

Epidemiologic studies of chrome and cancer mortality: A series of meta-analyses

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Abstract

We used 49 epidemiologic studies based on 84 papers published since 1950 to develop an array of meta-analyses relating exposure to chrome-six compounds with 10 causes of death. Most exposures occurred in occupational settings. Studies were assessed for quality, and for control of smoking or economic status if they related to lung or stomach cancer. There was no excess mortality from all causes combined among chrome-exposed persons. A minimal excess of cancer (SMR = 112), overall, was due primarily to an excess of lung cancer (SMR = 141) but the SMR was 112 among the better-quality, smoking-controlled studies. The overall SMR for stomach cancer was 113 but it was 82 among the studies that were controlled for economic status. Findings were unremarkable for the six other cancers evaluated: prostate, kidney, and central nervous system cancer and leukemia, Hodgkin's disease and other lymphatohematopoietic cancer. This series of meta-analyses indicates that chrome-six is a weak cause of lung cancer and is not a cause of any of the other seven forms of cancer evaluated.

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1. Introduction

Since the early 1980s both the International Agency for Research on Cancer (IARC, 2000) and the National Toxicology Program of the United States (NTP, 2000) have categorized chrome as a human carcinogen. This is based on epidemiologic evidence that chrome in valence state six (Cr6) causes cancers of the lung, the nose, and the nasal sinuses. It is generally accepted that only Cr6 is carcinogenic. There is good evidence that chrome in valence state three is not (De Flora, 2000; Langard, 1993). There has been concern that Cr6 also may cause stomach cancer because some portion of chrome dusts inhaled in occupational settings would become trapped in mucus and swallowed. It is also possible that Cr6 in drinking water would reach the stomach.

This paper describes a series of meta-analyses that evaluate the world's epidemiologic literature on the relationship between Cr6 and cancer of the lung, the stomach, and six other organs. "All cause" and "all cancer" mortality also are evaluated for perspective.

2. Methods

An attempt was made to identify every epidemiologic study published in 1950 or later that was in English, or had an English abstract, and that evaluated the relationship between chrome and one or more of the following causes of death:

1. All cause.
2. All cancer.
3. Lung cancer.
4. Stomach cancer.
5. Prostate gland cancer.

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6. Kidney cancer.
7. Central nervous system (CNS) cancer.
8. Leukemia.
9. Hodgkin's disease (HD).
10. Other lymphohematopoietic cancers (OLHC).

The compilation of the literature began with 46 relevant papers that were at hand. Simultaneously, citations were identified from Medline (January, 1966 to October, 2004) by using an array of search terms such as "chrome," "chromium alloys," "chromium compounds," etc. Additional electronic and printed sources were used to identify possibly relevant literature. The search concluded in January, 2005 with 114 citations for possible inclusion in at least one of the meta-analyses. Each paper located was reviewed independently by the two authors and was scored on seven criteria relating to epidemiologic aspects of design, conduct, analysis, and interpretation and on one criterion relating to exposure assessment. The eight criteria and the maximum number of points that were allocated to each are shown in Table 1.

Each paper that included data on lung cancer also was designated as, or as not, being at least partially controlled for the cigarette smoking patterns of its subjects. Each paper that included stomach cancer was designated similarly with regard to economic status. Papers on lung cancer or stomach cancer that were negative or essentially negative with respect to chrome exposure were included with the papers that were controlled.

We excluded 30 of the 114 papers from all meta-analyses. The numbers of papers, according to the reason for their exclusion, were: two could not be located. Fourteen had no usable data. Twelve described occupational settings with little or no chrome exposure. Two were published before 1950. There remained 84 papers that contributed information to at least one of the meta-analyses.

In many instances a single investigation had produced two or more papers often over a period of years. These usually reported the sequential follow-up of the same, or nearly the same, study group. In other instances, the papers described exposure assessment procedures. We combined into one "study" all papers from a single

investigation. This combined the 84 papers into 49 studies. There were 30 studies with one publication, nine with two publications, six with three, three with four, no studies with five publications and one with six publications.

The bibliography that accompanies this paper is limited to the 10 papers cited in this text. Appendix 1 is a comprehensive bibliography that includes all 114 citations, designates the study of which each paper is a part and provides the reasons for the exclusion of each of the 30 studies not used. Appendix 1 is available as part of the online version of this paper.

We then scored each of the 49 studies on the same quality criteria used for the papers. A study received on each criterion the highest score earned on that criterion by any of its component papers. For analysis, the studies were divided into the 28 with scores of 75 or higher and the 21 with lower scores. Studies that contributed to the lung or stomach cancer meta-analyses were sorted further according to the presence or absence of control for smoking or economic status.

Most studies were of the retrospective follow-up (RFU) design and used the standardized mortality ratio (SMR) as the measure of association between chrome and cause of death. The 95% confidence interval of the SMR also was provided in most cases. Proportional mortality ratio (PMR) and case-control studies also are included in the meta-analyses. For these, the measure of association used was the PMR or the odds ratio (OR), respectively. Since nearly all studies reported SMRs, that term has been used consistently here to designate the measure of association.

For each meta-analysis, the studies to be included were sorted into two groups according to quality score and, for lung and stomach cancer, according to control for confounding. Data were compiled by recording the selected observed and expected numbers, the SMR, the related 95% confidence interval and the specific location of the selected data. For many studies there were several findings that could have been included in any given meta-analysis. For example, SMRs might be presented for different levels or durations of chrome exposure. In such instances we usually used the highest SMR from the study's most recent publication. The highest SMR was not used if it was excessively imprecise. The meta-SMR for each of the 12 meta-analyses that were done is the sum of the observed divided by the sum of the expected numbers. All 95% confidence intervals, including those for individual findings and those for the meta-SMRs were validated, or calculated, by the present authors.

3. Results

3.1. Quality score

We first evaluated the relationship between the quality scores of the studies and their results. We used all 12

Table 1
Maximum score for each criterion used to evaluate the publications and studies

No.	Criterion	Maximum possible score
1.	Subject inclusion criteria	15
2.	Completeness of follow-up	25
3.	Retrieval of death certificates	10
4.	Quality of analysis—overall	5
5.	Exposure restricted subgroup(s)	20
6.	Dose–response evaluated	5
7.	Lag/latency accommodated	5
8.	Critical, data-based interpretation	15
	Total	100

meta-analyses for this: one each for the two general meta-analyses (all cause, all cancer) and for six of the specific forms of cancer. For lung and stomach cancer two meta-analyses were done according to the presence or absence of control for a major cause of the disease. In addition each of the 12 meta-analyses provided two sub-meta-SMRs, one for higher-scoring and one for lower-scoring studies.

For seven of the meta-analyses the higher-scoring studies had lower SMRs and the reverse was true for five. The unweighted arithmetic mean of the SMRs for the higher-scoring studies was 105 compared with 126 for the lower-scoring studies. This difference appears small but note that the measure of “effect” ($SMR - 100$) is about five times larger for the lower-scoring studies than it is for the higher-scoring studies. We then limited attention to the four meta-analyses (all cancer, CNS cancer, HD, and OLHC) in which the difference between the SMRs of the higher- and lower-scoring studies was at least 20%. For all four the higher-scoring studies produced the lower SMR.

We infer that there is a minimal relationship between study quality and the meta-SMR with the higher-scoring studies tending to produce somewhat lower SMRs. This relationship results almost entirely from the findings of the three meta-analyses with the smallest number of observed deaths (CNS cancer, HD, and OLHC).

Table 2 shows summary findings for the 12 meta-analyses. For each set of summary findings there is a detailed tabulation available of the study-by-study results. These 35 tables comprise Appendix 2 is available as part of the online version of this paper.

The results of the meta-analyses are described and in some instances a brief commentary is offered here. An overall discussion appears at the end of this report. All line numbers refer to Table 2.

3.2. All cause mortality

The SMR for all cause mortality is 100 and is based on 18,395 observed deaths listed as due to “all cause” or “all causes” in 34 studies. It is 101 for the 23 higher-scoring studies and 96 for the lower-scoring studies. These two SMRs are not statistically significantly different from one another.

3.3. All cancer

Line 6 shows an overall statistically significant excess of all cancer, $SMR = 112$, based on 6011 observed deaths and 5358 expected. The SMR was 130 for the lower-scoring studies. There was a minimal excess, $SMR = 108$, of all cancer among the higher-scoring studies. The reasons for the excess deaths from “all cancer” are explored in the next section on lung cancer.

3.4. Lung cancer

Lines 9–18 describe findings for lung cancer. There is an overall elevated SMR of 141 and statistically significant elevations, ranging from 112 to 279, in all four of the subgroups of studies. A comparison of the results of studies that controlled for smoking, $SMR = 118$, with those that did not, $SMR = 181$, indicates that about three-fourths of the excess lung cancer risk in the uncontrolled studies is probably due to smoking. Similarly, the SMRs of the better-scoring studies are moderately lower than those of the lower-scoring studies (compare line 13 with line 14 and line 17 with line 18). Combined, these findings suggest that the accepted causal relationship between chrome exposure and lung cancer is valid but somewhat weaker than generally has been considered.

We addressed the question, “To what extent is the excess of deaths in the all cancer category due to excess deaths from lung cancer?” To do this, we focused on the 21 studies that provided data both for all cancer and for lung cancer and which had an excess of at least one death in each category. These studies reported 826 excess deaths from all cancer of which 597, or 72%, were due to lung cancer. The remaining 30% or so of excess cancer deaths may be due to some combination of chrome exposure, chance or to confounding factors including smoking and economic status. The potentially great effect of economic status is illustrated in the meta-analysis for stomach cancer.

3.5. Stomach cancer

There is a slight and marginally statistically significant overall increase in stomach cancer, $SMR = 113$, based on 474 observed and 419 expected deaths in 32 studies (line 20). However, findings differ strikingly between the studies in line 22, ($SMR = 82$, significantly reduced) which are controlled for economic status and those in line 26, ($SMR = 137$, significantly elevated) which are not. These two SMRs are highly statistically significantly different from one another. However, findings among the studies are remarkably consistent within each of these two subgroups. Of the 14 studies with control for economic status (line 22) 12 have an SMR below 100 (the other two have SMRs of 102 and 156). In contrast, of the 18 studies without control for economic status (line 26) all but two have SMRs greater than 100.

These results indicate that the weak association between Cr6 and stomach cancer seen in the overall data is derived entirely from the studies that lacked control for the low economic status of chrome workers.

3.6. Prostate gland cancer

Lines 29–32 show findings for prostate cancer. The overall SMR of 114 (100–129) is weak and not quite sta-

Table 2
Summary findings of the 12 meta-analyses

Line No.	Cause of death	No. of deaths				SMR	95% CI
		Studies	Papers	Obs.	Exp.		
1.	All cause						
2.	Total	34	59	18395	18329	100	(99–102)
3.	Score 75+	23	46	16636	16501	101	(99–102)
4.	Score <75	11	13	1759	1828	96	(92–101)
5.	All cancer						
6.	Total	40	66	6011	5358	112	(109–115)
7.	Score 75+	25	49	4617	4287	108	(105–111)
8.	Score <75	15	17	1394	1071	130	(123–137)
9.	Lung cancer—all						
10.	Total	47	82	2454	1741	141	(135–147)
11.	Lung cancer—smoking controlled						
12.	Total	26	46	1325	1118	118	(112–125)
13.	Score 75+	20	39	851	762	112	(104–119)
14.	Score <75	6	7	474	356	133	(121–146)
15.	Lung cancer—smoking not controlled						
16.	Total	21	36	1129	623	181	(171–192)
17.	Score 75+	8	15	839	519	162	(151–173)
18.	Score <75	13	21	290	104	279	(249–313)
19.	Stomach cancer—all						
20.	Total	32	52	474	419	113	(103–124)
21.	Stomach cancer—econ. status controlled						
22.	Total	14	27	150	183	82	(69–96)
23.	Score 75+	11	24	111	134	83	(68–100)
24.	Score <75	3	3	39	49	79	(56–107)
25.	Stomach cancer—econ. status not controlled						
26.	Total	18	25	324	236	137	(123–153)
27.	Score 75+	8	14	191	137	140	(121–161)
28.	Score <75	10	11	133	99	134	(112–160)
29.	Prostate cancer						
30.	Total	22	37	251	221	114	(100–129)
31.	Score 75+	15	30	202	178	113	(98–130)
32.	Score <75	7	7	49	43	115	(85–152)
33.	Kidney cancer						
34.	Total	17	30	90	80	112	(90–137)
35.	Score 75+	11	24	72	63	114	(89–144)
36.	Score <75	6	6	18	17	103	(61–163)
37.	CNS cancer						
38.	Total	13	22	44	50	88	(64–118)
39.	Score 75+	8	17	27	40	68	(45–99)
40.	Score <75	5	5	17	10	163	(95–261)
41.	Leukemia						
42.	Total	20	35	88	103	86	(69–106)
43.	Score 75+	15	30	74	84	88	(69–111)
44.	Score <75	5	5	14	19	74	(40–124)
45.	Hodgkin's disease						
46.	Total	9	16	23	21	111	(70–167)
47.	Score 75+	7	14	15	17	90	(51–149)
48.	Score <75	2	2	8	4	195	(84–384)
49.	Other lymphohematopoietic cancer						
50.	Total	13	23	64	76	84	(65–108)
51.	Score 75+	9	19	53	66	81	(60–106)
52.	Score <75	4	4	11	10	109	(54–195)

tistically significant. The SMRs are virtually identical for the higher- and lower-scoring studies. The combined data set is large with 251 observed deaths in 22 studies. However, 12 of these studies were small with five or fewer observed deaths. There also were five studies each with 20 or more observed deaths. Four of these had an SMR greater than 120. However, in none of these four relatively large and positive studies was there evidence of a dose–response or an employment duration–response effect.

3.7. *Kidney cancer*

Lines (33–36) show unremarkable findings for cancer of the kidney. The overall SMR is 112 and the values are similar among both the higher- and the lower-scoring studies.

3.8. *CNS cancer*

Lines 37–40 show findings for 13 studies with information on central nervous system cancer. The overall finding is an unremarkable SMR of 88, based on only 44 observed deaths. The SMR is 68 for the higher-scoring studies. An elevated SMR of 163 is seen in the lower-scoring studies. Although the data for CNS cancer are sparse, the two SMRs of 68 and 163 differ significantly.

3.9. *Leukemia*

Lines (41–44) show the findings for the 20 studies that addressed all leukemia. Eighty-eight deaths were observed, giving an unremarkable overall SMR of 86. Findings for the higher- and lower-scoring studies did not differ appreciably. Data were not sufficient to evaluate any specific form of leukemia.

3.10. *Hodgkin's disease*

Lines 45–48 show findings for the nine studies that provided data on Hodgkin's disease (HD). There were only 23 observed deaths giving an overall SMR of 111. The higher-scoring studies, SMR = 90, and the lower-scoring, SMR = 195, are just barely significantly different from one another.

3.11. *Other lymphohematopoietic cancer*

This category includes data for the lymphohematopoietic cancers from studies that explicitly excluded HD, the leukemias and, in most instances, multiple myeloma. It is intended to be descriptive of the non-Hodgkin's lymphomas. Lines 49–52 show findings for the 13 studies that included 64 deaths observed from OLHC. As was true for leukemia and HD the findings for OLHC are

unremarkable, with an SMR of 84. The SMRs of the higher- and lower-scoring studies do not differ significantly.

4. Discussion

Exposure to Cr6—usually heavy occupational exposure—is not associated with an excess overall mortality. A minimal 12% excess mortality from all forms of cancer combined was found, but about 70% of this excess appears to be due to an excess of lung cancer. If the excess deaths from lung cancer were excluded, the residual excess of cancer mortality among Cr6-exposed persons would amount to an SMR of 105 and possibly less.

The established causal relationship between chrome exposure and lung cancer was found to be weak. Previous views of a strong relationship appear to be based on findings that were not controlled for the excess smoking of chrome-exposed persons. When that control was applied, the Cr6-lung cancer association has an SMR of about 120. Lower-scoring studies tended to produce higher SMRs for lung cancer than did the better-scoring studies. However, this “quality” effect was relatively small.

De Flora (2000) has suggested that the relationship between Cr6 and lung cancer is weak because of the great capacity of the lung to reduce Cr6 to the non-carcinogenic chrome-3. He suggested further that only very heavy exposure to Cr6 could overwhelm the lung's reducing capacity and produce cancer. Crump et al. (2003) also inferred from statistical modeling of findings at one plant that Cr6 was only weakly carcinogenic for the lung. They estimated that the increase in lung cancer risk, on the relative risk scale, was 0.002 for a 45 year working life at $1 \mu\text{g}/\text{m}^3$. Further, such an experience ($45 \mu\text{g year}/\text{m}^3$), is only about 5% of the lowest exposure ($1.0 \text{ mg year}/\text{m}^3$) that consistently was associated with an increase in lung cancer risk. Proctor et al. (2004) evaluated exposure at the same plant studied by Crump et al. and found that the average airborne exposures were $0.72 \text{ mg}/\text{m}^3$ in the 1940s and decreased progressively to $0.034 \text{ mg}/\text{m}^3$ after 1964. If we apply these concentrations to a working life of 45 years they would produce cumulative exposures of from 32 down to $2 \text{ mg year}/\text{m}^3$. These equate to 32 to two times the minimum cumulative exposure shown to be linked to a lung cancer excess.

The meta-analysis for stomach cancer indicates that the principal determinant of a study's outcome is the presence or absence of control for the economic status of its subjects. It is remarkable that the studies without control for economic status produced a statistically significantly elevated SMR of 137 while those with control led to a significantly reduced SMR of 82. We conclude that the available data provide firm evidence against a

causal relationship between exposure to Cr6 and stomach cancer.

This interpretation supports the findings of Proctor et al. (2002) who reviewed both the toxicologic as well as the epidemiologic literature on Cr6 and cancer of the digestive tract. They concluded that the current federal standard allowing 100 parts-per-billion of (total) chromium in drinking water, and levels even up to 10 times as high, would not be carcinogenic for the digestive system. There are three studies (Armienta-Hernandez and Rodriguez-Castillo, 1995; Bednar and Kies, 1991; Zhang and Li, 1997) that evaluated the possible adverse health effect, especially carcinogenesis, of chromium in drinking water. Each of these studies has limitations and only one, that of Zhang et al., could be included in the present meta-analyses. However, taken together with the work of Proctor et al. (2002) and the present findings, they suggest that the current federal standard of 100 ppb of chromium in drinking water is not associated with any increased risk of stomach cancer.

The findings for prostate cancer show a weak, marginally significant association with chrome exposure with an SMR of 114 (100–129). This association is unlikely to reflect causality as none of the larger, positive studies showed a dose–response relationship.

For cancer of the kidney and CNS the overall SMRs were, respectively, 112 and 88. Cr6 appears to have no relationship to these forms of cancer.

The final three causes of death evaluated are leukemia, HD, and OLHC. For these conditions the overall SMRs, respectively, 88, 111, and 86, provide no support for a causal relationship with chrome. All the SMR estimates for these three diseases are imprecise.

Several issues arise as to the overall picture that this collection of meta-analyses provides of the chrome–cancer relationship. For one, it may be asked why the results are not more positive considering that chrome is, in fact, a human carcinogen. Chrome's long association with cancer in human beings is based on its relationship with lung cancer and sinonasal cancer. The present findings imply that the perception of a strong relationship with lung cancer reflects the fact that nearly half of the available studies were not controlled for cigarette smoking. However, even the uncontrolled studies had an overall SMR for lung cancer of only about 180. Contrary to our expectation and plan we were unable to conduct a meta-analysis relating to sinonasal cancer. We found that the relevant literature consists almost entirely of case reports.

As another issue, it may be asked why the findings are not more negative considering that most of the studies related to occupational settings where the “healthy worker effect” (HWE) might be expected to lead to SMRs below 100. Perhaps somewhat surprisingly, then, is the fact that for three (prostate, kidney, and HD) of

the six meta-analyses (excluding lung and stomach), the meta-SMR exceeds 100. However, all three of these “elevated” SMRs are under 115 and none is statistically significant. One factor possibly leading to the SMRs over 100 is that we extracted from each study, for each form of cancer, the highest SMR that was reasonably precise. Had we chosen a “representative” SMR the meta-SMRs would have been lower. A second factor elevating the meta-SMRs: for none of them, except lung and stomach cancer, was any control available for alternative causes. For example, the minimal excess of kidney cancer could be, and probably is to some degree, due to the uncontrolled effect of cigarette smoking.

Meta-analysis has been used widely in epidemiology for about 25 years. Its principal value lies in enhancing the precision of the estimate of an association. In addition, it may sometimes provide insight into causation by revealing the reasons for study-to-study variations in findings.

The present paper is unusual in four respects. First, we included every study that provided at least one usable finding for at least one of the meta-analyses. The number and variety of studies included in a meta-analysis is sometimes reduced to increase the homogeneity of the studies evaluated. However, this potentially reduces the amount of information on factors that influence the outcome of individual studies. Second, it presents not one, but an array of related meta-analyses which, together, explore the relationships between exposure to Cr6 and a series of malignant diseases. In this way a broad profile of the effect, or lack of effect, of Cr6 exposure is described. Third, the units of observation are “studies” and not individual publications. This permits a thorough evaluation of the strengths and limitations of the research available. Fourth, we dealt with issues of study quality and control of confounding directly and by design. For each of two forms of cancer, lung, and stomach, we controlled confounding by study stratification. In both instances this control greatly reduced (for lung cancer) or eliminated (for stomach cancer) the disease's apparent relationship with chrome exposure.

Finally, we used no detailed analyses—not even heterogeneity testing—to explore the reasons for overall findings and study-to-study variations in findings. Heterogeneity testing typically is used to determine whether the studies under consideration are sufficiently similar, in their findings or in other characteristics, to allow their being grouped in a single meta-analysis. We suggest that heterogeneity testing is fundamentally inappropriate for this purpose. It is, after all, no more than significance testing and its results are as dependent on the sizes of the studies under evaluation as they are on their findings. For example, a series of large studies with similar but not identical findings could falsely appear to be statistically significantly heterogeneous. Conversely, a series of small studies may not be significantly heterogeneous even though their results differ strikingly.

Our alternative to excluding studies from the meta-analysis and to heterogeneity testing was to make a detailed interpretation of the available studies both as to their quality and, when relevant, their control of important confounders. This interpretation led to the grouping of studies by quality and by the presence or absence of control for confounding when that could be done. The resulting findings of the meta-analyses are that chrome is only weakly carcinogenic for the lung and not at all for other organs.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.yrtph.2005.06.009](https://doi.org/10.1016/j.yrtph.2005.06.009).

References

- Armienta-Hernandez, M., Rodriguez-Castillo, R., 1995. Environmental exposure to chromium compounds in the valley of Leon, Mexico. *Environ. Health Perspect.* 103 (Suppl. 1), 47–51.
- Bednar, C., Kies, C., 1991. Inorganic contaminants in drinking water correlated with disease occurrence in Nebraska. *Water Resources Bull.* 27, 631–635.
- Crump, C., Crump, K., Hack, E., et al., 2003. Dose–response and risk assessment of airborne hexavalent chromium and lung cancer mortality. *Risk Analysis* 23, 1147–1163.
- De Flora, S., 2000. Threshold mechanisms and site specificity in chromium (VI) carcinogenesis. *Carcinogenesis* 21, 533–541.
- IARC, 2000. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 49: Chromium, Nickel and Welding. IARC Press: Lyon, France, 1990.
- Langard, S., 1993. Role of chemical species and exposure characteristics in cancer among persons occupationally exposed to chromium compounds. *Scand. J. Work Environ. Health* 19 (Suppl. 1), 81–89.
- NTP, 2000. National Toxicology Program, 9th edition, Report on Carcinogens. U.S. Department of Health and Human Services, 2000.
- Proctor, D., Otani, J., Paustenbach, D., et al., 2002. Is hexavalent chromium carcinogenic via ingestion? A weight-of-evidence review. *J. Toxicol. Environ. Health A* 65, 701–746.
- Proctor, D., Panko, J., Liebig, E., Paustenbach, D., 2004. Estimating historical occupational exposure to airborne hexavalent chromium in a chromate production plant: 1940–1972. *J. Occup. Environ. Hyg.* 1, 752–767.
- Zhang, J., Li, S., 1997. Cancer mortality in a Chinese population exposed to hexavalent chromium in water. *J. Occup. Environ. Med.* 39, 315–319.