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Lung cancer risk and exposure to inhalation 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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Abstract:
Background and Purpose: Hexavalent chromium (CrVI) is known to cause lung cancer among workers exposed to high concentrations in certain historical industries. It is also a toxic air contaminant considered to pose potentially significant cancer risk at comparatively low concentrations in urban air. Past studies 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. This study reconstructs individual-level exposures among 3,723 CrVI-exposed aircraft manufacturing workers, including 440 women, with long-term low-level CrVI exposures and long-term mortality follow-up, such that these data are more representative of current occupational and environmental exposure conditions. Further, these data were combined with that of two cohorts of chromate production workers, with much higher exposures, for the purpose of providing 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 lends itself to Bayesian hierarchical analyses.
Methods: Exposure reconstructions for the aerospace worker cohort were conducted using a job-exposure matrix (JEM) and Bayesian methods with industrial hygiene data to calculate cumulative CrVI exposures, by worker, from 1960-1998. The individual-level aerospace worker cohort data were also combined with data from two smaller cohorts of chromate production workers, both of which included only male workers exposed to higher concentrations of airborne CrVI. The QRA of the pooled cohort used standardized logistic regression to relate person-year-specific weighted cumulative exposures to the probability of lung cancer mortality. A variety of weighting schemes and dose-response functions were examined. Inhalation unit risks (IURs) were calculated using a life table analysis. IURs are estimates of the upper-bound of lifetime increased cancer risk from continuous inhalation exposure to 1 $\mu g/m^3$ and are commonly used in QRAs.
Results: CrVI-exposed painters, electroplaters, and aircraft assembly workers, with 1 to 37 years of exposure (median: 8 years) had mean and median cumulative exposures of 16 $\mu g/m^3$-yrs and 2.9 $\mu g/m^3$-yrs, respectively. With 147 observed lung cancer deaths, the lung cancer standardized mortality ratio (SMR) was significantly elevated 1.39 (95% CI 1.17-1.63) overall and more highly elevated among women (SMR 2.61; 95% CI:1.66-3.92). However, no relation between cumulative exposure and lung cancer risk was observed in internally or externally referenced assessments of the CrVI-exposed aerospace worker cohort, possibly due to elevated smoking rates. The pooled analysis, which incorporates lung cancer risks from two cohorts of chromate production workers, included 264 lung cancer deaths, 180,827 person years of follow-up and cumulative exposures ranging over five orders of magnitude. In the pooled QRA, the best fit dose-response function was a Michaelis-Menten relationship. Estimated lung cancer IURs based on the pooled analysis ranged from 0.0084 to 0.0262 per $\mu g/m^3$, and upper 95th percentiles ranged from 0.011 to 0.034 per $\mu g/m^3$. These results are generally consistent with that derived from studies of the all-male chromate production cohorts, both of which have shown significant relations between cumulative exposure to CrVI and lung cancer risk individually. Sensitivity analyses demonstrated that the inclusion of women from the aerospace cohort increased the IUR values by approximately 3-fold, despite their lower exposures. However, this finding should be considered cautiously as the aerospace women contributed only 24 lung cancer deaths among the pooled cohort.
Conclusions: While the lower CrVI exposures among the aerospace workers were not significantly associated with lung cancer rates, a 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 resulted in IUR estimates that are roughly comparable to, and supportive of, those derived previously for individual cohorts. However, the observed differences in risk among men and women should be considered in the absence of evidence confirming no sex-based biological difference.

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