1 and p = 1 (B) is preferred over other combinations, including unweighted cumulative exposures (A); it is also preferred over the best-fitting Power model (W1; p = 1) (C)



$f_2(d) = \frac{d^p}{kp + d^p}$ $f_1(d) = d^p$

Figure 5. Including dose significantly improves predictions

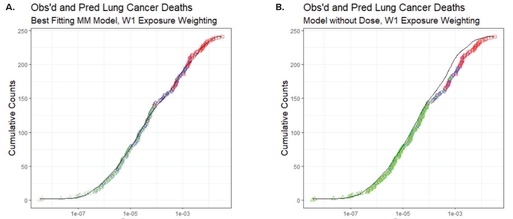
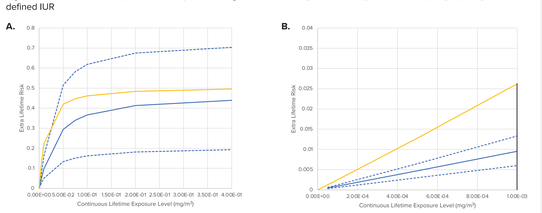


Figure 6. Extra lifetime risk estimation for A) the full range of observed exposures and B) the lower-dose exposure up to the defined IUR



Conclusions

- The lower CrVI exposures among the aerospace workers were not significantly associated with increased lung cancer risk.
- The pooled analysis of the three cohorts benefitted from the inclusion of a broader range of exposure levels, and a substantial increase in the number of observations and person-years at risk.
- The pooling of the three cohorts best suited to estimating the relationship between CrVI exposures and lung cancer mortality resulting in IUR estimates that are roughly comparable to, and supportive of, those derived previously for individual cohorts (Proctor et al., 2016; EPA, 2022)
- The observed differences in risk among men and women should be considered in the absence of evidence confirming no sex-based biological difference; however, only 24 lung cancer deaths were observed among women and may be influenced by smoking behavior.

Possible Follow-on and Additional Analyses — Bayesian Dose-Response Analysis

- Exposure reconstruction for Burbank cohort used a Bayesian approach. A Bayesian approach to dose-response analysis could unify consideration of uncertainties and prior information.
- Consideration of priors for model parameters would allow one to extend and "integrate over" the dose-response functions and exposure weightings already considered.
- A Bayesian hierarchical meta-analysis could further address cohort-to-cohort variability while yielding a "pooled" estimate of a dose-related effect.
- Such an analysis could further investigate the male/female difference, especially with respect to a potentially different susceptibility to CrVI exposure.
- Possible uncertainty analyses could be used to handle smoking effects and missing data with respect to smoking

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References:
Available upon request.

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