Science Question 1: Methodological Considerations for Evaluating Epidemiologic Studies

Key Points

1. **There are many methodological characteristics for Cr(VI) occupational cohort studies of lung cancer to be considered relative to their use in risk assessment.**
2. **Overall, the effects of potentially biasing characteristics of the primary studies will result in an overestimate of lung cancer risk at low environmentally-relevant exposures**

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Comparison of occupational and environmental ambient Cr(VI) exposure concentrations

Baltimore and Painesville cohort studies:

- Painesville 1940-1972
- Average exposures ranged from 39 to 720 μg/m^3 (Proctor et al. 2003)
- Baltimore 1950-1986
- Average exposures ranged from 31 to 213 μg/m^3 (Braver et al. 1985; Gibb et al. 2000)

Ambient monitoring data

- NJ 1990s: 1.2 ng/m^3 (Falerios et al. 1992)
- Ontario 1996: 0.55 ng/m^3 (Bell and Hipfner 1997)
- Southern California 2008:
  - Mean 0.2 ng/m^3
  - Upper bound near cement plants was ~ 5 ng/m^3

  (SCAQMD 2008)

Difference in airborne concentration is in the range of 10^5-10^6 between historical chromate production industries and current environmental exposures

Lung Cancer Risk Assessment for Cr(VI): Judging Validity and Bias

"A study is externally valid if the study results for the study population can be extrapolated to external target populations. An internally valid study is free from different types of biases, and is a prerequisite for generalizing study results beyond the study population" **EPA 2014, Preliminary Materials page 1-10/11**

- **No exposure-response study of Cr(VI)-exposed populations exist that is "free from different types of bias" and is externally valid, without limitations, for environmentally-exposed populations in the US.**
- **Nonetheless, it is expected that data from workers studies will be used to develop a cancer risk assessment.**
- **How will EPA judge/address internal and external validity for these studies and others is the critical question.**

Chromate Production Industry Studies: Factors that May Bias Risk Estimates

Dose-rate effect

- Both animal (Steinhoff et al. 1986) and human (Gibb et al. 2011) studies indicate that a dose-rate effect exists for lung cancer

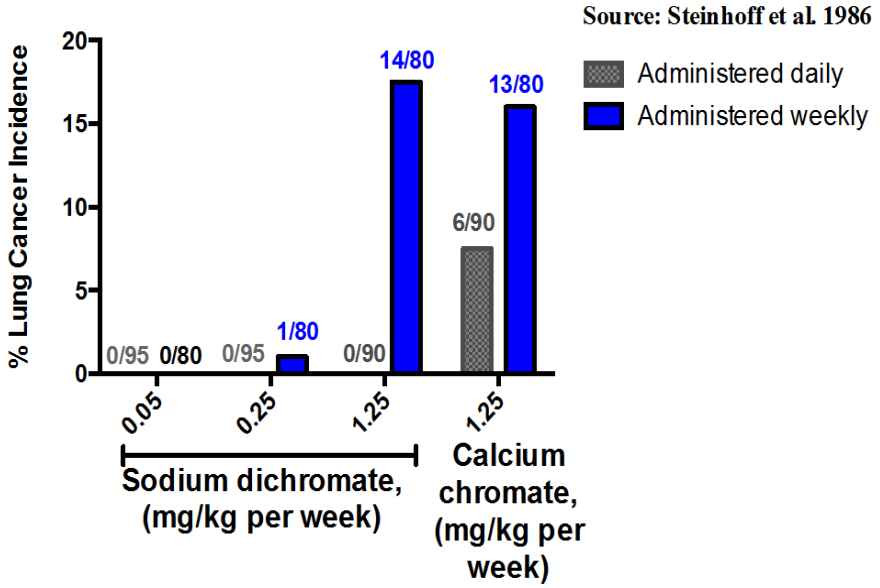

Table 4. Relative risks (95% Confidence Intervals) of Lung Cancer Mortality for Exposure to 0.339 mg/m^3-Years of Cumulative Hexavalent Chromium (the Median of the 4th Quartile of Exposure) for Smokers and Nonsmokers for Different Work Durations Adjusted by Age at Hire, Work Duration, and Associated Cr6 Interaction Terms

	30 Days	6 Months	1 Year	5 Years	10 Years
Smokers	1.41 (1.07 – 1.85)	1.40 (1.05 – 1.85)	1.39 (1.03 – 1.86)	1.32 (0.87 – 2.27)	1.24 (0.68 – 2.27)
Non-Smokers	1.82 (1.21 – 2.74)	1.81 (1.21 – 2.72)	1.80 (1.20 – 2.71)	1.71 (1.06 – 2.75)	1.61 (0.87 – 2.98)

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Chromate Production Industry Studies: Factors that May Bias Risk Estimates

Workers had high rates of clinical respiratory effects in both Baltimore and Painesville cohorts

- If the MOA involves high dose effects, lung cancer risk in workers from these industries may be not be generalizable with a reasonable degree of confidence to environmentally-exposed populations
- Not all industries with Cr(VI) exposure have increased lung cancer rates associated with Cr(VI) exposure (e.g., aerospace and welding)
    - These industries also did not have significant respiratory irritation
- Draws into question the use of linear low dose extrapolation and cumulative exposure metric

Chromate Production Industry Studies: Factors that May Bias Effect and Risk Estimates

- **Asbestos and Mesothelioma**
  - Mesothelioma classification was added for ICD 10
  - In ICD 8A and 9, coding for mesothelioma is ambiguous and mesothelioma could be coded for lung cancer
  - 6 mesothelioma cases in Painesville cohort, 3 coded ICD 8A&9 as lung cancer, and 3 as mesothelioma under ICD 10
  - All of Baltimore cohort coded by ICD8A
  - As a result, some mesothelioma cases could be coded as lung cancer
- **Chemical forms**
  - Chromate production workers were exposed to sparingly soluble calcium chromates, concentrated chromic acid, soluble and insoluble salts
  - Baltimore plant also produced pigments
  - Animal data support that slightly soluble forms of Cr(VI) are of greater potency (Levy et al. 1986; Steinhoff et al. 1986)
- **Smoking/Reference Rates**
  - Preferable to use Baltimore reference rates because of higher lung cancer background rate in Baltimore
  - Smoking prevalence high in these cohorts
- **No evidence of healthy worker or survivor effect**

Chromate Production Industry Studies: Factors that May Bias Exposure and Risk Estimates

- **Exposure misclassification and error in measurement is a potential issue, especially with the older studies**
- Cr(VI) needs to be collected in a media in which it is stable to prevent reduction to Cr(III) prior to analysis
- Extraction typically conducted using water which would not extract water-insoluble fraction (~20% in roast and roast residue [PHS 1953])
- Lack of personal monitoring data, likely to result in underestimation of exposure for batch process jobs [Gibb et al. 2000])

- **For the Painesville cohort**
- Quality control evaluation supports that the data are reasonably valid (Proctor et al. 2003)
- Strong and consistent exposure-response relationship supports that exposure misclassification does not confound the exposure-response (Proctor et al. 2004)

Conclusions and Recommendation

- **Considering dose-rate effects, and based on MOA considerations, it is expected that lung cancer risk will be overestimated at low environmentally-relevant exposures by applying linear extrapolation models**
- **It is recommended that non-linear approaches be considered and compared to default linear approaches**
- Example: Haney et al. (2012, 2014), TCEQ (2014)

Approach	Chronic Reference Value (ReV)	Basis
Non-threshold	0.0043 µg/m^3	URF= 2.3 x 10^{-3} (µg/m^3)$^{-1}$
Threshold	0.24 µg/m^3	POD/UF = 7.1 µg/m^3 ÷ 30

Non-threshold ReV based on 10^{-5} risk
URF = Unit Risk Factor
POD/UF = Point of Departure/Uncertainty Factor