

Science Question 1: Cancer Classification by Inhalation

Overview

- **Studies with exposure-response and quantitative risk assessments for lung cancer**
- **Updated mortality study of the Painesville cohort [EPRI Funded]**
- **Inhalation unit risk (IUR) values developed by agencies**

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The logo for ToxStrategies, Inc. features the company name in a white, sans-serif font. The letter 'x' is stylized with a small dot above it. The text is set against a green, curved background that resembles a hill or a wave.

ToxStrategies

Question 1: Key Points

- 1) **Cr(VI) should be classified as “Carcinogenic to Humans” based on increased lung cancer risk among workers in several industries**
- 2) **There are two cohorts—Baltimore and Painesville production workers—for which data exposure-response data are available and useful for quantitative risk assessment**
- 3) **Published risk assessments and those by OSHA, NIOSH and TCEQ provide best approaches to quantify risk based on available data**
- 4) **The Painesville cohort mortality study is being updated and a new risk assessment from these data will be completed this year**
 - Greater statistical power, particularly in low dose range

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 workers
 - Environmental IUR = $9.78 \times 10^{-3} (\mu\text{g}/\text{m}^3)^{-1}$
 - Occupational IUR = $2.05 \times 10^{-3} (\mu\text{g}/\text{m}^3)^{-1}$
- **Park et al. 2004** *Risk Analysis* 24(5): 1099-1108
 - Based on Gibb et al. 2000 mortality study of Baltimore workers
 - Smoking adjusted
 - Occupational IUR = $5.1 \times 10^{-3} (\mu\text{g}/\text{m}^3)^{-1}$ [$2.55 \times 10^{-3} (\mu\text{g}/\text{m}^3)^{-1}$ for CrO_3]
- **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
 - For Baltimore cohort, Cox Proportional Hazard model was used and smoking adjusted; Meta Analysis used to combine studies
 - Environmental IUR = $2.3 \times 10^{-3} (\mu\text{g}/\text{m}^3)^{-1}$

New Study: Updated Study of the Painesville Chromate Production Workers and Risk Assessment

- **Previous follow-up of the Painesville cohort is through 1997 (Luippold et al. 2003)**
 - Did not include short-term workers (<1 y work tenure)
- **Study Objectives for Update:**
 - Update mortality
 - Includes short-term workers
 - Conduct dose-response modeling to quantify risk from environmental exposure
- **Funded by EPRI, the study started ~2 years ago and is being conducted by ToxStrategies, Scimetrika, and Dr. Kenny Crump**
- **A manuscript will be submitted to peer-reviewed publication in Fall 2014**

Updated Study of the Painesville Chromate Production Workers: **Preliminary Data**

Study Results	Updated Study	Luippold et al. (2003)
Eligible study population (N)	729	493
Follow-up period	January 1, 1940 to January 31, 2014	January 1, 1940 to December 31, 1997
Total person years at risk	21,833	14,048
Deaths from:		
All causes (n)	629	303
Cancer of the trachea/bronchus /lung (n)	77	51
Workers with < 1 mg/m ³ -year Cr(VI) (cumulative exposures)	533	280
Workers with < 0.05 mg/m ³ Cr(VI) (highest monthly exposure)	158	103

Updated Study of the Painesville Chromate Production Workers: **Preliminary Data**

SMRs (95 %CIs)	Updated Study	Luippold et al. (2003)
Cancers of the trachea/bronchus/lung		
Ohio	206 (160 to 252)	241 (180 to 317)
US	226 (176 to 277)	268 (200 to 352)

- **SMR calculations by exposure level are on-going and to be completed by July:**
 - **Exposure-response to be evaluated with cumulative and highest monthly exposures**
 - **Positive exposure-response both exposure metrics**
- **Work expected to be complete this fall and published this year**

Inhalation Unit Risk Factors Developed by Agencies

Source	IUR (MLE) ($\mu\text{g}/\text{m}^3$) ⁻¹	Source Data	Comment
CalEPA (2011)	Env IUR Range: 1.28 E-2 (4 dose groups) to 1.4 E0 (2 dose groups)	Gibb 2000 (Baltimore)	Did not work from original data and the published summaries are highly limited Used IUR based on Mancuso 1975 in PHG
IPCS (2013)	Env IUR: 4E-2 Occ IUR: 6E-3	Park 2004 (Baltimore)	Env IUR adjusted from occupational IUR No life table analysis
OSHA (2006)	Occ IURs: Baltimore: 9.1E-3 Painesville 2.1E-3	Crump 2003 (Painesville) Environ 2004 (Baltimore)	Modeled Baltimore raw data and Painesville separately to produce risk range. Baltimore reference rates
NIOSH (2013)	Occ IUR: 6E-3	Park 2004 (Baltimore)	Smoking adjusted, US reference rates Possible thresholds observed at 16 $\mu\text{g}/\text{m}^3$ or 208 $\mu\text{g}/\text{m}^3$ -year
TCEQ (2014)	Env IUR Crump 2.08E-3 Env IUR Gibb: 2.75E-3 (w/ > 1yr) 3.35E-3 (all workers) Supporting IUR: 4.56E-3 IUR combined: 2.4E-3	Crump 2003 (Painesville) Gibb 2000 (Baltimore)	Used TX background lung cancer rates, similar results with US rates (IUS presented here)

Summary of Quality Environmental IURs

✓ **Calculated from Original Data**

✓ **Used Life-table analysis**

Source	Study	IUR($\mu\text{g}/\text{m}^3$) ⁻¹ (MLE)	Difference compared to current
EPA 1984	Old Painesville (Mancuso 1975)	1.2E-2	--
Crump 2003	New Painesville (Luippold 2003)	9.8E-3	<30%
Haney/TCEQ 2014	New Painesville (Luippold 2003)	2.1E-3	
	Baltimore (Gibb 2000)	2.8E-3	
	Combined Studies	2.4E-3	<80%