Inhalation Cancer Dose-Response Modeling and Risk Assessment based on the Painesville Cohort Updated Mortality Study

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Study Funded by the Electric Power Research Institute (EPRI)

Presentation Overview

Introduction

- Published Quantitative Risk Assessments
- Inhalation Unit Risks Developed by Agencies

Study Background

- Data Sources and Mortality Follow-Up
- Exposure Reconstruction

Study Results

- Comparison of Mortality Follow-Ups
- Modeling Results

Discussion and Conclusions

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Introduction

Hexavalent chromium [Cr(VI)] is a known human carcinogen associated with increased lung cancer risk among workers, and in particular chromate production and pigment production workers (IARC, 2012)

- In the US, the estimated number of Cr(VI)-exposed workers is >558,000 (mostly stainless steel welders) (NIOSH, 2013)
- Common environmental sources includes combustion of fossil fuels, metal finishing industry, cement kilns and steel foundries, aerospace, as well as past releases to the environment.

Ambient monitoring of Cr(VI) has shown decreasing levels through time

- In California, levels are generally below 0.1 ng/m^3 (CARB, 2015)
- In Texas, ambient Cr(VI) is reported to range from 0.0059 to 0.17 ng/m^3 (TCEQ, 2014)
- Environmental exposure levels are orders of magnitude below historical occupational exposures associated with lung cancer (>25,000 ng/m^3)

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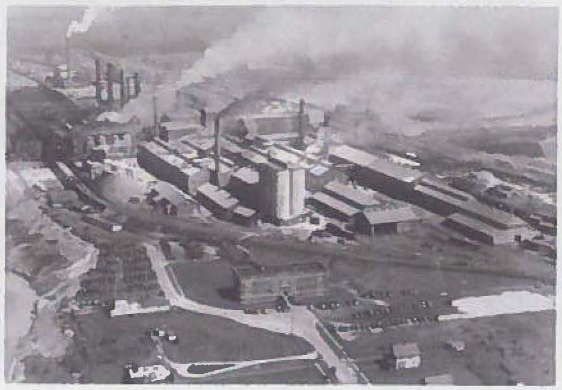
Introduction


Diamond Shamrock chromate production plant, 1937, Painesville, Ohio

Mortality data from Baltimore and Painesville chromate production workers have been used in several quantitative risk assessments and were the basis of the OSHA Cr(VI) Rulemaking (2006)

Older study of Painesville workers is the basis of the current USEPA inhalation cancer slope factor of 1.2 x 10^{-2} ($\mu g/m^3)^{-1}$ (Mancuso 1975)

- Workers starting in 1930s
- Very limited exposure data

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Published Quantitative Health Risk Assessments for Inhalation of Cr(VI)

Crump et al. 2003 *Risk Analysis* 23(6): 1147-1163

- Based on Luippold et al. 2003 mortality assessment of Painesville chromate production workers
- Calculated both environmental and occupational inhalation unit risk factors (IURs)

Park et al. 2004 *Risk Analysis* 24(5): 1099-1108

- Based on Gibb et al. 2000 mortality study of Baltimore chromate production workers
- Calculated occupational IUR ~ 2.4-times higher than Crump et al. 2003

Haney et al. 2014 *Regulatory Toxicology and Pharmacology* 68: 201-211

- Based on Painesville and Baltimore cohort studies, with supporting analysis from low-exposure plants in Germany and the US
- Cox Proportional Hazard model, and smoking adjusted
- Meta analysis-based environmental IUR = 2.3 x 10^{-3} ($\mu g/m^3)^{-1}$—approximately 5-times lower than current IRIS value

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Study Objectives

- Expand the Painesville cohort to include 198 short-term workers
- Conduct updated mortality assessment of the workers through Dec 31, 2011
- Conduct exposure-response modeling to quantify lung cancer risk from lifetime occupational and continuous environmental exposures to airborne Cr(VI)

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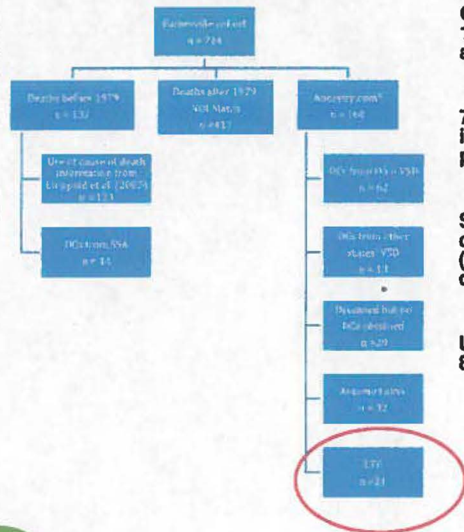
Study Methods: Ascertainment of Vital Status



Only those workers employed after Dec 31, 1939 and having a valid social security number and date of birth were included

714 workers were identified as meeting the inclusion criteria (Follow-up 1940-2011; 24,535 person-years)

Source of data: Ancestry.com, death certificates (DCs), CDC National Death Index (NDI) Plus, and state vital status (VSD) department

Underlying cause of death coded using ICD 8(a), 9, and 10

24 (3.4%) workers considered loss to follow-up (LTF)

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Study Methods: Mortality Calculations

Person-years at risk for each cohort member began the first day of hire and continued until the date of death, the last date of follow-up , or the last known date alive (i.e., last exposure date) if considered LTF

SMRs and 95% confidence intervals for selected causes of deaths were calculated based the reference United States white male or Ohio white male populations

Age-specific and cause-specific mortality rates for both US and Ohio reference populations for 1968 to 2010 were calculated based on the National Center for Heath Statistics (NCHS) mortality files

Lung cancer SMRs were further stratified using the Ohio reference rates and Poisson trend statistic was used to test monotonic exposure-response relationship

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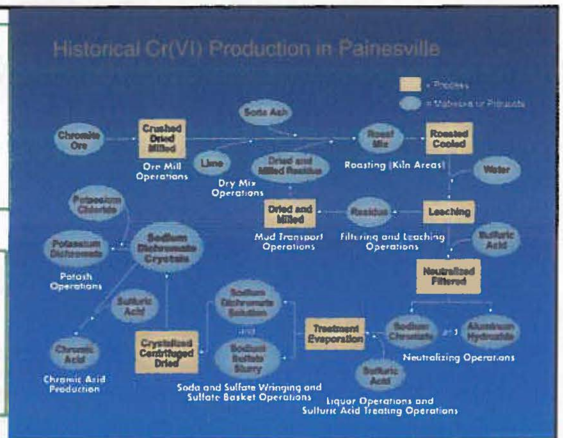
Workplace Airborne Hexavalent Chromium Concentrations for the Painesville, Ohio, Chromate Production Plant (1943–1971)

Estimating Historical Occupational Exposure to Airborne Hexavalent Chromium in a Chromate Production Plant: 1940–1972

D.M. Proctor, J.P. Panko, E.W. Liebig, and D.J. Paustenbach



Exposure Reconstruction

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Review IH Data Review

- Identify all historical exposure data
- Assess the usability for
  - Exposure reconstruction
  - Cancer risk assessment
- Assess validity

Chromate Plant Survey - April 1959/May 1959
( ) = 1957 Survey

Sample Location Date - Time	Sample #	mg. CrO_3/ cu.meter Cr^{+6}	mg. CrO_3/ cu.meter Cr^{+3}	mg. CrO_3/ cu.meter Total Cr
#5 Bldg. - Ground floor cooler feed area. North & south doors open. All kilns operating.				
4-1-59 1:00 P.M.	C-1	0.01	-0-	0.01
(1957)	C-1	0.11	-0-	0.11
#5 Bldg. - Ground floor dust collector cleanout area. North & south doors open. Sample taken while cleaning out process was in operation.				
4-1-59 10:30 A.M.	C-2	0.01	-0-	0.01
(1957)	C-2	0.03	-0-	0.03
#5 Bldg. - On firing floor in center of floor between kilns and panel board. All				

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Data Requirements

- Representative of long-term exposures
- Valid methods and reproducible results
- Speciated for Cr(VI)
  - ➢Considered a Study Priority to Use Only Reliable Exposure Measures
  - ➢Extensively investigated all data and methods

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Conclusions Regarding IH Data

- Data quality indicators suggest data are valid and reproducible
- Data are representative of average normal working conditions by study design
- Nearly 800 data points for exposure reconstruction
- Exposures were concurrent with airborne sampling
- Data may be used for exposure reconstruction and cancer risk assessment

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Exposure Reconstruction Data Sources

Key Source was Discussions with Former Workers

- IH Surveys
- Specimen Collection Lists
- Union Records
- Personnel Records
- Medical Files
- Tenure Lists
- Insurance/Retirement lists
- Death Certificates
- Mancuso's records
- COHESS
- Disability Lists
- Plant phone directory
- Historical Accounts
- Production Records
- Pension Information

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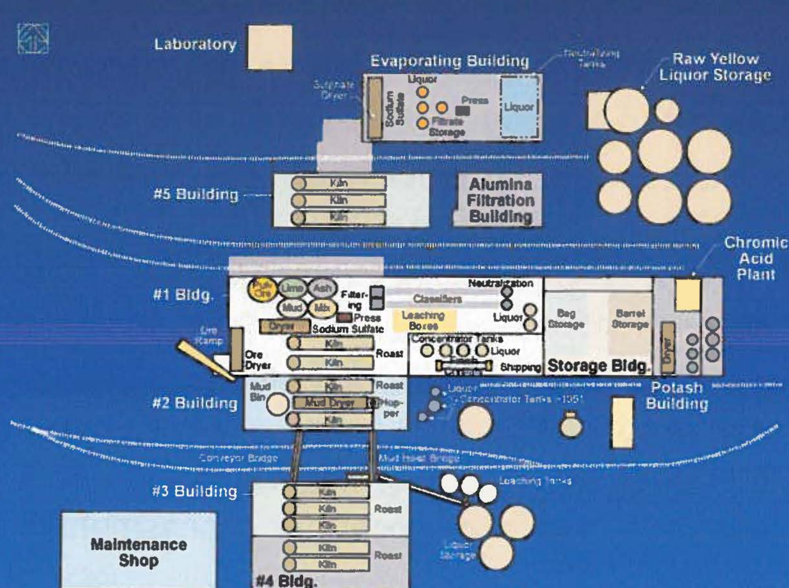
Painesville Chromate Production Facility



Job Exposure Groups (JEGs)

117 job titles

22 Job Exposure Groups

JEGs correlated job title with area in plant (some are time-period specific)

Airborne concentrations by JEG provided the cells of the JEM

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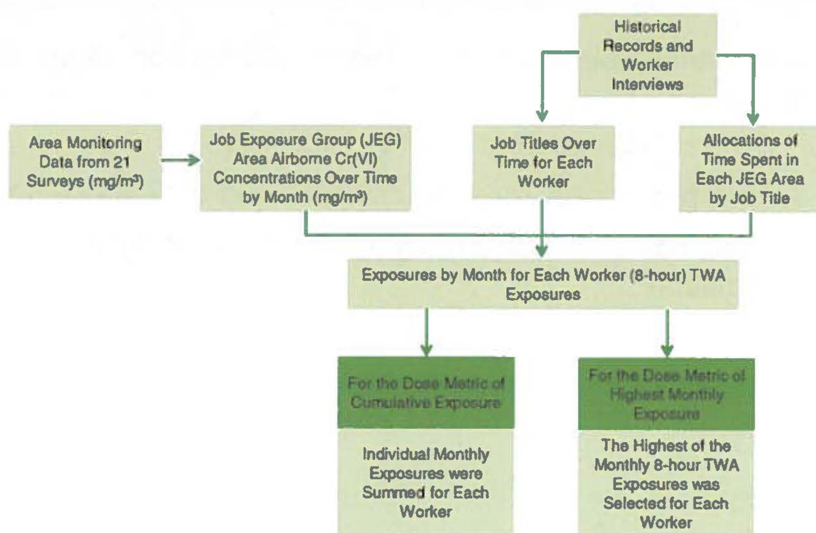
Exposure Reconstruction: Job Exposure Matrix Approach



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Source: Proctor et al. 2004, Crump et al. 2003

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Exposure Construction Data Gaps

No data regarding strikes, vacations, or overtime

Respirator usage factors not applied
- Urinary Cr data suggests they were not effective when worn

Missing some individual pieces of data (job titles for periods of time, few start and ending dates)

Used professional judgment and average exposures estimates to fill data gaps

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Quality Assurance

- Job histories were reconstructed separately from mortality status
  - –Different researchers at different locations
- Written procedures for data collection and database entry
- QA/QC included double entry to ensure accuracy of information

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- **Comparison of Mortality Follow-Ups**
- **Modeling Results**

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Comparison of the Mortality Follow-Ups

Study Variable	Proctor et al. (2015)	Luippold et al. (2003)
Study population (N)	714	482
Follow-up period	January 1, 1940 to January 31, 2011	January 1, 1940 to December 31, 1997
Total person-years at risk	24,535	14,048
Deceased, n Alive LTF, n (%)	658 32 24 (3.4%)	303 136 43[a] (8.9%)
Deaths from cancer of the trachea/bronchus/lung, n	77	51
Cumulative exposure, mg/m^3-year	Mean: 1.10 Range: 0.0002 to 22	Mean: 1.58 Range: 0.003 to 23
Workers with ≤1.00 mg/m^3-year	518 (73%)	290 (60%)

a Forty-seven employees had unknown vital status at the end of study. Four did have substantial follow-up, just short of the end of the study period (Luippold et al. 2003)

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Updated Mortality Assessment of the Painesville Cohort (Select Endpoints)

SMRs (95% CIs)	Proctor et al. (2015)	Luippold et al. (2003)
All Causes		
Observed (n)	658	303
Ohio	138 (127 to 148)	129 (115 to 144)
US	145 (127 to 148)	134 (120 to 150)
All Cancers		
Observed (n)	167	90
Ohio	146 (124 to 168)	155 (125 to 191)
US	155 (132 to 179)	166 (133 to 204)
Cancers of the trachea/bronchus/lung		
Observed (n)	77	51
Ohio	**186 (145 to 228)**	**241 (180 to 317)**
US	205 (159 to 250)	268 (200 to 352)

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Characteristics of the Short-Term Workers (Updated Mortality Study)

Study Variable	Results
Population (N)	198
Deceased LTF	185 7 (**30% of LTFs)
Cumulative exposure, mg/m^3-year	Mean: 0.12 Range: 0.0002 to 0.69
All-cause SMR (95% CI)	
Observed (n)	185
Ohio	152 (130 to 174)
US	160 (137-183)
Lung cancer SMR (95% CIs)	
Observed (n)	14 (18% of LC deaths)
Ohio	134 (64 to 204)
US	147 (70-224)

Higher all-cause SMR compared to the entire cohort with lower cumulative exposure—Indicative of poor health status

Consistent with what TCEQ noted in regards to short-term workers (Gibb et al. 2000, Baltimore cohort)

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Mortality Results: Other Cancer Sites

89 non-respiratory cancers were observed and consisted of various cancer types including those of the gastrointestinal (GI) tract

GI tract cancers were not numerous or significantly elevated

Cause of Death (ICD 8a, ICD 9, and 10 codes)	Compared to Ohio Reference Rates
Oral cancer (observed =2)	SMR = 77 (95% CI 0 to 183)
Stomach cancer (observed = 5)	SMR = 144 (95% CI 18-270)

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Mortality Results: Mesothelioma

- 3 deaths identified as lung cancer were due to mesothelioma based on death certificates; however, they were coded as lung cancer under ICD 8a and 9. Three other cases were coded as mesothelioma under ICD 10
  - ➢ *Anyone who died before 1992 (prior to ICD 10) with mesothelioma would be coded as a lung cancer death*
  - ➢ *Consistent problem for all historical cohorts*
- For all mesothelioma cases, latency from first exposure in the Painesville plant was long (25 to 55 years)
- Asbestos exposure in Painesville plant seems probable
- Exposure to asbestos in the plant could not be ruled out and lung cancer SMRs were likely increased.

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Exposure-Response Modeling and Risk Assessment

Dr. Kenny Crump

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Lung Cancer Exposure-Response Modeling: Poisson Regressions Models

Relative Risk Model

Expected number of lung cancer deaths in a cell =

α Expected $(1 + \beta x + \gamma x^2)$

Additive Risk Model

Expected number of lung cancer deaths in a cell =

α Expected + $PY(\beta x + \gamma x^2)$

Expected = expected lung cancers based on Ohio rates

x = CRVI exposure (cumulative)

PY = person-years

α, β, γ = estimated parameters

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Lung Cancer Exposure-Response Modeling: Cox Regressions Models

The relative risk model by Cox regression was assumed to have the form

$\exp(\beta x + \Sigma_i \beta_i \text{covariate}_i)$ (exponential model), or

$(1 + \beta x) \exp(\Sigma_i \beta_i \text{covariate}_i)$ (linear model).

Covariates explored included smoking, age first exposed (i.e., age at hire), and duration of exposure as a continuous variable

Smoking information was quantified using three categories: known smoker (n=157), known nonsmoker (n=43), and no smoking information available (n=514)

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Life Table Analysis and Trend Tests

Additional lifetime risks of lung cancer mortality associated with occupational (45 years) or environmental lifetime exposure were estimated using a life-table analysis based on the regression results and the reference US mortality rates (from 1968 to 2011) by 10-year age intervals for both sexes and all races

Trend tests were conducted to determine the lowest exposure for which a statistically significant increase in relative risk of lung cancer is observed

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Exposure-Response Modeling

Using Poisson regression models, there was no statistical evidence for nonlinear exposure-response for Cr(VI) (γ=0).

Likewise there was no statistical evidence that Ohio death rates were not applicable to Painesvile cohort (α =1).

Cox regression was applied involving both the exponential model and linear model and four lags for cumulative exposure (0, 5, 10 and 15 year lags)

Exponential Cox models gave better fits than the comparable linear Cox models. When 3 subjects with highest cumulative exposures were removed, linear models gave better fits

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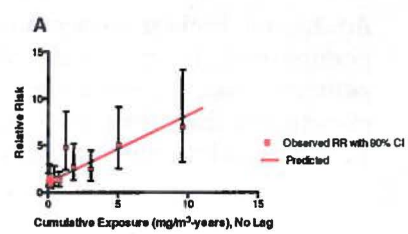
Results from Poisson Regression

Potency Factors from Poisson Regression			
Model	Crump et al. (2003)	Proctor et al. (2015)	- 2 Log Lik. (2015)
Relative risk model			
Lag = 0 y		0.73	232.3
Lag = 5 y	0.79	0.73	230.2
Lag = 10 y		0.70	226.4
Lag = 15 y		0.70	226.9
Additive risk model			
Lag = 0 y		0.0012	230.0
Lag = 5 y	0.0016	0.0013	228.2
Lag = 10 y		0.0014	224.9
Lag = 15 y		0.0017	221.7

No significant quadratic non-linearity (γ = 0).
No evidence that Ohio death rates are not appropriate (α = 1).



β = (mg/m³-year)⁻¹ for the relative risk model

β= (mg/m³-year per person-year)⁻¹ for the additive risk model

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Smoking data, 2015

714 total workers
200 of 714 (28%) with smoking status available at time of employment
157 of 200 (79%) were smokers.
43 of 200 (21%) were nonsmokers.

No evidence that smoking status was correlated with CrVI exposure ($p = 0.61$).

Smoking was controlled in some analyses using an indicator variable with 3 values:

1. Nonsmoker
2. Smoker
3. Unknown

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Cox Regression Analyses, 2015

Exponential Model

Results from Cox Regression

		β (mg-y/m^3)$^{-1}$		
variables in model	Deviance	MLE	95% CI	p-values[a]
CRVI	1248.1	0.22	(0.16, 0.28)	
CRVI, **smoking**	1234.95	0.19	(0.12, 0.25)	0.001
CRVI, smoking, **age exposure began**	1223.14	0.17	(0.10, 0.24)	0.0006
CRVI, smoking, age exposure began, **years of exposure** (continuous variable)	1222.48	0.15	(0.064, 0.23	0.42

[a] P-values are for the bolded variables.

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Testing for a Dose-Rate Effect

In the Baltimore cohort, Gibb et al. (2011) found that exposure duration was a significant explanatory variable; lung cancer mortality risk was greater for the same cumulative exposure over a short period of time compared with the same cumulative exposure spread over a much longer duration. In order to determine whether a dose-rate effect was present in the Painesville cohort, analyses were conducted using three indicators of exposure duration: exposure duration as a continuous variable (previous slide) and categorized two ways. **None of these analyses found statistical evidence of exposure duration effect in the Painesville cohort.**

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Unit Risks from Cox Linear Model

Comparison of Unit Risks[a] from Cox Linear Model

	2003		2015[b]	
Lag (y)		90% CI		90% CI
0	0.0076	(0.0011, 0.014)	0.0083	(0.0036, 0.017)
5	0.0082	(0.0014, 0.015)	0.0073	(0.0031, 0.015)
10	0.0075	(0.0014, 0.014)	0.0056	(0.0022, 0.012)
15	0.0059	(0.0012, 0.011)	0.0041	(0.0014, 0.0089)

[a] Additional lifetime risk from lifetime exposure to 1 μg/m^3 CrVI

[b] Controlled for smoking

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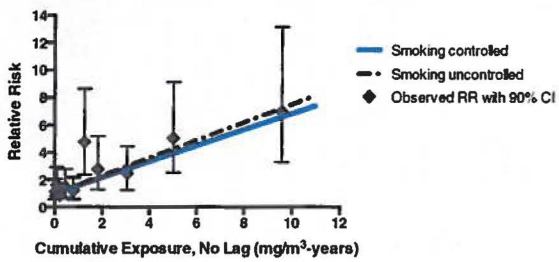
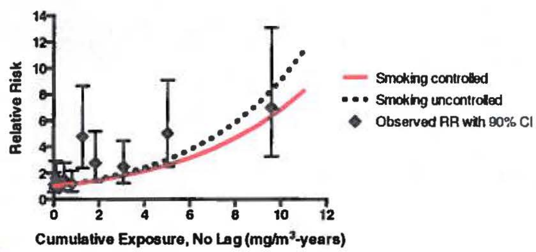
Cox Regression Model with Unlagged Cumulative Exposure (Including All Cohort Members)



Linear



Exponential

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Test for Cumulative CrVI Exposure at which a Statistically Significant Trend Occurs

Highest cumulative exposures included (mg-y/m³)	2003[a] P-value	2015[b] β (mg-y/m³)⁻¹	2015[b] P-value
0.3	0.26		
0.35		-1.4	0.51
0.46	0.04		
0.47		0.43	0.75
0.67	0.45		
1	0.18		
1.12		0.05	0.9
1.41		0.89	0.04
1.63	<0.001		
2.14		0.48	0.05
2.6	<0.001		
4.15		0.22	0.07
4.45	<0.001		
6.27		0.29	0.0004
All	<0.001	0.19	<0.0001

[a]2003 analyses used Poisson regression, lag = 5y.

[b]2015 analyses used Cox regression and controlled for smoking, lag = 0y.

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Summary

- Achieved Goal of expanding the size and statistical power of the data set and increased power for workers with lower levels of exposure
- Found decreased lung cancer SMR and ~20% lower environmental unit risk compared to previous follow-up of this cohort
- With full cohort, Cox exponential model provided optimal fit, but removing highest three workers, resulted in optimal fit for Cox linear model with control for significant risk factors; however the risk is ~2-3-fold higher with linear model
  - Preferred linear model and exclusion of three most highly exposed workers
- Environmental unit risk supports that typical Cr(VI) airborne exposures in the US are associated with increased lung cancer risk of < 1/million—assuming optimal linear model and cumulative exposures can be extrapolated from high-level occupational exposure to low-level environmental exposures

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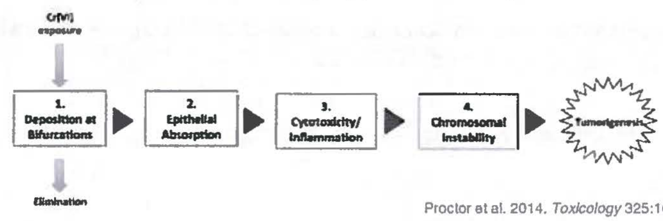
Discussion: Considerations for Low Dose Extrapolation

- **Modeling of epidemiology data does not allow for differentiation of linear or non-linear low dose extrapolation approaches—that requires understanding of MOA (Crump 2011)**
- **Linearity is the default assumption, but there is a basis for considering non-linearity:**
  - *Extracellular reduction of Cr(VI) to Cr(III) in the lung prior to absorption—Haney et al (2012) approach for threshold based risk assessment with Reference Value = 240 ng/m^3*
  - *MOA review (Proctor et al. 2014) supports non-mutagenic MOA*



Proctor et al. 2014. *Toxicology* 325:160-179

  - *Evidence of dose-rate effect in Baltimore cohort and chronic animal study data, and observed association between tissue damage and lung cancer risk/tumor formation*

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Discussion: Comparison with Baltimore Cohort

- **Finding from these studies are comparable and generally consistent**
- **Both are historical chromate production worker cohorts have limitations regarding extrapolation from high to low exposures and involve exposures to similar chemical forms**
  - Both plants produced chromate salts and had chromic acid production
  - Baltimore also had a pigment production plant
  - Both had high incidence of nasal irritation, ulceration and perforation, and possible confounding by smoking and mesotheliomas coded as lung cancer
- **Baltimore study (Gibb et al. 2000 and 2015) has more cohort members and greater statistical power; however most are short-term workers**
  - 42% worked < 3 months; 15% of cohort worked >5 yrs
  - Short-term workers have generally poorer health status
- **Baltimore exposure-assessment is based a far larger number of IH samples; however JEM is based on RAC samples, and exposures from RAC samples are lower than that from personal samples (Gibb et al. 2000)**
- **Published *environmental* risk assessment based on 2000 Baltimore data are only available from Haney et al. (2014); *occupational* assessments are available in Park et al. (2004; 2006) and OSHA (2006). Gibb et al. (2015) updated data have not been modeled to calculate unit risk in published literature so it is difficult to specifically compare results.**

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Questions? Please contact dproctor@toxstrategies.com or kennycrump@email.com

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References

IARC Chromium, nickel, and welding. IARC Monograph on the Evaluation of arcinogenic Risks to Humans1990;49:1–648.

NIOSH Criteria for a Recommended Standard. Occcupational Exposure to Hexavalent Chromium. DHHS (NIOSH) Publication No. 2013–128. 2013.

IARC IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Chromium (VI) Compounds. Volume 100C Lyon, France: International Agency for Research on Cancer, 2012.

Crump C, Crump K, Hack E, Luippold R, Mundt K, Liebig E, et al.. Dose response and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal. 2003;23: 1147–1163.

Proctor DM, Suh M, Mittal L, Hirsch S, Salgado, RV, Bartett C, et al. Inhalation cancer risk assessment of hexavalent chromium based on updated mortality for chromate production workers. Journal of Exposure Science and Environmental Epidemiology (2015). (See this publication for other references)

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