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Appendix E

Chrome Coalition Comments on Gibb et al. (2000) Comment 5

Critique of Two Studies by Gibb et al.:

Lung Cancer Among Workers in Chromium Chemical Production

Clinical Findings of Irritation Among Chromium Chemical Production Workers

(American Journal of Industrial Medicine [2000] 38:115–126; 127–131)

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Executive Summary

Gibb et al. (2000a) reported the results of a prospective mortality analysis on a cohort of chromate production workers who worked at a chromate production plant in Baltimore, Maryland. Lung cancer death is the primary outcome of interest, because hexavalent chromium [Cr(VI)] exposure has been reported as a risk factor in lung cancer mortality. The study population consisted of a cohort of 2,357 males who were hired between August 1, 1950, and December 31, 1974. The cohort is characterized by a very large number of short-term workers. More than 40% worked less than 90 days, and 75% of the cohort worked less than *2* years.

The authors report a "strong" dose-response relationship for lung cancer associated with cumulative Cr(VI) exposure. Clinical signs of irritation, cumulative trivalent chromium [Cr(III)] exposure, and duration of work were not found to be associated with a risk of lung cancer. There was no association between cumulative Cr(III) exposure and excess lung cancer risk, and the association between excess risk of lung cancer and cumulative Cr(VI) exposure was not confounded by smoking status.

In the second paper, Gibb et al. (2000b) reported data regarding skin and nasal irritation among the same cohort of workers, and they evaluated the relationship between Cr(VI) exposure and the first occurrence of each clinical finding. Nasal irritation and ulceration were reported in approximately 60% of the cohort, and the symptoms appeared, on average, within **3** months of first exposure. Median exposure to Cr(VI) at the time of occurrence for nasal irritation and ulceration was approximately 20 $\mu g/m^3$, and the mean was 50 $\mu g/m^3$.

Exponent conducted a review and critique of the manuscripts and our findings are summarized briefly below:

- For several reasons, it has been concluded that the methods used to measure airborne Cr(VI) in the Baltimore plant likely underestimated Cr(VI) exposures.

- The exposure reconstruction methods are not well described, and it is not possible to critique the approaches used. Based on the information provided, the exposure reconstruction did not characterize peak exposures, which would be the most meaningful dose metric for assessing irritation effects. The airborne concentration data for 12 years, approximately one-third of the exposure period, was missing and could not be incorporated into the exposure reconstruction, and only incomplete data were available for an additional **9** years.

- The Cr(III) exposure estimates are based on measures of total chromium and Cr(VI) in rafter dust, collected several years after the plant was closed, and correlated to measured levels of Cr(VI) in airborne samples. These exposure estimates are not reliable for many reasons.

- Short-term workers (e.g., those who worked for less than **1** year) may have different risk factors than longer-term workers and the general population. Because short-term workers make up a large fraction of the population (more than **40%** worked less than 90 days), the impact of short-term workers in this cohort could be substantial. The analysis should be reevaluated without the data from short-term workers to determine their effect on the conclusions. Conclusions regarding risk in the low dose range, which was derived from only short-term workers, should be judged cautiously.

- The authors present smoking-adjusted risk estimates from the Cox regression models; however, the authors did not control for smoking in the standardized mortality ratio *(SMR)* analysis, and the results could be substantially biased. Confidence intervals (CIs) for the smoking-adjusted relative risk estimates should be presented.

- The reference mortality rates used in Gibb's *SMR* analysis are the population mortality rates for the state of Maryland; however the largest proportion, **45%** of the cohort, died in the city of Baltimore, and hence Baltimore reference rates should have been used in the *SMR* analysis. **A** sensitivity analysis

demonstrated that a smaller number of expected deaths are generated when using death rates from the state of Maryland as compared to either Baltimore County or the city of Baltimore. Similarly, SMRs are almost uniformly higher based on Maryland reference rates as compared to those calculated using death rates from the city or county of Baltimore. When Baltimore City rates are used in place of Maryland rates, *SMRs* for lung cancer are **24%** lower for the entire cohort and **30%** lower for whites. The curious findings of statistically significantly elevated lung cancer *SMR* among whites at the second and third exposure quartiles may be explained, at least in part, by these findings.

- The conclusions regarding clinical signs of irritation in this study is of limited usefulness because of the potential biases in measuring the health outcome and the relatively poor dose measures.

- The value of these data for quantitative cancer risk assessment seems to be overstated. The authors conclude that they have observed a "strong" dose-response for airborne Cr(VI) exposure and lung cancer and that they have provided the data necessary for use in quantitative cancer risk assessment. However, CIs for relative risks, calculated using the first quartile as a reference group in the proportional hazards model, with smoking included in the model as a variable, were not presented. Thus, it is difficult to assess the precision of those risk estimates. The SMRs, which are typically used for cancer risk assessment, were not adjusted for smoking. The utility of these data for cancer risk assessment would be substantially improved if the *SMRs* were adjusted for smoking. Finally, the appropriateness of extrapolating lifetime cumulative exposures, averaged over a very long period of time (e.g., 45 years), from relatively short duration exposures (e.g., 2 years) is highly questionable and not generally considered an acceptable risk assessment practice. It would be far more appropriate to assess the risks of lung cancer based on a subset of these data, focused on the longer-tern workers and a larger number of exposure groupings.

In summary, the findings of this study should be judged cautiously because of the many uncertainties in the information presented. In particular, risk estimates for lung cancer at the lower levels of cumulative Cr(VI) exposure may be inaccurate for several reasons and should not be relied upon for health risk assessment. **A** review of the raw data is currently on-going and we expect that the analysis will: 1) confirm the appropriateness of the Baltimore reference rates for calculating SMRs, **2)** improve upon the ***S M R*** analysis by adjusting for smoking, and 3) allow for a more complete understanding of the risks for short-term workers in this cohort. Ultimately, a reevaluation of the raw data should enable a more accurate and complete analysis of the dose-response relationship from these data.

Introduction and Summarv of Studies

On behalf of the Chrome Coalition, Exponent reviewed and critiqued the methods and findings of the Gibb et al. (2000a,b) studies published in the *American Journal* of *Zndustrial Medicine,* and our draft comments are presented herein.

Gibb et al. (2000a) reported the results of a prospective mortality analysis on a cohort of chromate production workers who worked at a chromate production plant in Baltimore, Maryland. This study follows up, in part, on the cohort of chromate production workers studied previously by Hayes et al. **(1979)** and Braver et al. **(1985).** Lung cancer death is the primary outcome of interest, because hexavalent chromium [Cr(VI)] exposure has been reported as a risk factor in lung cancer mortality. Other mortality outcomes also reported in Gibb's study include overall deaths, overall cancer deaths, arteriosclerotic heart diseases, prostate cancer, mental disorders, suicide, and accidents.

One primary objective of the Gibb et al. study was to assess the excess lung cancer risk associated with trivalent chromium [Cr(III)] exposures. Airborne Cr(III) concentrations were not reported; rather, Cr(III) concentrations were estimated by sampling settled dust in the plant (after the plant closed) and analyzing it for Cr(VI) and Cr(III). From these data, the Cr(III)/Cr(VI) concentration ratios in dust were determined in various areas of the plant, and were used with the air sampling data, which were specific to Cr(VI), to estimate workers' exposure to Cr(III). The only dose metrics evaluated in the mortality study were lifetime cumulative Cr(VI) (quantified in terms of chromic acid [CrO_3]) and Cr(III) airborne exposures (units of mg/m^3-year). Smoking data (yes/no at the time of hire), and information on when clinical signs of irritation (e.g., irritated nasal septum) were reported, were also available for this cohort.

The study population consisted of **a** cohort of **2,357 (1,205** white, **848** non-white, and **304** unknown race) male workers who were first employed at the Baltimore chromate production plant between August **1, 1950,** and December **31, 1974.** This cohort of workers excluded women (N=160), workers who had an unknown length of employment **(N=24),**

workers with unknown work history (N=16), and a worker whose age could not be determined (N=1). Unlike the population analyzed by Hayes et al. (1979), Gibb et al. chose to include short-term workers (those who worked less than 90 days, N=990). This cohort definition even included those who worked for only one day at the facility. Employment in this facility ended in July 1985 when the facility was closed. Vital status ascertainment was conducted at various times using information from the Social Security Administration, Department of Motor Vehicles, the National Death Index, voter registration records, and by other means. The final follow-up ended on December 31, 1992. The cohort is characterized by a very large number of short-term workers. More than 40% worked less than 90 days, and 75% of the cohort worked less than 2 years.

The authors report a "strong" dose-response relationship for lung cancer associated with cumulative Cr(VI) exposure. Clinical signs of irritation, cumulative Cr(III), and duration of work were not found to be associated with a risk of lung cancer in the Cox proportional hazards modeling analysis, when cumulative Cr(VI) and smoking status were included in the models. There was no association between cumulative Cr(III) exposure and excess lung cancer risk, and the association between excess risk of lung cancer and cumulative Cr(VI) exposure was not confounded by smoking status.

In the second paper, Gibb et al. (2000b) report data regarding skin and nasal irritation among the same cohort of workers, and they used a proportional hazards model to evaluate the relationship between Cr(VI) exposure and the first occurrence **of** each clinical finding. Nasal irritation and ulceration were reported in approximately 60% of the cohort, and the symptoms appeared, on average, within 3 months of first exposure. Median exposure to Cr(VI) at the time of occurrence for nasal irritation and ulceration was approximately 20 $\mu g/m^3$, and the mean was 50 $\mu g/m^3$. The proportional hazards model indicated that ulcerated nasal septum, irritated skin, and perforated eardrum were significantly associated with ambient Cr(VI) exposures.

Evaluation of Study Approaches and Conclusions

The following sections provide critique and discussion of the approaches and conclusions presented in the published manuscripts. The key elements of these two studies study are discussed within the following framework:

1. Industrial hygiene air sampling methods and data
2. Exposure reconstruction
3. Epidemiological methods, including
   - Control for confounding due to smoking
   - Cohort selection criteria
   - Selection of a control (e.g., reference) population
   - Statistical modeling methods
   - Data presentation and interpretation
4. Clinical findings of irritation
5. Risk assessment conclusions.

Critique of Industrial Hygiene Methods and Measures

One strength of this study is that thousands of industrial hygiene air sampling measures were collected in this plant to characterize workers' exposures over time. As discussed in detail below, both area and personal samples were collected. Further, it is important to recognize that the authors report that the sampling program was designed specifically to assess average worker exposures. This is an important consideration, because historical air monitoring data were typically collected for the purposes of identifying fugitive sources and improving equipment efficiency and/or industrial hygiene (Corn **1992).** Sample collection and analytical approaches were discussed in Gibb et al. (2000a) and also in Braver et al. **(1985).**

From **1950** through **1961,** the Baltimore Cr(VI) air monitoring data were collected through a wand—likely to be an extension probe used to collect samples from the breathing zone—into midget impingers (Gibb et al. 2000a; Braver et al. **1985).** The analysis method was the commonly used diphenylcarbizide reaction followed by colorimetric analysis. One advantage of these data is that the samples were analyzed specifically for Cr(VI), as compared to the Mancuso **(1975)** study, which relied on total chromium airborne monitoring data.

The efficiency of this sample collection method for particulates is not known; however, following a thorough review of the historical methods, Braver et al. **(1985)** concluded that these data provide a valid exposure measure within a reasonable degree of uncertainty. However, Braver et al. **(1985)** reported a "usual" (e.g., average) exposure for workers in the Baltimore plant from **1950** to **1959** of **0.218** mg Cr(VI)/m^3. This exposure level is also generally consistent with that reported by the Public Health Service in **1953** for the Baltimore plant (PHS **1953).**

While the published study does not provide detailed exposure measures, the second paper provides average exposures by year, in graphical format, for three job titles—Leaching **A** Operator, Evaporator Operator, and Potash Operator, and the raw data from the Freedom of Information Act (FOIA) request includes a spreadsheet table with the data used to create the published figure. Both provide exposures by year for **1950** through **1985** for these job titles in

units of mg CrO_3/m^3. The raw data appear to be consistent with the published data; however, the average exposure estimates for each year and for each job title are lower than the average reported for that time frame for the entire facility by Braver et al. (0.218 mg Cr(VI)/m^3), which was estimated from a survey conducted in 1950. The average exposures for those three job titles reported by Gibb et al. from 1950 through 1960 are approximately an order of magnitude lower than the "usual" exposure reported by Braver et al.—only 0.048, 0.019, and 0.039 mg Cr(VI)/m^3 for the Leaching A Operator, the Evaporator Operator, and the Potash Operator, respectively—and there is no consistent downward trend in exposures from 1950 to 1960 in the data presented.

Further, the 1953 PHS document reports average exposures in three operating chromate production plants—including the Baltimore plant—for leaching and potash operators of 0.11 and 0.17 mg Cr(VI)/m^3, respectively, and there are no data for "evaporator" operations. Although only limited industrial hygiene data are presented in both of the Gibb et al. papers and in the raw data, we note that the data presented are consistently lower than those reported for the same time period by alternative sources (Braver et al. 1985; PHS 1953). Finally, it is important to recognize that the impinger method would not have measured water-insoluble Cr(VI); however, Braver et al. (1985) concluded that there was very little water-insoluble Cr(VI) in the Baltimore plant.

During the latter years of the Baltimore plant operation (starting in the mid-1960s), Cr(VI) samples were collected on a RAC tape sampler (Gibb et al. 2000a). The RAC tape sampler's operation involved a combination of linear and rotary motion for advancement of the sampling tape upon which particulates were captured (ACGIH 1978). Very little information could be identified regarding the use of the RAC sampler for collection of Cr(VI) or total chromium, and the method is not discussed in the 1975 National Institute for Occupational Safety and Health **(NIOSH)** criteria document for Cr(VI), although other methods, including impinger sampling, are discussed.

The RAC tapes were made of 98%–100% pure cellulose (Whatman 2001). Previous studies have shown that significant reduction of Cr(VI) to Cr(III) may occur on the cellulose filters **(NIOSH** 1975; Abell and Carlberg 1974; Thomsen and Stem 1979). Unpublished studies

conducted by NIOSH in the early 1970s to determine the proper sampling filter for Cr(VI) found that the Cr(VI) recovery from cellulose filters spiked with potassium dichromate was only 69% at 2 hours after spiking (Abell 2001, pers. comm.). It is also noteworthy that Braver et al. (1985) believed that the potential for reduction of Cr(VI) to Cr(III) was sufficient in the RAC samples to exclude workers who started after 1960 in the new Baltimore plant from their analysis, because their exposure levels were believed to be underestimated. The usual exposure level estimated by Braver et al., which was believed to be underestimated, was 0.031 mg Cr(VI)/m^3, and is generally consistent with the few exposure measures reported by Gibb et al. The concerns of Braver et al. (1985) regarding the underestimation of exposures in the RAC samples collected in the Baltimore plant should be considered when using the Gibb et al. findings for health risk assessment.

Finally, full-shift personal air samples were collected in addition to the RAC area samples from 1977 (or 1978—the date of personal monitoring is reported differently in the fourth and fifth full paragraphs of page 117) until the plant closed in 1985. Cr(VI) concentrations from personal samples were reported to correspond well with the results from the stationary RAC samplers for most jobs. The RAC stationary samplers were reported to underestimate Cr(VI) concentrations only for jobs that involved point sources for fugitive emissions (e.g., packers) (Gibb et al. 2000a), and the authors reported adjusting the exposure estimates accordingly. It is unclear whether these authors adjusted all exposure estimates generated using the RAC data (e.g., those collected prior to 1978) or only those since the personal samples were also collected (e.g., after 1978). Although it may be an artifact of the limited data available to assess exposures from the published sources, it is interesting to note that exposures for the three job titles with reported data (Leaching A Operator, Evaporator Operator, and Potash Operator) are generally higher from 1978 until plant closure in 1985—the time period for which personal samples were collected—as compared to the period from approximately 1965 to 1975, for which only RAC data were available (Gibb et al. 2000b).

In conclusion, the Cr(VI) airborne concentrations used in the exposure reconstruction should be considered carefully because the reported values are generally lower than those reported by other sources for the Baltimore plant and the method used to collect much of the data is of

questionable reliability. If the airborne concentrations are underreported, the relationship between exposure and lung cancer risk cannot be accurately quantified.

Critique of Exposure Reconstruction

One of the strengths of this study is the availability of extensive quantitative exposure data; this type of exposure information is typically not available for most epidemiological studies of Cr(VI)-exposed workers. In addition, the industrial hygiene data were collected to represent "typical" worker exposures, rather than for other purposes such as regulatory compliance with the ceiling value permissible exposure limit (PEL), or characterizing high exposures associated with equipment failures or poor maintenance. Exposure assignments were constructed by linking industrial hygiene data, including breathing-zone (1950–1960) and fixed-site measurements (1960–1985), and personal sampling (collected after 1977 or 1978). This information was used to create a job-exposure matrix **(JEM)** using yearly average Cr(VI) and Cr(III) concentrations by job title. Despite the comprehensive exposure database that presumably is available, there are several notable limitations in the areas of missing data, lack of information on the determination of 8-hour time-weighted average exposures by job title, and representativeness of the industrial hygiene data. Each area is discussed below.

Gibb et al. had to extrapolate for **12** of 36 years of the exposure period due to missing air sampling data. They acquired data for 1950–1956, 1960–1961, and 1971–1985 (total 24 years). However, no data were available for 1957–1959 and 1962–1970, which constitutes approximately one-third of the exposure period.[1] Further, only incomplete data sets were available for an additional 9 years. Gibb et al. state that they used various extrapolation procedures to fill in the missing cells of the JEM; however, inspection of the raw data for the only three job titles, for which exposure profiles were presented (Leaching **A** Operator, Evaporator Operator, and Potash Operator), for the periods of "missing data" from 1957–1959 and 1962–1970 leads one to wonder how the extrapolation method was used to fill the missing cells of the JEM because the concentrations entered for each of these job titles is neither

[1] It may be relevant to note that Allied Chemical Company acquired and **took** control of the plant **in** 1957, corresponding with the first data gap.

systematic nor entirely consistent with exposures for periods for which there are reportedly measured data.

Gibb et al. did not provide sufficient detail regarding the assumptions that went into the JEM for readers to review the data and evaluate the process used to develop the quantitative exposure estimates. As presented, the JEM is a "black box" that reviewers must trust was assembled correctly and in the most accurate fashion. At a minimum, it would have been appropriate to include a table showing average exposures by job-title groups and calendar periods, as well as the assumptions that went into the determination of time-weighted exposures based on data from area samples.

Gibb et al. used dust samples collected in 1985 to assess proportional levels of Cr(III) and Cr(VI). The use of these data requires several strong assumptions: **1)** that dust samples represent airborne levels in local areas of plant, **2)** that samples in 1985 represent all years of facility operation, **3)** that Cr(VI) was not converted to Cr(III) by reducing agents such as iron, and **4)** that plant closure procedures and cleanup did not affect the levels and distribution of settled dust. The fact that the measurements were made **3** years after the plant closed further limits the usefulness of these data. In addition, there seems to be significant variability in the ratios of Cr(III) to Cr(VI), which ranged from **1.2** to **64** for different job titles, and from 0.02 to 77 across the different fixed sampling locations within the facility. This variability could represent true exposure conditions, or it could be the result of other factors. Further, different areas/operations of chromate production plants, including the plant in Baltimore, produce and handle different chromium chemicals and materials. For example, the "wet side" handled only the leached Cr(VI) product **(PHS** 1953), and workers on the wet side would be exposed to very little, if any, Cr(III). However, the Gibb et al. exposure assessment accounts for more trivalent than Cr(VI) exposure for each job title (i.e., ratios range from **1.2** to **64);** however, there were surely some job titles on the wet side for which there would be far more Cr(VI) exposure and likely no exposure to Cr(III). This draws into question the accuracy of the Cr(III) exposure estimation method.

Gibb et al. state that there was substantial individual variability in exposure within job titles, although they assigned one value, the annual average by job title, for each cell in the JEM. This

could produce significant exposure misclassification and is a limitation of most exposure reconstructions based on a **JEM,** and not one unique to this study.

Gibb et al. do not discuss the effect of respirator use. Braver et al. recognized that the workers in the Baltimore plant used respirators. While it is not known whether the use of respirators was required or if they were appropriately fit-tested, the effect, if any, of respirator use in the plant should have been discussed.

Gibb et al. state that they log-transformed the data to control variability in their statistical tests. The mean values presented for exposure in each quartile appear to be arithmetic means, based on the cumulative exposures for each worker in each quartile. However, it is unclear whether the exposures for each worker are representative of yearly average exposures as estimated by the arithmetic mean or the geometric mean (e.g., the average in each cell of the JEM). The more appropriate dose metric for cancer risk assessment is the average exposure calculated from the arithmetic mean, rather than the geometric mean (Crump 1998; Seixas et al. 1988; Smith 1992).

In conclusion, it is difficult to determine the overall impact of the aforementioned uncertainties in the exposure reconstruction or dose-response data. It should be recognized that the reconstruction did not characterize peak or upper-bound exposures, and thus it cannot be cbncluded that the signs of irritation reported in the second manuscript are due to the levels of exposure reported in the study. Further, it is important to note that exposure data were lacking for 12 years **(30%** of the exposure period) and that the data were incomplete for an additional 9 years (an additional 25% of the exposure period).

Critique of Epidemiological Analysis

Cohort Definition and Enumeration

The cohort enumeration procedures used by Gibb et al. relied on the earlier work by Hayes et al. (1979) in constructing the worker cohort. However, the cohort defined in the Gibb et al. study was different from that of Hayes et al. in two important ways: 1) the Gibb et al. cohort includes workers who had less than 90 days work history at the chromium facility (the Hayes et al. cohort excluded this group, N=1,915), and **2)** the Gibb et al. cohort excludes workers who started employment at the facility between 1945 and 1950 (N=734).

Although Gibb et al. contend that increasing the size of the low-exposure group was their justification for including a large number of workers with very little time spent at the plant, the inclusion of this group in the study cohort is not appropriate. As discussed in detail below, short-term workers may be different from longer-term workers in a number of ways that could influence disease and risk: short-term workers are likely to have significant exposures from other jobs, and they may have a different socio-economic status than longer-term workers. Further, the short-term workers were included specifically to provide information regarding the lung cancer risk due to low-level exposures. While these short-term workers do represent the lower bound of exposure in terms of lifetime cumulative dose, it is important to note that their short-term exposures may have been to very high concentrations of Cr(VI) (i.e., short-term workers are typically assigned to the worst and highest exposure jobs). Hence, their inclusion in the cohort does not provide useful information for assessing lung cancer risk from low-level exposure as presumed by the authors because the data are extrapolated to a 45-year working lifetime exposure in the discussion section.

Numerous researchers have demonstrated that the mortality of short-term workers is different than that of longer-term workers. For example, Bonffetta et al. (1997) found that among a cohort of man-made vitreous fiber workers, those with less than 1 year of employment had a statistically significant increased standardized mortality ratio ***(SMR = 1.43;*** confidence interval

[CI]: 1.37–1.53), whereas workers with greater than 1 year of employment (contributing 65% of the person-years in this study), had a much lower SMR at 1.05 (CI: 1.02–1.09). Further, in the man-made fiber worker cohort, there was only an increased risk of lung cancer when the short-term workers were included (i.e., there was no increase in lung cancer among workers with greater than 1 year of employment). It should be noted that in the Gibb et al. cohort, 60% of the person-years at risk were contributed by workers who worked less than 6 months (approximate median of exposure) and that 83% of the person-years were contributed by workers with less than 2 years of employment tenure. Thus, any effect due of short-term workers in the Baltimore chromium worker cohort, similar to that observed by Bonffetta et al., could have a substantial impact on the study results.

The mortality experience of short-term workers has also been recently studied by Kolstad and Olsen (1999) and Steenland et al. (1998). These researchers found that increased mortality is often reported among workers with short-term employment. In studying these workers, Kolstad and Olsen found an increase in hospitalizations related to alcohol abuse and violence. An unhealthy lifestyle was also identified as a determinant of short-term employment. This seems to fit well with the findings of Gibb et al. (2000a) that among the Baltimore cohort, there was a statistically significant increased rate of death due to mental disorders, suicide, and heart disease. Clearly, these data suggest that the short-term workers should be evaluated separately, if at all, and that the data for longer-term workers is more relevant for risk assessment. An excess risk attributed to Cr(VI) exposure, mainly present when short-term workers are included in the analysis, could easily be attributable to another characteristic of the short-term worker group.

On the other hand, the motivation for excluding the 1945–1950 group is not clear. This group could be expected to improve statistical precision (they are older and would increase the cohort size by 33%), and many of these workers worked in the new facility, which was opened in 1950. There were additional facility changes in 1960, and it is our understanding that not all workers immediately moved into the 1950 facility. In any case, it would be better to include this group in the study cohort and perform subcohort analysis to see if there are differences in health risks when including/excluding the 1945–1950 group.

In conclusion, because short-term workers, who make up the lower two exposure groups, may have different risk factors as compared with the general population, the dose-response reported for the low dose range may not be reliable (i.e., excess risk may not be associated with Cr(VI) exposure). Further, exclusion of the **1945-1950** workers reduced the power and statistical precision of the Gibb et al. study.

Control for Confounding due to Smoking

The key confounder in any study of lung cancer is smoking. Gibb et al. have only limited smoking data that reflect smoking status at the time of hire. (There was no information available subsequent to hire, and only limited information on the amount smoked contained in the raw data.) Using this information, they present smoking-adjusted risk estimates from the Cox regression models. However, the authors did not control for smoking in the ***SMR*** analysis, and the results could be substantially biased. Therefore, the author's statement that Table V has great value for risk assessment is inappropriate, because these results do not control for smoking. Further, the relative lung cancer risks reported in the text on page **123,** which were corrected for smoking, are of questionable usefulness because CIs are not presented and it is not possible to judge the statistical significance of these results.

The prevalence of smoking in this cohort was reported to be more than 80%, and may have been even higher if workers started smoking after start of employment. This rate is likely higher than the prevalence of smoking in Maryland (the reference group for the SMR analyses). The smoking prevalence in Baltimore may be higher than Maryland as a whole and closer to the smoking patterns **of** the chromium workers. This observation is one additional justification for using Baltimore as a comparison group, rather than the state of Maryland (as discussed further below).

The observed relative **risk** for smoking, near **6.0** (Tables VII and VIII), also appears to be too low relative to results from many other studies, which have found **risks** in the range of **10–15** fold (even higher for heavily exposed groups), depending on the amount smoked and the duration of smoking (Baron and Rohan **1996).** This could imply that, although they have

smoking information corresponding to the start of employment, the data may be misclassified (i.e., if a significant fraction of workers quit smoking subsequent to their employment date, the start-of-employment data would not accurately represent the group). Alternatively, these findings could suggest that the combined risks associated with smoking and Cr(VI) inhalation exposure are less than additive.

Presentation of Results

Gibb et al. present only mortality outcomes with statistically significant excesses or deficits. It would be preferable to present a larger list of cancer findings to produce a better health status profile of the cohort. Although they present a fair amount of descriptive data in Tables II–IV, they do not present a key summary: age group/smoking status/final exposure group/lung cancer status. In the discussion section of the paper, it is stated that that **67** out of 71 lung cancer cases were smokers at the start of employment, but further breakdowns of smoking, occupation, cumulative exposure, and demographic factors are not provided.

These data would be useful but have no impact on the reported association between lung cancer risk and Cr(VI) exposure.

Modeling Results

Gibb et al. evaluated several models in Tables VII and VIII:

- Model **1:** Cr(VI) and smoking
- Model **2:** Cr(III) and smoking
- Model 3: smoking and years worked
- Model **4:** Cr(VI), Cr(III), and smoking
- Model ***5:*** Cr(VI), years worked, and smoking.

In Models 1 and 2 (Table VII), the results for Cr(VI) and Cr(III) are nearly the same (i.e., risk ratio equal to 1.32 or 1.38), yet when both terms are in the model (Model 4, Table VIII), the relative risk for Cr(VI) is much higher than for Cr(III), and the relative risk for Cr(III) is in the opposite direction of what is reported in Table VII. These significant changes in the risk estimates highlight the problem of multicollinearity between the chromium exposure variables. One immediate consequence of this multicollinearity is the inability to precisely estimate the effects of exposure variables on the occurrence of lung cancer.

Cumulative exposure was computed using a 5-year lag period ("...only exposure occurring 5 years before a given age was counted."[2]). The authors do not present any specific clinical or biological considerations for the chosen lag period, but they performed additional analyses using lag periods of 0, 2, 10, and 20 years and chose the lag that results in the best-fitting model. Although the authors mention the use of different lag periods for cumulative exposure, and the use of average exposure,[3] they do not present results from these analyses. We recognize the limitations imposed by journals on the length of a manuscript, but a more complete presentation of the results on different lag-period assumptions is warranted.

Interpretation of Findings

One conclusion that Gibb et al. state in their abstract is the presence of a "strong dose-response" relationship between Cr(VI) and lung cancer. This conclusion is based on the comparisons of quartiles of exposure (comparing the second, third, and fourth quartiles to the lowest quartile), while controlling for smoking. However, 67 of the 71 lung cancer cases in this analysis were known smokers. Also, Gibb et al. do not provide CIs to assess the statistical precision and significance of these exposure quartile risk estimates. Conclusions such as the existence of a strong dose-response relationship cannot be evaluated given the data presented.

[2] See the statistical methods section of the cancer mortality manuscript.

Vital Status Follow-Up

Despite publication in 2000, mortality follow-up only goes up to 1992. Currently, mortality data are available through 2000 from the National Death Index. Assuming that 1,500 workers were still alive as of December 31, 1992, a potential maximum of 10,000 person-years of follow-up is available but was not included. Given that a portion of these workers probably died before 2000, one could expect to observe 5,000 to 7,000 additional person-years of follow-up accounting for the expected number of deaths during this period. Total person-years in the study is 70,000, so extending the cohort could lead to an additional 8–10% of follow-up years, but more importantly, we would observe a substantial number of new deaths for an updated analysis. This additional vital status follow-up would improve the assessment of lung cancer risk in this study.

Sensitivity and Influence Analyses

The Gibb et al. presentation of results lacks any formal sensitivity or influence analyses. Sensitivity analysis refers to evaluating the impacts of different assumptions or methods applied to the cohort data. Examples of appropriate sensitivity analyses for the Gibb et al. presentation would be examining the effect on results of using a different comparison group (e.g., Baltimore mortality data), different exposure cut-points, different statistical modeling assumptions, and various lag assumptions. Influence analysis refers to the impact of specific data points on results. These types of analyses can identify specific individuals or subgroups that have substantial impacts on the data findings. The more consistent or robust the findings are across different sensitivity and influence analyses, the more confidence one has in the study results. The more that study findings depend on specific assumptions or are driven by just a few data points, the less confidence we have in the overall interpretation of findings and use of the data for risk assessment. The sensitivity analysis described below demonstrates the importance of these types of data evaluation.

Reference Population Sensitivity Analysis

Cohort mortality analyses (e.g., SMR) rely on comparing the number of deaths in the cohort with the corresponding number of deaths that could be expected on the basis of the death rate of a reference population adjusting for age, race, and sex. Whether the observed number of deaths will be more or less than expected depends critically on the choice of reference population from which the "expected deaths" are calculated. In the case of a worker health study, the preferred reference population is one that represents the general population of the local region where the workers reside. Using a local population as the reference group will help to minimize potential bias due to regional variation in cancer rates. At the same time, the reference population must be sufficiently large to provide statistically stable mortality rates, even for rare cancer outcomes. Depending on the choice of reference population, the number of observed deaths could be made to appear "excessive" or "less than expected" when, perhaps, neither conclusion is completely justified if a more closely matched reference population is used.

The reference mortality rates used in Gibb's SMR analysis are the population mortality rates for the state of Maryland. The chromate production facility was located in the city of Baltimore in the Inner Harbor. Although the addresses of the workers while they were employed at the factory are not available, it is reasonable to assume that the vast majority likely resided in the city of Baltimore. The justification offered by Gibb et al. for using the Maryland mortality rates is that many deaths in the cohort occurred outside of Baltimore. Gibb et al. reported that **16%** of the deaths occurred in Maryland, outside of Baltimore, and **39%** in other states (not Maryland). However, this line of reasoning ignores the fact that the largest proportion, 45%, died in the city of Baltimore. Because it is probable that most of the workers resided in the city of Baltimore while working at the plant and the largest proportion died in the city of Baltimore, reference rates for the city of Baltimore are arguably more applicable than either the county of Baltimore or the state of Maryland. The study population had more in common with the population of the city of Baltimore than the population of the entire state of Maryland on factors that could affect health. Further, many of the out-of-state deaths were probably workers who resided in Baltimore while they worked at the chromium facility, and likely before and after, but retired elsewhere.

Hayes and his colleagues (Hayes et al. 1979), who analyzed the mortality experience of the same cohort in 1979, chose the city of Baltimore as the reference population, because lung cancer rates were recognized to be 25% higher among residents of Baltimore than of the state of Maryland. Gibb et al. acknowledged the higher lung cancer mortality rates in the city of Baltimore, but nevertheless used the state of Maryland mortality rates in their analyses. Given this information, it is reasonable that the expected number of deaths from lung cancer and other causes would be higher if reference rates from the city and county of Baltimore had been used in the analysis, and that the corresponding *SMRs* would be lower.

The present analysis examines the potential effect of the choice of reference population by comparing the number of expected deaths based on the mortality rates for the city of Baltimore, the county of Baltimore, and the state of Maryland. Variations in the number of expected deaths illustrate the effects of different reference populations on the *SMR*, and the potential for under- or over-reporting of the *SMRs* and relative risks for lung cancer in the Gibb et al. (2000a) study.

Alternative Reference Population Analysis: Methods

Cohort Population

The original cohort individual and vital status data were not readily available. However, Gibb et al. provided detailed summary measures (mean, standard deviation, quartiles, minimum, maximum) on the key characteristics of this cohort: year entering workforce, age when employment began at the chromium plant, length of employment, and years of follow-up. Using this information, we generated a simulated cohort whose characteristics mimic closely those reported by Gibb et al. for the original cohort. Although individual records from the simulated cohort may not correspond to any one member of the actual cohort, their collective characteristics are closely matched. Using this reconstructed cohort database, applied to each of the three comparison populations to estimate expected numbers, any differences in expected deaths would correctly reflect the effect of the choice of reference population.

A total of 2,357 records with date of birth, date of first employment at the plant, and date of the termination were simulated to mimic the characteristics of the actual cohort. This simulated cohort is also assumed to consist of all male workers. A certain number of records were randomly chosen within the simulated cohort as white or non-white workers, to match the race composition in the Gibb et al. cohort. Among each race category of the simulated cohort, some records were again randomly chosen to represent diseased workers. The "diseased workers" in the simulated cohort were chosen such that the total number of deaths from each of the race categories matches that of the original cohort. For those who were assigned as "diseased" in the simulated cohort, the date of death was randomly selected between the last date of work and the end of follow-up on December 31, 1992.

We used the age-, sex-, race-, and calendar period mortality rates for the city of Baltimore, the county of Baltimore, and the state of Maryland. These rates were obtained from the Mortality and Population Data System (MPDS) files of the Occupational Cohort Mortality Analysis Program (OCMAP) at the University of Pittsburgh, consistent with the source of the reference rates used by Gibb et al. The mortality rates are presented according to sex (male, female), race (white, non-white), age (in 5-year groups: 0–4, 5–9,..., 85+), and calendar year period (5-year groups: 1950–1954, 1955–1959, …, 1995–1998). The OCMAP mortality rates are given in the number of deaths per 1,000.

Analysis

Person-Years

Person-years for the cohort were accumulated for every year of the study follow-up period, from the beginning of employment through December 31, 1992, or until the worker died if the death occurred before the end of the follow-up period. Each person-year is indexed by the calendar year worked and the age of the worker. Person-years are grouped in the same 5-year age and calendar year groups corresponding to the mortality rates in OCMAP. Workers who were employed for many years contributed person-years to several age and calendar year groups

during their tenure. The total person-years of observation is simply the sum of person-years over each age and calendar year group:

$$\textit{Person Years} = \sum_{Age=A,Year=Y} PY_{A,Y}$$

A worker who completed an entire year of work is credited with 1.0 person-year of exposure. When appropriate, a fraction of a person-year was calculated for those individuals who worked less than a year.

Expected Deaths

Expected deaths were calculated using the mortality rates of the state of Maryland, the county of Baltimore, and the city of Baltimore. Expected deaths were calculated for all causes of death, all cancers, arteriosclerotic heart disease, cancer of the lung, and cancer of the prostate. Expected deaths were determined by multiplying the person-years of observation for an age and calendar year category (e.g., 34–39 year olds in 1970–1974) by the mortality rate (of a certain disease outcome) for the corresponding age and calendar year category. The total number of expected deaths is the sum of these individual expected death values, with the summation taken across all the age and calendar year categories. Expressed in an algebraic expression, the total expected deaths, $E(Death)$, is given by:

$$E(Death)^{Cause} = \sum_{Age=A,Year=Y} PY_{A,Y} \times Rate_{A,Y}^{Cause} / 1{,}000$$

If race- and sex-specific mortality rates are available, as is the case with OCMAP/MPDS data, the expected deaths are calculated for specific race and sex combinations, with the total expected deaths being the sum of these subgroups.

Standardized Mortality Ratio

The SMR compares the number of deaths observed during the follow-up period to the number of deaths expected. Following the notation used by Breslow and Day (Breslow and Day 1987),

if λ_j is the mortality rate of stratum j corresponding to a certain combination of age, calendar year, race, and sex category, the ***SMRs*** can be calculated as the ratio between the observed number of deaths from stratum j (d_j) and the expected number of deaths across the various strata $j=1,2,3,...,J$, where n_j is the pcrson-years of observation in stratum j:

$$SMR = \frac{\sum_{j=1}^{J} dj}{\sum_{j=1}^{J} n_j \lambda^*_i} = \frac{D}{E^*},$$

where ***D*** is the total observed deaths and E^* is the expected deaths based on the "standard" or reference population. Upper- and lower-bound confidence limits of the **SMR** are given by the ratio of the upper and lower limits of the observed deaths and the expected deaths:

$$SMR, = \mu_L / E^* \quad and \quad SMR, = \mu_U / E^*$$

The upper and lower limits **of** the observed deaths are also readily calculated (Rothman and Boice 1979) and reportedin the text by Breslow and Day (1987, p. **69):**

$$\mu_L = D\left(1 - \frac{1}{9D} - \frac{Z_{\alpha/2}}{3D^{1/2}}\right)^3 \quad and \quad \mu_U = (D+1)\left(1 - \frac{1}{9(D+1)} + \frac{Z_{\alpha/2}}{3(D+1)^{1/2}}\right)^3$$

where $Z_{\alpha/2}$ denotes the $100(1-\alpha/2)$ percentile of the unit normal distribution.

Alternative Reference Population Analysis: Results

Using the simulated dates (date of birth, first date of employment, date of termination, and date of death) from the simulated cohort, the years of follow-up, the age at follow-up, and the number of years worked can be calculated as:

$$Years\ of\ Follow\text{-}Up = \begin{cases} (Date\ of\ Death - Date\ Start\ Work)/365.25, & if\ Diseased \\ (December\ 31,1992 - Date\ Start\ Work)/365.25, & Otherwise \end{cases}$$

$$Age\ at\ Hire = (Date\ Start\ \mathbf{Work} - Date\ of\ Birth)/365$$

$$Years\ Worked = (Date\ Work\ End - Date\ Start\ Work)/365.25$$

Characteristics of the simulated cohort are displayed in Table 1. The corresponding values from the original cohort in Gibb's report are also provided as **a** comparison. The simulated data for years of follow-up, age at hire, and years of employment closely resemble those of the original study cohort. For example, the means for "age at hire" in the original cohort and the simulated cohort are 30.2 and 29.6, respectively. The simulated data for years-of-work are less closely matched to the original cohort data and show greater deviation from the report values for the mean and maximum. The mean and maximum years-of-work are 3.1 and 37.7 years, respectively, for the original cohort, but only 1.85 and 18.9 years, respectively, for the simulated cohort, For the median, minimum, and 25th and 75th quartiles, however, the simulated cohort matches the original cohort well. The simulated cohort can be refined further by a Monte Carlo simulation where parameters like means and standard deviations are estimated by averages of randomly generated values following a pre-specified probability distribution (e.g., normal, exponential). This allows for more precise parameter estimates with smaller variability. It should be noted that there appears to be an error in the published information for the original cohort, because the maximum reported value for years-of-work, 37.7 years, is not technically feasible. [If a worker started on the first possible start date (August 8, 1950) and worked continuously until the last possible employment date (July 1985), the total number of years worked would be only 35, not 37.7.] Nonetheless, employees who worked many years at the facility, greater than the 75th percentile for the total cohort, seem to be underrepresented in the simulated cohort.[3]

[3] **As noted below,** in **the 4th quartile** of **the actual cohort, there are approximately four employees with very high cumulative exposures that appear to** be **outliers.**

Table 1. Reported and simulated cohort characteristics

	Years of Follow-up		Age at Hire		Year of Hire (19xx)		Years Worked	
Statistic	*Gibb*	*Simulated*	*Gibb*	*Simulated*	*Gibb*	*Simulated*	*Gibb*	*Simulated*
Mean	30.0	29.7	30.2	29.6	57.7	57.7	3.1	1.85
S.D.	9.6	11.5	7.5	6.8	7.7	7.1	6.5	3.25
Median	31.2	32.4	28.6	28.6	54	54.0	0.39	0.39
Minimum	0.3	0.1	16.9	16.9	50	50.6	0.003	0.003
Maximum	42.3	42.4	62.9	60.1	74	74.8	37.7	18.93
Q1 (25%)	22.6	22.1	24.3	24.3	51	51.0	0.088	0.09
Q3 ***(75%)***	38.9	40.4	34.4	34.4	65	65.0	2.0	1.97

The total person-years of observation for both age and race groups are summed across all calendar periods and provided in Table **2.** The total person-years from the simulated and the original cohorts are also displayed for comparison. The total person-years of observation reported by Gibb et al. is 70,736 (p. **119).** The person-years of observation from the simulated cohort is **70,158,** which differs by less than **1%.** It should be noted that when the total person-years were tallied from either Table **V** or Table VI in Gibb's report, a different value **(71,994)** was determined compared to the value reported on p. **119.**

Within the total years of observation, the original cohort has more person-years in the older age groups (70 and above), but none in the youngest age group **(15–19).** Compared to race-specific person-years reported by Gibb et al., the simulated cohort has slightly fewer person-years from white workers **(-6.1%)** and more from non-white workers (+3.0%).

Table 2. Reported and simulated total person-years of observation

	Person-Years	
Age	***Gibb***	***Simulated***
15–19	0.0	133.1
20–29	6,009.0	6,037.3
30–39	17,217.0	16,518.3
40–49	20,178.0	20,009.0
50–59	16,495.0	17,695.5
60–69	9,341.0	9,546.6
70–79	2,405.0	207.3
80+	349.0	11.0
Total	71,994.0	70,158.2

	Person-Years	
Race	***Gibb***	***Simulated***
White	43,831.1	41,148.3
Non-White	28,162.9	29,010.0
Total	71,994.0	70,158.2

Using the simulated cohort person-year calculations, the expected deaths from lung cancer and several other causes were calculated. The three expected death values correspond to the number of deaths expected using death rates from the city of Baltimore, the county of Baltimore, and the state of Maryland. Generally, expected deaths computed from mortality rates for the city of Baltimore yield the highest number, while rates from the state of Maryland usually result in the lowest number (Table 3). The number of observed deaths reported by Gibb is also provided for comparison."

[4] As mentioned in Gibb et al., the observed deaths **from** workers **of** unknown race have been distributed into white and non-white race groups in the same proportion as the known values.

Table 3. Model predicted and reported observed deaths

	White	Non-White	Total
All Deaths			
Gibb Reported Observed"	507.6	347.4	855.0
Predicted Expected			
Baltimore City	482.2	506.0	988.2
Baltimore County	362.9	485.6	848.5
State of Maryland	316.5	405.3	721.8
All Cancer			
Gibb Reported Observed"	128.8	106.2	235.0
Predicted Expected			
Baltimore City	122.4	127.8	250.2
Baltimore County	102.7	122.5	225.2
State of Maryland	91.5	105.7	197.2
Lung Cancer			
Gibb Reported Observed[a]	73.4	48.6	122.0
Predicted Expected			
Baltimore City	50.8	47.5	98.3
Baltimore County	40.9	45.7	86.6
State of Maryland	35.4	39.0	74.4
Arteriosclerotic Heart Disease			
Gibb Reported Observed[a]	163.1	88.9	252.0
Predicted Expected			
Baltimore City	178.6	146.5	325.1
Baltimore County	138.2	140.5	278.7
State of Maryland	118.5	116.1	234.6
Prostate Cancer			
Gibb Reported Observed	5.0	11.0	16.0
Predicted Expected			
Baltimore City	3.7	7.8	11.5
Baltimore County	3.5	7.6	11.1
State of Maryland	3.5	6.9	10.4

[a] The reported observed deaths for the race-unknown subcohort were apportioned to numbers for the observed deaths for whites and non-whites; hence, the observed number of deaths by race are not whole numbers as would be typically expected.

As might be predicted from the smaller number of expected deaths using death rates from the state of Maryland, the corresponding *SMRs* are almost uniformly higher than those calculated using death rates from the city or county of Baltimore (Table **4).** For example, the *SMR* for all deaths among white workers is 1.60 when death rates from Maryland are used. This number is reduced to 1.40 and 1.05 when *SMRs* are computed using mortality rates from the county of Baltimore and the city of Baltimore, respectively. Similarly, the *SMRs* for lung cancer for all workers are reduced from 1.64, according to the state of Maryland mortality rates, to 1.24 when using the city of Baltimore mortality rates. A similar reduction in SMR occurs when the ratio of 1.25—based on Maryland's mortality rates for non-white workers—is lowered to 1.02 using corresponding mortality rates from the city of Baltimore.

For lung cancer, white males continue to have a statistically significant increase in mortality, although the magnitude is substantially reduced when the city of Baltimore rates are used (CI for Maryland reference rates is 1.63–2.61; CI for city of Baltimore reference rates is 1.13–1.82). The lung cancer rate for non-white males is non-significant regardless of the different population death rates used (Maryland CI: 0.92–1.65; city of Baltimore CI: 0.76–1.35) which is a curious finding considering that the lung cancer SMR for non-whites in the Gibb et al. study is statistically significantly elevated using Maryland reference rates (1.88; CI: 1.38–2.51). This may be attributable to the lower number of person-years-at-risk in the older age categories of the simulated cohort.

Table 4. Standardized mortality ratio and associated 95% confidence intervals

	White	Non-White	Total
All Deaths			
Gibb	1.09 (1.00–1.20)	1.02 (0.91-1.14)	1.06 (0.99-113)
Simulated			
Baltimore City	1.05 (0.96-1.15)	0.69 (0.62–0.76)	0.87 (0.81–0.93)
Baltimore County	1.40 (1.28-1.53)	0.72 (0.64–0.79)	1.01 (0.94-1.08)
State of Maryland	1.60 (1.47-1.75)	0.86 (0.77–0.95)	1.18 (1.11-1.27)
All Cancer			
Gibb	1.114 (0.94-1.36)	1.44 (1.17-1.75)	1.25 (1.10-1.42)
Simulated			
Baltimore City	1.05 (0.88-1.25)	0.83 (0.68-1.01)	0.94 (0.82-1.07)
Baltimore County	1.25 (1.05–1.49)	0.87 (0.71-1.05)	1.04 (0.91-1.19)
State of Maryland	1.41 (1.17-1.67)	1.01 (0.82-1.22)	1.19 (1.04-1.35)
Lung Cancer			
Gibb	1.86 (1.45–2.34)	1.88 (1.38-2.51)	1.80 (1.49-2.14)
Simulated			
Baltimore City	1.45 (1.13-1.82)	1.02 (0.76–1.35)	1.24 (1.03-1.48)
Baltimore County	1.79 (1.41-2.25)	1.06 (0.79-1.41)	1.41 (1.17-1.68)
State of Maryland	2.08 (1.63–2.61)	1.25 (0.92-1.65)	1.64 (1.36-1.96)
Arteriosclerotic Heart Disease			
Gibb	1.07 (0.91-1.26)	1.32 (1.05–1.63)	1.14 (1.01-1.29)
Simulated			
Baltimore City	0.91 (0.78-1.06)	0.61 (0.49-0.75)	0.78 (0.68–0.88)
Baltimore County	1.18 (1.01-1.38)	0.63 (0.51–0.78)	0.90 (0.80-1.02)
State of Maryland	1.38 (1.17-1.60)	0.77 (0.62–0.94)	1.07 (0.95–1.22)
Prostate Cancer			
Gibb	0.71 (0.23-1.67)	2.03 (1.01–3.63)	1.22 (1.00–1.98)
Simulated			
Baltimore City	1.35 (0.43-3.14)	1.41 (0.70-2.53)	1.39 (0.79-2.26)
Baltimore County	1.42 (0.46-3.30)	1.45 (0.72-2.59)	1.44 (0.82-2.33)
State of Maryland	1.41 (0.46–3.30)	1.59 (0.79-2.85)	1.53 (0.87-2.49)

In order to focus attention on the effect that different reference populations have on the *SMR*, we calculated the differences in the SMR as a percentage, using the SMR calculated from the State of Maryland as the comparison (Table 5). With the exception of prostate cancer among whites, the SMRs calculated using death rates from the state of Maryland yielded anywhere from 6% to **34%** higher *SMRs* than when the death rates for the city or county of Baltimore were used.

Table 5. Percent difference among SMR values (simulated cohort only)

	White	Non-White	Total
All Deaths			
Simulated			
Baltimore City	**1.05 (34%)**	**0.69 (20%)**	**0.87 (27%)**
Baltimore County	**1.40 (13%)**	**0.72 (17%)**	**1.01 (15%)**
State of Maryland (reference)	**1.60**	**0.86**	**1.18**
All Cancer			
Simulated			
Baltimore City	**1.05 (25%)**	**0.83 (17%)**	**0.94** (21%)
Baltimore County	1.25 (11%)	0.87 (14%)	1.04 (12%)
State of Maryland (reference)	**1.41**	**1.01**	**1.19**
Lung Cancer			
Simulated			
Baltimore City	1.45 **(30%)**	**1.02 (18%)**	**1.24 (24%)**
Baltimore County	**1.79 (14%)**	**1.06 (15%)**	**1.41 (14%)**
State of Maryland (reference)	**2.08**	**1.25**	**1.64**
Arteriosclerotic Heart Disease			
Simulated			
Baltimore City	**0.91 (34%)**	**0.61 (21%)**	**0.78 (28%)**
Baltimore County	**1.18 (14%)**	**0.63 (17%)**	**0.90 (16%)**
State of Maryland (reference)	**1.38**	**0.77**	**1.07**
Prostate Cancer			
Simulated			
Baltimore City	**1.35 (5%)**	**1.41 (11%)**	**1.39 (9%)**
Baltimore County	**1.42** (<1%)	**1.45 (9%)**	**1.44 (6%)**
State of Maryland (reference)	**1.41**	**1.59**	**1.53**

Alternative Reference Population Analysis: Discussion

The present analysis clearly shows the sensitivity of the SMRs calculated by Gibb et al. as a function of the reference population selected. These results call into question the reported findings of excess lung cancer risk reported by Gibb et al., especially for the lower second and third exposure quartiles, for which the SMRs for lung cancer were not substantially higher than expected. The elevation seems to be partially attributable to the selection of Maryland reference rates. A better approach would have been to present findings using both the state of Maryland and the city of Baltimore as reference populations and discuss the resulting differences.

The reference rate sensitivity analyses presented here are unadjusted for smoking behavior. The smoking prevalence in this cohort, as reported by Gibb et al., is greater than 80%. The higher lung cancer rates in the Baltimore area are undoubtedly due, at least in part, to the high smoking prevalence in Baltimore. If taken into account, the high smoking prevalence among this worker cohort can be expected to reduce the observed SMR even further than the reduction that resulted from the reference population sensitivity analysis.

The simulated cohort, derived from detailed information provided in the Gibb et al. report, provides valuable insight into the relationship between reference population and the SMR. The relatively small discrepancies between the simulated and actual cohort characteristics should not affect the results presented in this analysis. In addition, because we used the data to evaluate potential bias, and because the simulated cohort data were applied to all three potential reference populations, the discrepancies between the two cohorts do not affect the overall conclusions, namely that selecting different reference populations can result in important differences in SMRs. Using the original cohort data, more exact estimates of the effect of different reference populations on the SMR calculated for the simulated population, and the effect of including short-term workers in the cohort, can be characterized for the entire cohort and for subgroups of the cohort defined by exposure level.

Comments Regarding Irritation Effects

The second study, entitled "Clinical Findings of Irritation Among Chromium Chemical Production Workers" *[American Journal of Zndustrial Medicine* 38:127–131; 20001, examines a variety of clinical symptoms, descriptive of irritation, among the Baltimore worker cohort. Medical data were available for more than **97%** of the cohort over the study period, and the analysis relied on the same exposure assessment procedures as the cancer mortality study, such that limitations regarding missing data, the representativeness of the data, and the lack of information regarding the JEM also apply to the analysis of clinical symptoms.

The source of clinical data was reported as "physician and first aid reports." This description does not allow for a determination as to whether these reports represent regular, systematic surveillance or complaint incidents. **As** such, the presented results need to be viewed with caution because of potential study biases that may exist, depending on the methods by which the data were collected. Bias in epidemiology is defined as any systematic error in the design of a study, its implementation, or the analysis of the data.

Surveillance bias refers to differential disease ascertainment (e.g., via medical monitoring) among those who are known to be exposed compared to the non-exposed. In this study, it is likely that a focus on certain symptoms produced a differential probability of detecting them. Without the emphasis and preconception, many of these nonspecific symptoms may have gone unnoticed. It is worthwhile to note that the associations are strongest for non-specific symptoms (irritated and ulcerated nasal septa and perforated eardrum). Nasal perforation, a symptom that is more likely to be detected objectively and is well recognized to be associated with inhalation of Cr(VI), was not as strongly associated with chromium exposure as other, more subjective symptoms. Further, if the medical records were based on complaint incidents, it is important to understand whether any additional motivating factors may have led some workers to make a complaint (e.g., compensation for injury).

Information bias refers to errors in collecting data that result in differential accuracy of information about comparison groups. Specific examples of information bias include ***reporting***

bias and *observation bias.* Increased awareness about nasal symptoms could lead to both reporting and observation bias. Although the overall rates of these symptoms appear quite high, the actual excess prevalence is hard to quantify without an external reference group, and without using appropriate blinding procedures.

While the authors acknowledge that the effects reported were more likely to be associated with peak (i.e., upper-bound) exposures, they selected to use the dose metric of annual average time-weighted average exposure by job title. This exposure measure clearly underestimates peak exposures and is subject to misclassification. Considering the vast amount of industrial hygiene measures available for this study, a re-evaluation of peak exposures for the purpose of correlating peak exposures with the onset of subjective symptoms would have been more appropriate and valuable.

Further, Gibb et al. compare their findings of nasal irritation with those of Lindberg and Hedenstierna (1983). Because the effect levels in the Lindberg and Hedenstiema study are lower than those identified by Gibb et al., the authors conclude that the differences could be due to the fact that the Lindberg and Hedenstierna cohort was exposed to highly irritating chromic acid. While this conclusion is probably true, Gibb et al. had the data within their JEM to assess whether the workers, who worked in the production of chromic acid, reported irritation symptoms at exposures lower than those for workers in other areas of the plant. These data would be very useful for understanding the potential irritation effects of various Cr(VI) chemicals and should have been evaluated by these researchers. Finally, hand-to-nose and hand-to-ear contact, and the potential for direct contact exposures—as opposed to airborne exposures—is recognized as a potentially significant confounding factor for assessing irritation effects associated with airborne Cr(VI) (Cohen et al. **1974).** In assessing the potential for airborne Cr(VI) to cause the effects reported at the reported airborne exposures, it is important to consider any additional confounding exposure due to direct contact. Clearly, the effects of irritated and ulcerated skin, dermatitis, and burns are more likely due to what a worker might have touched in the plant rather than airborne exposures to Cr(VI). Yet the proportional hazards analysis found a stronger association between cumulative Cr(VI) exposure and irritated skin, than with perforated nasal septum.

In summary, this study is of limited usefulness because of the potential biases in measuring the health outcome and the relatively poor dose measures.

Risk Assessment Implications

The authors conclude that they have observed a "strong" dose response for airborne Cr(VI) exposure and lung cancer and that they have provided the data necessary for use in quantitative cancer risk assessment. However, as identified throughout these comments, there are several significant concerns with the data, and the analyses that were used to evaluate them, which directly affect any risk estimates derived from these data and severely limit their utility.

For instance, the SMRs were not adjusted for smoking, although the data needed to do so were available and used in other analyses. The smoking-adjusted relative risks calculated from the Cox proportional hazard modeling analyses were based on exposure data which were log transformed. As a result, Gibb et al. presents a linear relationship between excess cancer **risk** and the log of exposure; however, the authors do not support this conclusion in their discussion. The dose-response model based on this relationship would predict very large changes in the excess cancer **risk** associated with very small adjustments in lifetime cumulative exposure at the lower bound and the opposite (e.g., very small changes in **risk** associated with large changes in lifetime cumulative exposure) at the upper bound of the dose-response curve.

This relationship is not supported by the available mechanistic data for carcinogenicity. Specifically, the mechanism by which Cr(VI) is recognized to cause lung cancer has been studied rigorously, both ***in vitro*** and *in vivo* (DeFlora and Wetterhann 1989; Xu et al. 1996). The basic mechanism by which Cr(VI) is genotoxic is via intracellular reduction from the hexavalent to the trivalent state. During that process, oxygen radicals and intermediate chromium species [e.g., Cr(V)] are created, and these may be mutagenic if they interact with DNA inside the cell. However, because Cr(VI) may also be reduced to the trivalent state—which cannot penetrate the cell membrane—before Cr(VI) is absorbed into the cell, the dose response is more consistent with a threshold for carcinogenicity (DeFlora 2000). The well recognized mechanism of action is not consistent with a **risk** proportional to the log of cumulative exposure—except possibly at very high exposure levels, far above a threshold, where a saturation of response could theoretically occur.

Further, relative risks were calculated using the first quartile as a reference group in the proportional hazards model, with smolung included in the model as a variable, and the median exposure level. The resulting relative lung cancer risk values of 1.83, 2.48, and 3.32 for the 2nd, 3rd, and 4th quartiles were estimated; however, the confidence bounds around those relative risks were not presented, and thus, it is difficult to assess the precision of those risk estimates.

Gibb et al. (2000a) offer conclusions regarding their findings in reference to the Occupational Safety and Health Administration PEL and the NIOSH recommended exposure limit (EL), using the highly conservative assumption that workers will spend a 45-year worlung lifetime exposed continuously to the current PEL, which is a ceiling value at 100 μg CrO_3/m^3 [52 μg Cr(VI)/m^3] or to the E L of 1 μg Cr(VI)/m^3. Continuous occupational exposure to the PEL falls in the 4th quartile of cumulative exposure, and continuous exposure at the REL falls in the 3rd quartile of cumulative exposure in the Gibb et al. study. At both of these exposure levels, an excess cancer risk was observed in the total cohort. While this is mathematically correct, it is important to note that none of the workers in this study were exposed for **45** years. The maximum reported exposure was for 37 years (although a maximum of only 35 years is technically feasible), and the number of years worked at the 75th percentile (the longest tenure of workers in the 3rd quartile) was only 2 years. The appropriateness of extrapolating lifetime cumulative exposures, averaged over a very long period of time (e.g., 45 years), from relatively short duration exposures (e.g., **2** years) is highly questionable and not generally considered an acceptable risk assessment practice. Hence, conclusions regarding risks from 45 years of exposure at the PEL or REL are not supported by the data presented. It would be far more appropriate to assess the risks of lung cancer based on a subset of these data, focused on the longer-term workers (e.g., those with at least 1 year of tenure), than to extrapolate the Gibb et al. findings to occupational standards designed to protect against exposures for an occupational lifetime. The findings at the lower dose levels are highly questionable and extrapolation of the risks due to short-term exposures to long-term cumulative exposures is not scientifically defensible.

Gibb et al. elected to determine lung cancer *SMRs* and relative risks based on only four exposure groupings. Further subdivision of exposure levels or treatment of exposure as a continuous variable appears to be feasible. For example, the highest exposure quartile (essentially those workers with at least 2 years of tenure) had an exposure range of 0.077 to 5.25 mg CrO_3/m^3-years, and 13,409 person-years at risk. This quartile could have been evaluated individually, with several exposure groupings, to determine the slope of the dose-response curve among those individuals with significant exposure. Further, inspection of the raw data acquired by the Chrome Coalition from the **U.S.** Environmental Protection Agency in the FOIA request suggests that the "strong" dose-response association reported by quartiles of cumulative Cr(VI) exposure, and the excess lung cancer risk, in the published paper is only really "strong" for non-whites and only positively correlated for this subcohort at the highest decile of exposure. The differences in lung cancer incidence by exposure decile and by race are substantial and should have been discussed in detail in the published papers. The current publication may be misleading, in that it demonstrates a nearly linear dose response, when in fact, the raw data suggest that the finding of a strong dose response and elevated cancer rates at very low levels of exposure may be an artifact of the manner in which the data are presented. Reevaluation of these data with different exposure groupings is very important to ensure that the risk assessment conclusions are correct. Further, alternative analyses should be performed with and without the very short-term workers, to determine the effect of including those workers in the analysis.

Finally, a statistically significant dose-response relationship exists only for the total cohort and for the non-white subcohort (p-value for goodness of fit with the multiplicative model = 0.002 and 0.0026, respectively); the dose-response relationship for whites is not statistically significant. Considering that whites make up the majority of the cohort and provide the majority of person-years at risk, this finding warrants further consideration. The authors do not provide a discussion or possible explanation for this observation, and it seems to be a clear oversight in the paper. The choice of Maryland reference rates may be the basis for this finding because whites have more highly elevated rates of lung cancer in the 2nd **and** 3rd exposure quartiles, than in the 4th, and the rates of lung cancer for whites was **30%** higher among a matched Baltimore City reference population as compared to a Maryland reference population

(as discussed earlier). Taking this into account, as well as the other possible concerns and shortcomings of this study, it is inappropriate to conclude that these data provide a "strong" dose-response relationship. While these data do present an opportunity for improved quantitative cancer risk assessment, further data analysis and more complete data presentation are required to ensure confidence in the findings.

Discrepancies

On close examination of the published papers, we identified several items that seem to be incorrect. These are likely to be typographical errors or accidental miscommunications and likely to do not have a substantial impact on the conclusions offered. In the first cohort manuscript, these items include:

- In Table II, for the minimum and maximum years worked, the maximum values for the total group and either the cases or the non-cases should be equal, but they are not. Also, the total number of years worked (37.7 for the total group and 37.9 for the cases) is longer than the study period (August 1950 through July of 1985). This is not possible, and this issue raises the question of whether time off due to medical leave, strikes, etc. was accounted for in the exposure reconstruction.
- There is a discrepancy between the average exposure reported for the 1st and 4th quartiles in the published analysis and in the raw data.
- Table XI provides a comparison of the Mancuso (1975, 1997) cohort and the Gibb et al. cohort. Cr(VI) exposures for both studies should be reported in mg/m^3-years (according to the identifying information); however, the actual values reported for the Gibb et al. study are in units of mg CrO_3/m^3-years, and are overstated by approximately 50%.
- There is a discrepancy in the year in which personal samples were first collected. On page 117, 1977 and 1978 are cited.
- On page 119, the total number of person-years at risk is cited as 70,158; however, the total number of person-years that can be summed from data in both Tables V and VI is 71,994.

Summary and Conclusions

Gibb et al. (2000a) reported the results of a prospective mortality analysis on a cohort of chromate production workers who worked at a chromate production plant in Baltimore, Maryland. Lung cancer death is the primary outcome of interest, because Cr(VI) exposure has been reported as a risk factor in lung cancer mortality. One primary objective of the Gibb et al. study was to assess the excess lung cancer risk associated with Cr(III) exposures.

The study population consisted of a cohort of **2,357** male workers who were first employed at the Baltimore chromate production plant between August 1, **1950,** and December **3**1, **1974.** The cohort is characterized by a very large number of short-term workers. More than **40%** worked less than 90 days, and 75% of the cohort worked less than **2** years.

The authors report a "strong" dose-response relationship for lung cancer associated with cumulative Cr(VI) exposure. Clinical signs of irritation, cumulative Cr(III) exposure, and duration of work were not found to be associated with a risk of lung cancer. There was no association between cumulative Cr(III) exposure and excess lung cancer risk, and the association between excess risk of lung cancer and cumulative Cr(VI) exposure was not confounded by smolung status.

In the second paper, Gibb et al. reported data regarding skin and nasal irritation among the same cohort of workers, **and** they evaluated the relationship between Cr(VI) exposure and the first occurrence of each clinical finding. Nasal irritation and ulceration were reported in approximately 60% of the cohort, and the symptoms appeared, on average, within **3** months of first exposure. Median exposure to Cr(VI) at the time of occurrence for nasal irritation and ulceration was approximately **20** $\mu g/m^3$, and the mean was 50 $\mu g/m^3$.

Exponent's comments and conclusions regarding the Gibb et al. (2000a,b) studies are summarized below:

The methods used to measure Cr(VI) in the Baltimore plant likely underestimated Cr(VI) exposures for several reasons:

- For the 1950s data, the exposure profiles presented are consistently lower than those reported for the same time period by alternative sources (Braver et al. 1985; PHS 1953), and the impinger method would not have measured water-insoluble Cr(VI).
- For the majority of plant operations, the samples were collected using RAC tape samplers. The RAC tapes were made of 98%–100% pure cellulose. Previous studies have shown that significant reduction of Cr(VI) to Cr(III) may occur on the cellulose filters.
- Braver et al. (1985) believed that the potential for reduction of Cr(VI) to Cr(III) was sufficient in the RAC samples to exclude workers who started after 1960 in the new Baltimore plant from their analysis, because their exposure levels were believed to be underestimated.
- The only available exposure measures support that exposures were generally higher from 1978 until plant closure in 1985—the time period for which personal samples were collected—as compared to the period from approximately 1965 to 1975, for which only **RAC** data were available.

- The exposure reconstruction methods are not well described and it is not possible to critique the approaches used. Based on the information provided, the exposure reconstruction did not characterized peak exposures, which would be the most meaningful dose metric for assessing irritation effects.
- Gibb et al. had to extrapolate for 12 of 36 years of the exposure period due to missing air sampling data, which constitutes approximately one-third of the exposure period. Further, only incomplete data sets were available for an additional 9 years.

- For several reasons, the reliability of the Cr(III) exposure estimates is questionable.

- Gibb et al. state that they log-transformed the data to control variability in their statistical tests. The mean values presented for exposure in each quartile appear to be arithmetic means; however, it is unclear whether the exposures for each worker are representative of yearly average exposures as estimated by the arithmetic mean.

- Short-term worker (e.g., those who worked for less than 1 year) may be different from longer-term workers in a number of ways that could influence disease and risk. Other studies have shown that short-term workers experience elevated mortality rates including lung cancer mortality rates. Because short-term workers make up a large fraction of the population (more than 40% worked less than 90 days) the impact of short-term workers in this cohort could be substantial. The analysis should be reevaluated without the short-term workers to determine their effect on the conclusions.

- The authors present smoking-adjusted risk estimates from the Cox regression models; however, they did not control for smoking in the *SMR* analysis, and the results could be substantially biased. CIs for the smoking-adjusted relative risk estimates should be presented.

- The statistical power of the study could be notably increased if vital status follow-up was extended through the year 2000, the most currently available data.

- The reference mortality rates used in Gibb's *SMR* analysis are the population mortality rates for the state of Maryland; however the largest proportion, **45%** of the cohort, died in Baltimore, hence Baltimore reference rates should have been used in the *SMR* analysis. Exponent's analysis examines the potential effect of the choice of reference population by comparing the number of expected deaths based on the mortality rates for the city of Baltimore, the county of Baltimore, and the state of Maryland.

- The simulated data for years of follow-up, age at hire, and years of employment closely resemble those of the original study cohort.
- **A** smaller number of expected deaths using death rates from the state of Maryland were calculated, and the corresponding SMRs are almost uniformly higher based on Maryland reference rates as compared to those calculated using death rates from the city or county of Baltimore.
- When Baltimore City rates are used in place of Maryland rates, SMRs for lung cancer are 24% lower for the entire cohort and 30% lower for whites.
- The curious findings of elevated lung cancer rates notably at the 2nd and 3rd exposure quartile may be explained, at least in part, by these findings.
- Using the original cohort data, more exact estimates of the effect of different reference populations on the ***SMR***, and the effect of including short-term workers in the cohort, can be characterized for the entire cohort and for subgroups of the cohort defined by exposure level.

- The conclusions regarding clinical signs of irritation this study is of limited usefulness because of the potential biases in measuring the health outcome and the relatively poor dose measures.
- The value of these data for quantitative cancer risk assessment seem to be overstated:
  - The authors conclude that they have observed a "strong" dose response for airborne Cr(VI) exposure and lung cancer and that they have provided the data necessary for use in quantitative cancer **risk** assessment. Gibb et al. conclude that excess lung cancer **risk** is proportional to the log of exposure; however, this relationship is not

consistent with the plausible biological mechanism for lung cancer associated with inhalation of Cr(VI).

- Relative risks were calculated using the 1st quartile as a reference group in the proportional hazards model, with smoking included in the model as a variable, and the median exposure level; however, the confidence bounds around those relative risks were not presented, and thus, it is difficult to assess the precision of those risk estimates.
- The appropriateness of extrapolating lifetime cumulative exposures, averaged over a very long period of time (e.g., **45** years), from relatively short duration exposures (e.g., **2** years) is highly questionable and not generally considered an acceptable risk assessment practice. It would be far more appropriate to assess the risks of lung cancer based on a subset of these data, focused on the longer-tern workers.
- The current publication may be misleading, in that it demonstrates a nearly linear dose response, when in fact, the raw data suggest that the finding of a strong dose response and elevated cancer rates at very low levels **of** exposure may be an artifact of the manner in which the data are presented.
- Reevaluation of these data with different exposure groupings is very important to ensure that the risk assessment conclusions are reliable.

A review of the raw data is currently on-going and we expect that the analysis will: 1) confirm the appropriateness of the Baltimore reference rates for calculating ***SMRs*, 2)** improve upon the ***SMR*** analysis by adjusting for smoking, and 3) allow for a more complete understanding of the risks for short-term workers in this cohort. Ultimately, a reevaluation of the raw data should enable a more accurate and complete analysis of the dose-response relationship from these data.

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