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Lung Cancer Among Workers in Chromium Chemical Production

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Background *An elevated risk of lung cancer among workers in chromate production facilities has previously been reported. This excess risk is believed to be the result of exposure to hexavalent chromium. There have been mixed reports about whether trivalent chromium exposure is also associated with an excess lung cancer risk. Previous studies of measured hexavalent chromium exposure and lung cancer risk have not examined cigarette smoking as a risk factor.*

Methods *A cohort of 2,357 workers first employed between 1950 and 1974 at a chromate production plant was identified. Vital status of the workers was followed until December 31, 1992. Work histories of cohort members were compiled from the beginning of employment through 1985, the year the plant closed. Annual average exposure estimates, based on historical exposure measurements, were made for each job title in the plant for the years 1950–1985. These exposure estimates were used to calculate the cumulative hexavalent chromium exposure of each member of the study population. Following closure of the plant, settled dust samples were collected and analyzed for hexavalent and trivalent chromium. The trivalent/hexavalent concentration ratios in each plant area were combined with historic air-sampling data to estimate cumulative trivalent chromium exposure for each individual in the study cohort. Smoking status (yes/no) as of the beginning of employment and clinical signs of potential chromium irritation were identified from company records.*

Results *Cumulative hexavalent chromium exposure showed a strong dose–response relationship for lung cancer. Clinical signs of irritation, cumulative trivalent chromium exposure, and duration of work were not found to be associated with a risk of lung cancer when included in a proportional hazards model with cumulative hexavalent chromium exposure and smoking. Age-specific data on cumulative hexavalent chromium exposure, observed and expected numbers of lung cancer cases, and person-years of observation are provided.*

Conclusion *Cumulative hexavalent chromium exposure was associated with an increased lung cancer risk; cumulative trivalent chromium exposure was not. The excess risk of lung cancer associated with cumulative hexavalent chromium exposure was not confounded by smoking status. The current study offers the best quantitative evidence*

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INTRODUCTION

An excess risk of bronchogenic carcinoma was reported among workers in the German chromate-producing industry prior to World War II, but the conclusion that chromates should be considered as carcinogenic was not generally accepted by the medical profession in the United States until after the war [Public Health Service, 1951]. Following the war, several studies of the lung cancer risk among chromate production workers in the United States reported that an increased lung cancer risk did indeed exist [Machle and Gregorius, 1948; Baetjer, 1950; and Mancuso and Hueper, 1951]. As a result of these reports and additional reports from other countries, the U.S. Public Health Service (PHS) was requested to conduct an evaluation of the lung cancer risk in the U.S. chromate production industry and to make recommendations with respect to potential medical and engineering control measures. In 1951, the PHS report on the *Health of Workers in the Chromate Producing Industry* was issued. It concluded, based on environmental investigations and medical examinations at six chromate production plants and on a study of the mortality and morbidity experience of male members of "sick benefit associations" in seven chromate-producing plants that workers in the American chromate production industry did have an excess risk of bronchogenic cancer. The report further concluded that while chromium in some form was implicated, the exact causative agent had not yet been determined.

In 1980, the International Agency for Research on Cancer concluded that "chromium and certain chromium compounds" were known human carcinogens [IARC, 1980]. The U.S. EPA [1984], using IARC [1980] guidelines of classification, concluded that hexavalent chromium compounds were known human carcinogens but that trivalent chromium compounds could not be classified. IARC [1987] concluded that hexavalent chromium was a known human carcinogen and that metallic and trivalent chromium could not be classified. IARC [1990], ATSDR [1993] and Health Canada [1994] all indicated that an increased risk of lung cancer has been consistently demonstrated in studies of the chromate production, chrome plating, and chrome pigment production industries.

The EPA health assessment document [1984] estimated the excess lifetime lung cancer risk due to air containing 1 $\mu g/m^3$ hexavalent chromium based on the results reported by Mancuso [1975]. The Mancuso study also formed the basis of quantitative estimates of lung cancer risk by the Government of Canada [1994] and by K.S. Crump Division [1995]. The EPA document noted several limitations in the Mancuso data for exposure–response assessment of the lung cancer risk of hexavalent chromium: (1) risk was presented by exposure group and age for total chromium exposure but not for hexavalent chromium exposure; (2) no smoking data were available on the workers; and (3) the industrial hygiene survey that was relied on by Mancuso for his exposure estimates was done in 1949, while Mancuso's cohort was defined as having begun employment between 1931 and 1937. The current study has advantages over the Mancuso study for quantitative assessment of the lung cancer response to hexavalent chromium for a variety of reasons which will be discussed below.

As indicated above, the evidence of carcinogenicity of trivalent chromium is generally considered to be inadequate. Mancuso [1975], however, concluded that exposure to trivalent chromium was associated with an increased risk of lung cancer and maintained this position in his 1997 update of the study [Mancuso, 1997a]. Although airborne concentrations of trivalent chromium are greater than hexavalent chromium in chromate production facilities, these two exposure measures are generally correlated, and it is difficult to separate the effects of the two. The current study evaluates the risk of lung cancer from both trivalent and hexavalent chromium exposure.

MATERIALS AND METHODS

The cohort for the current study is based on that identified by Hayes et al. [1979] at a chromate production plant in Baltimore, MD. Hayes et al. identified 4,217 workers newly employed between January 1, 1945 and December 31, 1974. The cohort defined by Hayes et al. excluded workers employed less than 90 days (N = 1,915), women (N = 160), and those with unknown length of employment (N = 24), work history (N = 16), and/or age (N = 1). The resulting study group of 2,101 persons included 1,803 hourly employees and 298 salaried employees. The current study excluded those in the Hayes et al. cohort who began work before August 1, 1950 (N = 734) because on that date, the construction of a new mill and roast and bichromate plant was completed and extensive exposure information began to be collected. It was also decided to include workers in the current study who worked less than 90 days but began employment after August 1, 1950 (N = 990), to expand the size of the low exposure group.

The resulting group of 2,357 males constituted the cohort for this study.

In the Hayes et al. study, the vital status of the cohort was followed through July 1977 by a variety of means (e.g., Social Security Administration, Department of Motor Vehicles, voter registration lists, etc.). The current study utilized the National Death Index [McMahon, 1983] to identify deaths between January 1, 1979 and December 31, 1992. The National Death Index began on January 1, 1979 and thus was not available to Hayes et al. at the time of their study. Between July 1977, the end of follow up of the Hayes study, and December 31, 1978, the current study utilized Social Security data to determine deaths among cohort members. Death certificates were requested from the states where the former employees died. Causes of death were coded to the 8th Revision of the ICDA. Person-years of observation were calculated from beginning of employment until death or December 31, 1992, which was the last date to which the National Death Index was queried for the current study. Work histories on all the workers were updated through July 1985 when operations at the plant ceased. The work histories in the Hayes et al. study were available through 1974.

Smoking status (yes/no) as of beginning of employment was identified for 2,137 (93.3%) of the cohort of 2,357 from company medical records. Data on cigarette, pipe, and cigar smoking were included.

Exposure

The hexavalent chromium exposure of each member of the cohort was estimated for the duration of their employment at the chromate production facility. Exposure estimates were assigned by job title and based on approximately 70,000 contemporary measurements of airborne hexavalent chromium concentration spanning the study period. These exposure estimates were merged with each study member's work history to provide a profile of annual average exposures throughout their period of employment at the chromate production facility.

Immediately following the completion of the new production facility in 1950, a program of routine air sampling for hexavalent chromium was undertaken. The air sampling program was highly unusual in that it was based on a written document that clearly specified the objectives of the program and strategies for air sampling. Historically, and to a large extent continuing to the present day, industrial hygiene air sampling has focused on the identification of problems and as a result has been a biased measure of the entire worker population exposure in a facility. According to the facility's program, air sampling was undertaken in order to characterize "typical/usual exposures" of workers. This point is particularly relevant to the conduct of this epidemiologic study in that the resulting exposure estimates can be reasonably assumed to represent average exposures.

During the period from 1950 to 1961, airborne dust samples were collected using high volume air sampling pumps and impingers with the sampling wand held by the industrial hygienist in the worker's breathing zone. The resulting exposure estimates were, of necessity, the result of short-term (tens of minutes) samples. Beginning in the mid-1960s a system of exposure estimation based on 24-hour routine measurements at fixed-site monitors throughout the facility combined with routine observation of how much time job titles spent in the vicinity of each of these monitors was instituted. In this system, approximately 20 RAC tape air samplers (Research Appliance Co., Allison Park, PA) were rotated through 154 fixed sites, representing discrete "exposure zones," in and around the production complex. Twenty-four 1-hour air samples were collected per day at each sampling location. (After 1979, the number of fixed sites and associated exposure zones was reduced to 27 and sampling was reduced to eight 3-hour samples at each location.) Direct daily observations by a plant employee of the location of persons (specified by job titles) with respect to these samplers were used to calculate job title-based exposure estimates by multiplying the fractional person-time spent by given job title in each sampling zone and summing these fractions. This system remained in use until 1985 when the plant closed. Beginning in 1977, this system was supplemented by routine full-shift personal sample collection, again based on job title, using NIOSH standard method P and CAM 169 [NIOSH, 1974]. Despite different dust collection methods throughout the period of this study, the sample analytical method remained essentially constant, using minor variants of the s-diphenylcarbazide colorimetric method; all analyses were conducted by an in-house laboratory.

The first step in the exposure estimation process was to convert all measurements to a common basis. During different time periods, airborne contaminant concentrations were presented in terms of mass of Cr and CrO_3; for this study all measurements were converted to CrO_3. Measurements used in this report are thus mg CrO_3/m^3, the metric used by the U.S. Occupational Safety and Health Administration [OSHA, 2000] in its current Permissible Exposure Limit for chromic acid and chromates. Note that the current Threshold Limit Value for soluble chromium published by the American Conference of Governmental Industrial Hygienists [1999] is specified in terms of mass of Cr.

Exposure estimates derived from the area sampling system described above were adjusted to an equivalent personal exposure estimate using job-specific ratios of the mean area and personal sampling exposure estimates for the period 1978–1985 when both systems were in use. The comparison of exposure estimates derived from area and personal samples showed no significant differences (i.e., ratio approximately 1) for approximately two-thirds of the job titles with a sufficient number of samples to make this comparison. For the remaining job titles, virtually all of which were associated with a significant point source of contamination and including job titles such as "soda packer" and "chromic acid packer," the area sampling method was found to significantly underestimate personal exposure estimates and were, thus, adjusted by the ratio of the two.

Exposure estimates were used to construct a job exposure matrix (JEM) displaying annual average exposure for each job title. The JEM included entries for annual average exposure estimates for 114 job titles and 36 years. (As jobs titles were eliminated and consolidated over the years, it was not necessary to provide exposure estimates for all cells in the matrix.) Wherever air sampling data were available, the annual average concentration was entered directly into the JEM. Data were virtually complete for most job titles for the years 1971–1985 and fairly complete for fewer job titles for the years 1950–1956 and 1960–1961. Although there is indirect evidence that air sampling was conducted in the interim periods, exposure measurements could not be located for these years.

Exposures were modeled for the cells in the JEM without direct measures. A protocol for utilizing the existing data to model missing cells in the matrix was developed and followed to provide a uniform approach to estimate historic exposures from existing exposure data. Several exposure estimation methods were used. The primary estimator for missing data was based on a simple model using the ratio of the measured exposure for a job title to the average of all measured job titles in the same department. A hierarchy was established in which data available for the closest year were used. This approach was found to produce stable and robust estimates of exposure. For periods in which there were extensive missing data, primarily the data gap in the 1960s, exposures were estimated through a simple straight-line interpolation between years with known exposures.

Airborne trivalent chromium concentrations were never measured in the facility. Using a method similar to that employed by Mancuso [1975, 1997a] to estimate the hexavalent chromium exposures, airborne trivalent dust concentrations were estimated through the use of measured airborne hexavalent chromium concentrations and the ratio of hexavalent chromium concentration to trivalent chromium concentration in settled dust in the facility. This approach is based on the assumptions that the Cr^{+3}:Cr^{+6} ratio of the settled dust collected was representative of the ratio when the facility was in operation, that the Cr^{+3}:Cr^{+6} ratio in respirable airborne dust was the same as that in the settled dust, and that this ratio did not change from 1950 to 1985. There is no way to verify or refute any of these assumptions.

Seventy-two composite settled dust samples were collected at or near 26 of the 27 fixed-site air monitoring stations approximately 3 years after the facility closed. The facility had been sealed from the ambient environment with very limited access during this period. The dust samples were extracted and analyzed for hexavalent chromium content using ion chromatography; trivalent chromium content was determined through inductively coupled plasma spectroscopic analysis of the residue. The Cr^{+3}:Cr^{+6} ratio was calculated for each area corresponding to the air sampling zones and the measured hexavalent chromium air concentration adjusted based on this ratio. The mean Cr^{+3}:Cr^{+6} ratio was 6.2 and ranged from 0.02 to 77 across these zones (two zones with only trace Cr^{+6} were excluded from the data summary). As described previously, worker exposures were calculated for each job title, and weighted by the fraction of time spent in each air monitoring zone. The Cr^{+3}:Cr^{+6} ratio was derived in this manner for each job title based on the distribution of time spent in exposure zones in 1978. Hexavalent chromium exposure estimates in the JEM were multiplied by this ratio to estimate trivalent chromium exposures. The resulting mean Cr^{+3}:Cr^{+6} ratio for individual job titles was 17 and ranged from 1.2 to 64. A separate JEM for trivalent chromium exposures was thus constructed and used in conjunction with subject work histories to provide individual profiles of trivalent chromium exposure for analysis.

Statistical Methods

Observed-to-expected mortality ratios were calculated for various causes of death for whites and nonwhites and the total cohort. Expected deaths were calculated using age-, calendar-, and race-specific U.S. mortality rates. The expected lung cancer deaths were a total of the expected lung cancer deaths for whites, nonwhites, and those with unknown race. The expected lung cancer deaths for those with unknown race was estimated from what would be expected if they had a race distribution similar to those for whom race was known.

Observed-to-expected ratios of lung cancer mortality were calculated for whites, nonwhites, race unknown, and the entire cohort by cumulative exposure quartile. Cumulative exposure was calculated in a dynamic fashion. In other words, for each person at any given age, cumulative exposure was counted as the exposure up to that age, lagged 5 years (i.e., only exposure occurring 5 years before a given age was counted). Although cumulative exposure was calculated in a dynamic fashion, the cut points for the quartiles are those that divide the persons in the cohort into four equal groups based on their cumulative exposure at the end of their working history. Expected deaths were estimated using race-, age-, and calendar year-specific mortality rates for the State of Maryland using OCMAP

[Marsh and Preininger, 1980]. Maryland, rather than U.S. rates, were used for this part of the analysis since Maryland has one of the highest lung cancer mortality rates in the U.S. [Riggan et al., 1983]. The lung cancer rates in Maryland are heavily influenced by the rates in Baltimore City which has even higher lung cancer rates than the State of Maryland (and is where the chromate production plant was located), but the Maryland rates were chosen because many of the deaths occurred in Maryland outside of Baltimore City (16%) and many occurred in other states (39%). A table of age-specific observed and expected lung cancer deaths and the person-years of observation by cumulative hexavalent chromium exposure was developed for the total cohort, again estimating cumulative exposure in a dynamic fashion and lagging exposures 5 years.

Proportional hazards models [Cox, 1972] using age as the time variable and cumulative exposure as a time-varying covariate were used to assess the relationship of chromium exposure to the risk of lung cancer. Various exposure metrics [e.g., cumulative exposure with different lag periods, average exposure (cumulative exposure/duration of work) with different lag periods, duration of work, etc.] were evaluated. Final models were developed for each exposure measure using a forward step-wise procedure with a *P*-value for entry and exit of 0.05; *P*-values were derived using the likelihood ratio test. The variables considered for inclusion were race (white/nonwhite/unknown), calendar decade, and cigarette smoking, in addition to the exposure measure.

The association of lung cancer with 10 different clinical findings of potential chromium irritation observed in the study cohort (irritated nasal septum, ulcerated nasal septum, perforated nasal septum, bleeding nasal septum, irritated skin, ulcerated skin, dermatitis, burn, conjunctivitis, perforated eardrum) was examined in 2 × 2 tables and by 10 different Cox proportional hazards models. These clinical findings were identified by routine examination and through complaints reported by the individual to the health clinic at the plant. All findings were diagnosed by a physician. In the Cox model, the clinical finding was time-varying in that the variable was treated as 0 for the person-years prior to the first onset of the finding and 1 afterward.

RESULTS

There was a total of 70,736 person-years of observation. A summary of selected causes of death is reported in Table I. These causes were selected from 55 causes of death that were examined because either white, nonwhite, unknown, or the total showed a significant excess or deficit risk. Deaths from all cancers, cancer of the lung, mental disease, psychoneurotic, and personality disorders, and suicide were significantly elevated in the total cohort. Deaths from cancer of the prostate and arteriosclerotic heart disease were elevated in the total cohort but of borderline significance. There was a deficit of deaths from accidents that was of borderline significance among nonwhites; this deficit was not statistically significant among whites or race unknown or in the total cohort.

Table II provides a description of the entire cohort, the lung cancer cases, and the noncases by selected continuous variables.

There were two categorical variables used in the analyses—race and smoking. The cohort included 1,205 (51%) whites, 848 (36%) nonwhites, and 304 (12.9%) race unknown. Seventy-one (58%) of the 122 lung cancer cases occurred in whites, 47 (39%) in nonwhites, and 4 (3%) in race unknown. A comparison by race of selected continuous variables is found in Table III. A description of the smoking status of the cohort is provided in Table IV. As indicated previously, smoking status was reported as of date of first employment.

TABLE I. Observed/Expected Ratios for Selected Causes of Death; Chromium Chemical Production Workers, USA[a]

	White			Nonwhite			Race unknown[b]			Total		
Cause of death	**O**	**O/E**	**95% CI**	**O**	**O/E**	**95% CI**	**O**	**O/E**	**95% CI**	**O**	**O/E**	**95% CI**
All causes	472	1.09	1.00–1.20	323	1.02	0.91–1.14	60	1.00	0.76–1.29	855	1.06	0.99–1.13
All cancers	120	1.14	0.94–1.36	99	1.44	1.17–1.75	16	1.21	0.69–1.97	235	1.25	1.10–1.42
Arteriosclerotic heart disease	154	1.07	0.91–1.26	84	1.32	1.05–1.63	14	1.05	0.57–1.76	252	1.14	1.01–1.29
Cancer of lung	71	1.86	1.45–2.34	47	1.88	1.38–2.51	4	0.83	0.22–2.13	122	1.80	1.49–2.14
Cancer of prostate	5	0.71	0.23–1.67	11	2.03	1.01–3.63	0	0	0–5.56	16	1.22	1.00–1.98
Mental, psychoneurotic, and personality disorders	8	2.44	1.05–4.82	10	1.78	0.85–3.27	6	5.61	2.05–12.21	24	2.41	1.54–3.58
Suicide	9	0.91	0.42–1.73	9	2.94	1.34–5.68	3	1.90	0.32–5.54	21	1.66	1.06–2.46
Accidents	25	0.99	0.64–1.45	15	0.60	0.34–0.99	2	0.33	0.04–1.21	42	0.75	0.54–1.01

[a] Expected deaths are based on age-, race-, and calendar-year specific rates for the USA.

[b] The expected deaths for those with race unknown was estimated from what would be expected if they had a race distribution similar to those for whom race was known.

TABLE II. Description of Entire Cohort by Cumulative Hexavalent Chromium Exposure, Cumulative Trivalent Chromium Exposure, Years of Work at the Plant, Age at Hire, Years of Follow up, and Calendar Year of Hire [N (Total Group) = 2,357, N (Lung Cancer Cases) = 122, N (Noncases) = 2,235]; Chromium Chemical Production Workers, USA

Variable Statistic	Cumulative hexavalent chromium exposure (mg/m^3-years)	Cumulative trivalent chromium exposure (mg/m^3-years)	Work years	Years of follow up	Age at hire	Calendar year of hire (19XX)
Mean						
Total group	0.134	1.98	3.1	30.0	30.2	57.7
Lung cancer cases	0.290	3.57	5.3	27.9	33.3	53.5
Noncases	0.125	1.90	3.0	30.1	30.0	58.0
Standard deviation						
Total group	0.357	5.28	6.5	9.6	7.5	7.7
Lung cancer cases	0.620	7.39	9.1	8.5	8.8	4.1
Noncases	0.335	5.13	6.3	9.7	7.4	7.8
Median						
Total group	0.009	0.11	0.39	31.2	28.6	54
Lung cancer cases	0.016	0.22	0.84	28.9	31.6	53
Noncases	0.009	0.11	0.41	31.3	28.5	54
Min/max						
Total group	0/5.3	0/64.7	0.003/37.7	0.3/42.3	16.9/62.9	50/74
Lung cancer cases	0/4.1	0/36.4	0.003/32.2	6.4/42.2	21.2/62.6	50/73
Noncases	0/5.3	0/64.7	0.003/37.9	0.3/42.4	16.9/62.9	50/74
25th percentile						
Total group	0.001	0.014	0.088	22.6	24.3	51
Lung cancer cases	0.002	0.024	0.167	22.1	26.3	51
Noncases	0.001	0.014	0.085	22.7	24.3	51
75th percentile						
Total group	0.076	0.98	2.0	38.9	34.4	65
Lung cancer cases	0.226	2.79	4.6	35.1	39.2	54
Noncases	0.072	0.94	2.0	39.2	34.2	65

TABLE III. Comparison of Mean Age at Hire, Mean Work Duration, Mean Follow-up, and Mean Cumulative Hexavalent and Trivalent Chromium Exposure By Race; Chromium Chemical Production Workers, USA

Race	Mean age at hire	Mean work duration (years)	Mean follow up (years)	Mean cumulative hexavalent chromium exposure (mg/m^3-years)	Mean cumulative trivalent chromium exposure (mg/m^3-years)
White (N = 1205)	31.4	3.3	31.6	0.13	1.88
Nonwhite (N = 848)	28.9	3.7	29.1	0.18	2.79
Unknown (N = 304)	28.6	0.6	26.4	0.03	0.28

There was a high proportion of cigarette smokers and "any smoking" among both whites (83 and 86%, respectively), nonwhites (82 and 86%, respectively), and race unknown (79 and 81%, respectively). The vast majority of the lung cancer cases occurred among cigarette smokers (116) vs. nonsmokers (4). For two lung cancer cases, the smoking status was unknown.

Table V presents the numbers of observed and expected lung cancer deaths, the observed-to-expected ratios, person-years of observation, and the mean cumulative hexavalent

TABLE IV. Smoking Status of the Cohort; Chromium Chemical Production Workers, USA

Smoking category	Smoking status Yes	No	Unknown
Cigarette smoking	1,753 (82%)	384 (18%)	220
Any smoking (includes cigarettes, cigars, and pipes)	1,834 (86%)	307 (14%)	216

TABLE V. Observed and Expected Lung Cancer Deaths, Person-years of Observation, Observed to Expected Ratios, and Cumulative Hexavalent Chromium Exposure By Age[a]; Chromium Chemical Production Workers, USA

Range of cumulative exposure (mg CrO_3/m^3-years)		Age 20–29	30–39	40–49	50–59	60–69	70–79	80+
0–0.00149	Observed lung cancer deaths	0	1	0	14	8	2	1
	Expected lung cancer deaths	0.018	0.39	2.50	7.56	10.79	5.00	0.88
	Person-years of observation	5,003	7,684	6,509	5,184	3,104	865	163
	Observed/expected	0	2.48	0	1.85	0.74	0.40	1.13
	Mean exposure (mg CrO_3/m^3-years)	0.00021	0.00041	0.00051	0.00053	0.00050	0.00046	0.00040
0.00150–0.0089	Observed lung cancer deaths	0	0	2	10	10	4	2
	Expected lung cancer deaths	0.001	0.18	1.97	6.09	7.85	3.25	0.44
	Person-years of observation	349	3,139	4,643	3,928	2,183	558	79
	Observed/expected	0	0	1.02	1.64	1.27	1.23	4.55
	Mean exposure (mg CrO_3/m^3-years)	0.0042	0.0043	0.0043	0.0042	0.0042	0.0039	0.0037
0.009–0.0769	Observed lung cancer deaths	0	0	3	10	11	4	2
	Expected lung cancer deaths	0.002	0.19	1.93	5.70	7.66	3.26	0.38
	Person-years of observation	457	3,520	4,732	3,720	2,128	559	78
	Observed/expected	0	0	1.56	1.75	1.44	1.23	5.27
	Mean exposure (mg/m^3-years)	0.031	0.031	0.030	0.030	0.028	0.029	0.027
0.077–5.25	Observed lung cancer deaths	0	0	8	8	18	3	1
	Expected lung cancer deaths	0.001	0.17	1.82	5.63	6.71	2.48	0.18
	Person-years of observation	200	2,874	4,294	3,663	1,926	423	29
	Observed/expected	0	0	4.41	1.42	2.68	1.21	5.43
	Mean exposure (mg CrO_3/m^3-years)	0.21	0.33	0.41	0.52	0.63	0.78	0.86

[a] Expected lung cancer deaths in this table are based on age-, race-, and calendar-year- specific rates for the State of Maryland. The expected lung cancer deaths for those with race unknown was estimated from what would be expected if they had a race distribution similar to those for whom race was known. Cumulative exposure is lagged 5 years.

chromium exposure by age category. The table has been further organized by cumulative exposure quartiles.

Table VI is an examination of lung cancer observed-to-expected ratios by race (white, nonwhite) and for the total cohort for the four cumulative hexavalent chromium exposure quartiles. For whites, the lung cancer risk increased from the first to the second quartile, leveled off in the third quartile and decreased in the fourth quartile. For nonwhites the lung cancer risk was not significantly elevated except for the fourth quartile. For those with race unknown, there were few lung cancer deaths. The total cohort, however, demonstrated a monotonic exposure–response relationship between cumulative hexavalent chromium exposure and lung cancer observed-to-expected ratio.

As indicated in the Methods section, proportional hazards models were used to assess the relationship between chromium exposure and the risk of lung cancer. Log transformation of cumulative exposure (for both cumulative trivalent chromium exposure and cumulative hexavalent chromium exposure) was found to improve the fit of the model (i.e., greater χ^2 statistic) as compared to using the untransformed exposure measure. This improvement was seen with all lag periods considered; with a 5-year lag the χ^2 increased from 35.9 to 42.1 for hexavalent chromium and

TABLE VI. Lung Cancer Observed and Expected Deaths, Person Years of Observation, and Observed-to-Expected Ratios By Race for the Four Exposure Quartiles; Chromium Chemical Production Workers, USA[a]

Cumulative hexavalent chromium exposure (mg CrO_3/m^3-years)	Race			
	White	Nonwhite	Unknown	Total
0–0.00149 Mean = 0.00045	O/E = 0.83 (95% CI = 0.47, 1.35) O = 14, E = 16.81 PY = 16,299	O/E = 1.15 (95% CI = 0.55, 2.07) O = 9, E = 7.85, PY = 8,400	O/E = 1.23 (95% CI = 0.3, 3.2) O = 3, E = 2.44 PY = 3,813	O/E = 0.96 (95% CI = 0.63, 1.38) O = 26, E = 27.1 PY = 28,512
0.0015–0.0089 Mean = 0.0042	O/E = 2.10 (95% CI = 1.31, 3.16) O = 20, E = 9.54 PY = 7,330	O/E = 0.93 (95% CI = 0.42, 1.72) O = 8, E = 8.63 PY = 5,296	O/E = 0 (95% CI = 0, 2.3) O = 0, E = 1.63 PY = 2,253	O/E = 1.42 (95% CI = 0.95, 2.01) O = 28, E = 19.80 PY = 14,879
0.009–0.0769 Mean = 0.030	O/E = 2.11 (95% CI = 1.33, 3.15) O = 21, E = 9.93 PY = 7,959	O/E = 1.16 (95% CI = 0.55, 2.08) O = 9, E = 7.79 PY = 5,588	O/E = 0 (95% CI = 0, 2.7) O = 0, E = 1.38 PY = 1,647	O/E = 1.57 (95% CI = 1.07, 2.20) O = 30, E = 19.1 PY = 15,194
0.077–5.25 Mean = 0.449	O/E = 1.71 (95% CI = 1.00, 2.69) O = 16, E = 9.35 PY = 7,149	O/E = 2.87 (95% CI = 1.81, 4.29) O = 21, = 7.30 PY = 5,716	O/E = 2.86 (95% CI = 0.2, 12.6) O = 1, E = 0.35 PY = 544	O/E = 2.24 (95% CI = 1.60, 3.03) O = 38, E = 17.0 PY = 13,409

[a] Expected lung cancer deaths in this table are based on age-, race-, and calendar year-specific rates for the State of Maryland. The expected lung cancer deaths for those with race unknown was estimated from what would be expected if they had a race distribution similar to those for whom race was known. Cumulative exposure is lagged 5 years.

from 28.8 to 38.9 for trivalent chromium. Square root transformations gave a poorer fit than did log transformations of the cumulative exposure for both hexavalent and trivalent chromium using the same lag periods. Average exposure (cumulative exposure/duration of work) and log average exposure also gave poorer fits than did log transformations of the cumulative hexavalent and trivalent chromium exposure using the same lag periods. Log transformation of duration of work at the plant also resulted in a worse fit than did the untransformed variable for all lags. Based on the above results, log transformations of cumulative trivalent chromium exposure and cumulative hexavalent chromium exposure, and the untransformed duration of work, were utilized in all subsequent models.

Consideration of different lag times showed that for each of the three exposure measures, the 5- and 10-year lags gave essentially identical χ^2 values, with the 0- and 2-year lags slightly lower and the 20-year lag considerably lower (at least for the two chromium dose measures). A 5-year lag was selected for use in all models.

Cumulative hexavalent chromium exposure (mg/m^3-years), cumulative trivalent chromium exposure, and work years were found to be roughly equivalent in predictive ability when smoking (yes/no) was included in the model, and each of these exposure measures was significantly associated with increased lung cancer risk at the $P = 0.0001$ significance level (see Table VII). In Table VII, the coefficient of 0.325 (95% CI of 0.180–0.469) associated with $\log_{10}$ of cumulative hexavalent chromium exposure indicates that a 10-fold increase in cumulative exposure (or equivalently an increase of 1 in $\log_{10}$ cumulative exposure) increases the risk, or hazard, by a factor of exp (0.325) = 1.38 (95% CI of 1.20–1.63). This can be compared to an increase of exp (0.274) = 1.32 (95% CI of 1.15–1.51) fold following a 10-fold increase in cumulative trivalent chromium exposure. For work duration at the plant, the coefficient of 0.044 indicates that working 10 additional years increases the risk by a factor of exp (10 * 0.044) = 1.55.

The proportional hazards models were used to estimate risks by exposure quartile using the first quartile as the reference group. Using the median exposure in each quartile as the measure of cumulative hexavalent chromium exposure and with smoking included as a variable in the

TABLE VII. Results of Cox Models for Three Different Exposure Measures, Each Combined With Smoking Status; Chromium Chemical Production Workers, USA

Model	Variable	Coefficient (95% CI)	Relative risk	*P*-value	χ^2
I	Cigarette smoking	1.80 (0.80, 2.80)	6.05	0.0004	42.2
	Log_{10} cumulative hexavalent chromium exposure	0.325 (0.180, 0.469)	1.38[a]	0.0001	
II	Cigarette smoking	1.79 (0.79, 2.79)	5.99	0.0005	38.9
	Log_{10} cumulative trivalent chromium exposure	0.274 (0.140, 0.412)	1.32[a]	0.0001	
III	Cigarette smoking	1.75 (0.75, 2.75)	5.75	0.0006	36.4
	Years worked	0.044 (0.023, 0.065)	1.55[b]	0.0001	

[a] The relative risk is for each 10-fold increase in cumulative exposure.

[b] The relative risk is for each 10-year increase in years worked.

TABLE VIII. Cox Models for Cumulative Hexavalent Chromium Exposure/Cumulative Trivalent Chromium Exposure and Cumulative Hexavalent Chromium Exposure/Duration of Work (Smoking also Included in Each Model); Chromium Chemical Production Workers, USA

Model	Variable	Coefficient	Relative risk	*P*-value	χ^2
I	Log_{10} cumulative hexavalent chromium exposure	0.509	1.66[a]	0.045	42.8
	Log_{10} cumulative trivalent chromium exposure	−0.177	0.17[a]	0.449	
	Cigarette smoking	1.8	6.05	0.004	
II	Log_{10} cumulative hexavalent chromium exposure	0.256	1.29[a]	0.010	43.2
	Years worked	0.016	1.17[b]	0.303	
	Cigarette smoking	1.78	5.93	0.005	

[a] The relative risk is for each 10-fold increase in cumulative exposure.

[b] The relative risk is for each 10-year increase in years worked.

model, relative lung cancer risks of 1.83, 2.48, and 3.32 for persons in the 2nd, 3rd and 4th cumulative exposure quartiles, in comparison to the first quartile, were estimated.

There was a strong correlation between the log of cumulative hexavalent chromium and the log of cumulative trivalent chromium (Pearson correlation coefficient = 0.95; Spearman rank correlation coefficient = 0.95). There were also strong correlations between the log of cumulative hexavalent chromium exposure and work duration (Pearson correlation coefficient = 0.71; Spearman rank correlation coefficient = 0.87) and between the log of cumulative trivalent chromium exposure and work duration (Pearson correlation coefficient = 0.63; Spearman rank correlation coefficient = 0.84).

Despite these strong correlations, we attempted to separate the effects in two proportional hazards models (Table VIII). One model incorporated the log of cumulative hexavalent chromium exposure, the log of cumulative trivalent chromium exposure, and smoking. The other model incorporated the log of cumulative hexavalent chromium exposure, work duration, and smoking. In each case, inclusion of the other dose measure (log of cumulative trivalent chromium exposure or work duration) resulted in cumulative hexavalent chromium exposure still being statistically significant ($P < 0.05$) with the other measure not being statistically significant. In addition, the coefficient for work duration decreased substantially compared to the value in Table VII, and the coefficient for cumulative trivalent chromium exposure actually became negative.

A significant ($P < 0.05$) correlation of lung cancer with the occurrence of ulcerated nasal septum, perforated nasal septum, ulcerated skin, dermatitis, burn, and conjunctivitis was found using separate 2 × 2 tables. When smoking, cumulative exposure to hexavalent chromium, and the 10 potential clinical findings of chromium irritation were included in 10 separate proportional hazards models as covariates, none of the clinical findings of irritation were found to be significantly ($P < 0.05$) predictive of the occurrence of lung cancer, although perforated nasal septum and burn reached borderline significance ($P = 0.07$).

DISCUSSION

The current study confirms the elevated lung cancer risk from hexavalent chromium exposure observed in other studies and presents the best opportunity to date of evaluating the lung cancer exposure–response relationship from exposure to hexavalent chromium. A comparison of key attributes of the current study with those of the study by Mancuso [1975, 1997a] which has to date been the study most frequently used for exposure–response assessment of the lung cancer risk from hexavalent chromium is found in Table IX.

As can be seen, the current study, in comparison with the Mancuso study, had a larger cohort, more lung cancer deaths, and had smoking information for most of the cohort. Many of the exposure estimates of the current study are from direct measurements; a portion were from models using contemporary data. More important, however, the ambient measures or estimates of exposure were concurrent with the work history and are of hexavalent chromium directly, not derived from other measures. Furthermore, the cumulative exposure groups in the current study represent lower exposures than those of the Mancuso study, providing better risk estimates at these lower levels of exposure, an important consideration for quantitative risk assessment. Nonwhites were found to have higher mean cumulative hexavalent chromium exposures than whites (Table III). Nonwhites had somewhat longer mean work durations than did whites but not enough to account for the large difference between whites and nonwhites in mean cumulative exposure. The difference is more attributable to two different distributions of job titles biased toward jobs with higher exposures experienced by the nonwhite population.

The lung cancer risk among those with race unknown was less than expected (Table I). This may reflect the fact that cumulative hexavalent chromium exposure among those with race unknown was considerably less than among those whose race was known (Table III).

A high proportion of the cohort were smokers as were a high proportion of the lung cancer deaths. Only four of those who died from lung cancer did not smoke at the time of initial employment. Nevertheless, increasing exposure to hexavalent chromium was still a statistically significant risk factor when included with smoking as a covariate in the proportional hazards model. It was not possible to examine the interaction of smoking and cumulative hexavalent chromium exposure in the Cox regression because of the small number of nonsmoking lung cancer cases.

Considerable effort was made in the current study to develop estimates of trivalent chromium exposures from measured hexavalent chromium exposures and chemical analysis of settled dust and to use this information to evalvate whether there is a risk of lung cancer from cumulative trivalent chromium exposure. Analyses indicated that cumulative trivalent chromium exposure was not

TABLE IX. A Comparison of the Current Study with Studies by Mancuso [1975, 1997a]; Chromium Chemical Production Workers, USA

	Current study	Mancuso [1975, 1997a]
Cohort	1205 white males 848 nonwhite males 304 race unknown males	332 white males
Industrial hygiene measurements vis-a-vis work history	Concurrent with the work history	Not concurrent with work history (Measurements made in 1949 were used to estimate exposure to workers who began employment in 1931–37)
Industrial hygiene measurements vis-a-vis chromium species measurement	Cr^{+6} (Cr^3 derived from settled dust)	Total Cr (Cr^6 and Cr^3 derived from settled dust)
Number of lung cancer cases	122	42 (1975 study); 66 (1997 study)
Person-years of observation	70,736	5,853 (1975 study); 12,881 (1997 study)
Smoking data	Yes/No for 91% of cohort at time of first employment	None
Exposure groups (mg/m^3-years)	0–0.00149, 0.0015–0.0089, 0.009–0.0769, 0.077–5.25	< 0.25, 0.25–0.49, 0.50–1.00, 1.00–1.99, 2.00
Analysis of cancer risk of Cr VI and Cr III	Multivariate	Univariate

associated with an excess lung cancer risk when evaluated together with cumulative hexavalent chromium exposure. Mancuso [1997a] concluded that lung cancer risk increased with increasing cumulative trivalent chromium exposure, but cumulative trivalent chromium exposure correlated with increasing hexavalent chromium exposure in his study as it did in this study. There was no effort by Mancuso [1997a] to examine the effects of the two in a multiple regression. Mancuso [1997b] presents additional argument using autopsy results that trivalent chromium is carcinogenic although, again, the results may be confounded by the presence of hexavalent chromium. There is no evidence from the current study that trivalent chromium is carcinogenic. If trivalent chromium is indeed carcinogenic, it is much less so than hexavalent chromium. Cumulative hexavalent chromium exposure was also a significantly stronger predictor of lung cancer risk than was duration of work, suggesting that it was hexavalent chromium and not other exposures in the workplace responsible for the excess lung cancer risk.

Although the exposure data in the current study offers an advantage over that of previous studies, it has its limitations. The cumulative exposure of each individual in the cohort was compiled from their work history and average exposures specified by job title by calendar year. Variability in exposures between individuals with the same job title and across a year are not captured in the current analysis. These variabilities could reasonably be expected to be high. Conversely, it should be noted that clinical findings of hexavalent chromium exposure (e.g., nasal, skin, eye, and ear irritation) were not found to be significant predictors of lung cancer risk when included as variables with cumulative hexavalent chromium exposure and smoking status in the Cox model. If such clinical findings are the result of high, short-term, ambient exposures, as might be expected, this suggests that cumulative hexavalent chromium exposure is a stronger predictor of lung cancer risk than is high, short-term exposure.

The availability of extensive smoking data is unusual for any occupational study. The measure of smoking in the current study was yes/no at the time of beginning employment. Such a measure does not provide information on the amount smoked or the number of individuals who smoked at time of employment and who subsequently quit or the number of nonsmokers who became smokers.

Recognizing that the data developed by this study may be useful to risk assessors doing quantitative risk assessment, we have presented the number of observed and expected lung cancer cases and person-years of observation by age and cumulative hexavalent chromium exposure (Table V). Such information is usually lacking in epidemiologic papers. Age and exposure are critical variables for an exposure response assessment using epidemiologic data. It is hoped that future epidemiologic papers on the cancer response to chemical carcinogens will also present information allowing the risk assessor to examine the concurrent effect of these two critical variables.

It should be noted that the current OSHA Permissible Exposure Limit (PEL) of 100 g CrO_3/m^3 [OSHA, 2000] and the American Conference of Government and Industrial Hygienists [ACGIH, 1999] threshold limit value of 50 g Cr/m^3 (equivalent to approximately 100 μg CrO_3/m^3) for water-soluble hexavalent chromium would both fall into the fourth quartile of cumulative hexavalent chromium exposure in the current study (assuming OSHA's standard 45-year working lifetime). OSHA has been petitioned to set a new PEL of 0.5 g CrO_3/m^3 [Public Citizen's Health Research Group and the Oil, Chemical, and Atomic Workers International Union 1993]. The NIOSH [1975] Recommended Exposure Limit (REL) for hexavalent chromium is 1 g Cr/m^3 (approximately 2 g CrO_3/m^3). Both the REL and the PEL which has been petitioned for would fall into the third quartile of cumulative hexavalent chromium exposure in the current study, again using the standard OSHA assumption of a 45-year working lifetime. The lung cancer observed-to-expected ratios for both the third and fourth quartiles of the current study were both significantly elevated. The lung cancer observed-to-expected ratio in the second quartile was elevated although not statistically significant (O/E = 1.42, 95% CI = 0.95, 2.01).

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