Chromium VI and stomach cancer: a meta-analysis of the current epidemiological evidence

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▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2014-102178).

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Received 13 March 2014
Revised 3 September 2014
Accepted 9 September 2014
Published Online First
17 September 2014

ABSTRACT

Objectives Chromium VI (hexavalent chromium, Cr(VI)) is an established cause of lung cancer, but its association with gastrointestinal cancer is less clear. The goal of this study was to examine whether the current human epidemiological research on occupationally inhaled Cr(VI) supports the hypothesis that Cr(VI) is associated with human stomach cancer.

Methods Following a thorough literature search and review of individual studies, we used meta-analysis to summarise the current epidemiological literature on inhaled Cr(VI) and stomach cancer, explore major sources of heterogeneity, and assess other elements of causal inference.

Results We identified 56 cohort and case–control studies and 74 individual relative risk (RR) estimates on stomach cancer and Cr(VI) exposure or work in an occupation associated with high Cr(VI) exposure including chromium production, chrome plating, leather work and work with Portland cement. The summary RR for all studies combined was 1.27 (95% CI 1.18 to 1.38). In analyses limited to only those studies identifying increased risks of lung cancer, the summary RR for stomach cancer was higher (RR=1.41, 95% CI 1.18 to 1.69).

Conclusions Overall, these results suggest that Cr(VI) is a stomach carcinogen in humans, which is consistent with the tumour results reported in rodent studies.

What this paper adds

- Few studies have investigated the possible association between exposure to hexavalent chromium (Cr(VI)) and cancers other than respiratory cancers.
- This meta-analysis includes many more results than previous meta-analyses of Cr(VI) exposure and stomach cancer.
- Studies that were positive for lung cancer, which may indicate higher exposures, produced a higher summary relative risk for stomach cancer than the full meta-analysis.
- Possible mechanisms by which Cr(VI) might induce carcinogenesis are biologically plausible.

INTRODUCTION

Inhalation of hexavalent chromium (Cr(VI)) has occurred in a number of industries, including leather tanning, chrome plating, cement work and stainless steel welding and manufacturing. Numerous studies have identified associations between lung cancer and inhaled Cr(VI) in occupational settings, and the International Agency for Research on Cancer has classified Cr(VI) as a group I carcinogen, based primarily on studies of chromate production, chromate pigment production and chromium electroplating involving high exposures.[1] Given that the lung is directly exposed to inhaled Cr(VI), it is not surprising that this organ is a target site. However, several studies suggest that Cr(VI) may also have carcinogenic effects in other internal organs, including the gastrointestinal tract.

The issue of whether Cr(VI) causes gastrointestinal cancer has implications not only in exposed workers, but also in people who ingest Cr(VI) in drinking water. In a recent survey of 35 large US cities, Cr(VI) was detected in 89% of the water systems tested.[2] All levels were below the US Environmental Protection Agency's (US EPA) regulatory standard for chromium of 100 μg/L. However, this standard is based on a health risk assessment over 20 years old and is for total chromium (Cr(VI) and Cr(III) combined), not the more toxic Cr(VI). Based at least partially on its possible carcinogenicity in the gastrointestinal tract, US EPA and others are in the process of evaluating the need for a new Cr(VI) drinking water standard. To date, however, the evidence linking Cr(VI) to gastrointestinal cancer comes primarily from animal studies and questions have been raised about their relevance to humans. Our goal was to evaluate whether evidence from human studies supports the hypothesis that Cr(VI) is a cause of gastrointestinal cancer.

We performed a meta-analysis of human studies of Cr(VI) and stomach cancer in order to provide a review of the current literature, evaluate causal inference, and assess potential sources of bias and heterogeneity. Although we examined several types of gastrointestinal cancer, including oesophageal, small intestine and colon cancer, initial analyses showed that the greatest number of studies and clearest associations were seen for stomach cancer; thus, stomach cancer is the focus of this meta-analysis.

METHODS

Databases including Medline and EMBASE were searched by two authors independently (RW and CS) for all epidemiological studies on Cr(VI) and stomach cancer (ICD-9 code 151). Searches included combinations of the keywords or phrases: stomach, gastric, gastrointestinal, cancer, chromium, leather, tanning, stainless steel, cement,

To cite: Welling R, Beaumont JJ, Petersen SJ, *et al. Occup Environ Med* 2015;**72**:151–159.

concrete, welding and metal plating. We also searched bibliographies of all publications included in the meta-analysis and all relevant review articles.

The meta-analysis included studies that provided relative risk (RR) estimates either specifically for Cr(VI) exposure or for workers in occupations known to be associated with Cr(VI) exposure, including chromate or chromium production and plating; leather work and tanning; Portland cement work; and stainless steel production, welding, polishing and grinding. Very few human studies have examined Cr(VI) in drinking water. Owing to this, and in order to maintain consistency by route of exposure, we excluded drinking water studies from the meta-analysis and review them in the discussion.

Only data published in peer-reviewed scientific journals were used, and government or industry reports were excluded. Studies of general foundry work and construction were also excluded because exposure is most likely low in many of these workers. Studies of asbestos cement workers and studies of shoe manufacturing, welding and metal plating that did not specifically evaluate chromium, stainless steel or leather workers were also excluded. Studies that reported no cases of stomach cancer were also excluded because of the inability to calculate a variance estimate, although this exclusion was evaluated in sensitivity analyses. In a few instances, a single paper reported separate RR estimates for men and women, or separate RR estimates for workers in different job categories or at different worksites. In these instances, we included all relative risks meeting our inclusion criteria when no clear overlap was present. We used Byar's approximation to estimate CIs in cohort studies in which they were not provided.[3] Each study was reviewed, and RR estimates and other information were abstracted independently by two authors (RW and CS).

Some studies gave RR estimates for several different metrics of Cr(VI) exposure, such as average exposure, peak exposure or exposure duration. In observational epidemiology, it is uncommon for all, or even most, studies to report findings using the same exposure metric. As a consequence, meta-analyses frequently involve combining data on different metrics. This meta-analysis is no different. When studies included RR estimates for different exposure metrics, we selected a single one in the following order: average exposure intensity, cumulative exposure and exposure duration. We chose this order a priori since analyses of other carcinogens have shown that exposure intensity may have a greater impact on cancer risks than exposure duration.[4 5] Several studies also reported relative risks for different levels of exposure (eg, high, medium, low). Since our goal was to evaluate whether an association exists, rather than defining exact dose–response relationships or exact low exposure risks, we selected the RR for the highest exposure category. If a true association exists, higher exposures will usually be associated with higher relative risks, and higher relative risks, all else being equal, have greater statistical power and are less likely to be due to bias or confounding than relative risks near 1.0.[6 7] The selected studies reported incidence rate ratios, ORs, standardised incidence ratios (SIRs) standardised mortality ratios (SMRs) or proportionate mortality ratios (PMRs). Some studies reported RR estimates adjusted for variables such as smoking, and these were used when available. For studies reporting data on incidence and mortality, incidence data were selected. Some studies reported results for different latency periods (ie, the time from first exposure to cancer diagnosis or death). Since many environmental agents can take decades to lead to detectable cancers, we chose the result for the longest latency, up to a maximum of 30+ years. For many cohort studies, publication of initial results was followed by updates, usually extending the period of follow-up. In these, we used the most recent publication giving the selected exposure metric or the largest number of cases. In a few publications of cement and leather work, Cr (VI) exposure was not specifically mentioned by the authors. These were included if the work processes described were those known to involve Cr(VI) exposure (eg, tanning or Portland cement). Inclusion and exclusion criteria are summarised in box 1.

In order to explore heterogeneity, we performed subgroup analyses on specific occupations, study design, incidence versus mortality, gender and country. Since it is possible that Cr(VI)

Box 1 Criteria for inclusion and exclusion of studies in the meta-analysis of Cr(VI) and stomach cancer

Inclusion criteria

- Epidemiological studies of stomach cancer and Cr(VI) exposure or work in an occupation known to be associated with Cr(VI) exposure including chromate or chromium production and plating; leather work and tanning; Portland cement work; and stainless steel production, welding, polishing and grinding
- Studies providing a relative risk estimate (including incidence rate ratios, ORs, standardised incidence ratios, standardised mortality ratios or proportionate mortality ratios) and the relative risk estimate's variance (or the data to calculate or estimate it)
- Published in peer-reviewed scientific journals
- If relative risk estimates are provided for different exposure metrics in a given study population, one metric was selected in the following order: average intensity, cumulative exposure, exposure duration
- If relative risk estimates are provided for different exposure levels in a given study population, the relative risk estimate for the highest level was selected
- Relative risk estimates adjusted for age, sex, smoking, diet and/or socioeconomic status were selected over unadjusted results
- If relative risk estimates for both stomach cancer mortality and incidence are reported in a given study population, the result for incidence was selected
- If relative risk estimates for different latency periods are reported in a given study population, the result for the longest latency period up to a period of 30+ years was selected
- For studies or relative risk estimates with overlapping populations, the most recent relative risk estimate with the selected exposure metric (eg, exposure intensity vs cumulative exposure; high vs low exposure level) or largest number of cases was selected

Exclusion criteria

- Unpublished data including government or industry reports
- Occupations such as painting, general foundry work, construction and shoe (non-leather) manufacturing
- Welding or metal plating studies that did not evaluate stainless steel or chromium work
- Studies involving work with asbestos cement
- Studies of all gastrointestinal cancers combined
- Studies of Cr(VI) in drinking water
- Studies reporting no cases of stomach cancer

exposures were too low in some studies to identify a true association, we conducted separate analyses of Cr(VI) and stomach cancer that included only studies in which elevated relative risks were identified for lung cancer, a well-established effect of high Cr(VI) exposure. In this analysis, since statistical significance is highly dependent on sample size (not just the presence of a true effect), we included all studies in which the RR of lung cancer was ≥1.5 regardless of statistical significance. Several subgroup and other analyses were done to evaluate potential confounding (eg, from smoking) and to compare our meta-analysis to other recent meta-analyses on this topic.

We calculated summary RR estimates using the fixed and random effects models.[8 9] We assessed heterogeneity among studies using the general variance-based method as described by Petitti.[10] Statistical heterogeneity was defined as present if the p value of the χ^2 test statistic was below 0.05. Some authors have suggested that because the random effects model incorporates between-study heterogeneity, it is more conservative than the fixed effects model.[10] However, a potential problem with the random effects model is that, unlike the fixed effects model, study weighting is not directly proportional to study precision. As a consequence, the random effects model gives relatively greater weight to smaller, less precise studies than the fixed effects model. This can sometimes lead to summary results that are less conservative than those produced using the fixed effects model.[11] To avoid this problem, we used the method presented by Shore *et al*[12] for our main results. In this method, the summary RR estimate is calculated by directly weighting individual studies by their precision, and between-study variability is only incorporated into calculations of variance (ie, the 95% CI). We assessed publication bias using funnel plots and Egger's and Begg's tests.[13 14] The funnel plot is a graphical presentation of each study's effect size versus an estimate of its precision. This plot can be asymmetric if smaller studies with results that are null or in the unexpected direction are not published. In Egger's test, asymmetry in the funnel plot is formally tested by performing a simple linear regression of the effect size divided by its SE on the inverse of the SE. In Begg's test, Kendall's rank order test is used to evaluate whether there is a correlation between the studies' effect sizes and their SEs. All calculations were performed using Microsoft Excel 2010 or STATA V.12 (College Station, Texas, USA) and all p values are two sided.

RESULTS

In total, 74 RR estimates, from 56 separate publications, met our inclusion criteria and were included in the meta-analysis (see online supplementalary table S1). Overall, 63 results (85%) were selected from cohort studies and 11 (15%) from case–control studies, and the meta-analysis involved studies that included 1399 cases of stomach cancer. Eighteen studies (24%) involved chromium production or plating, 23 (31%) involved cement workers, 17 (23%) involved leather work including tanning, four (5%) involved Cr(VI) or stainless steel welding, and 12 (16%) involved other occupations such as ferrochromium or other stainless steel work. Studies excluded from the meta-analysis and the reasons for their exclusion are shown in online supplementalary table S2.

The summary relative risk for all studies combined was 1.27 (95% CI 1.18 to 1.38; p<0.001; table 1). A forest plot summarising the results and weights applied to each study is shown in figure 1. Seventy per cent of the individual RR estimates in the overall analysis were >1.0. No single RR estimate received more than 14% of the total weight showing that no single study dominated the assigned weights. Summary relative risks were elevated for cement (1.29; 95% CI 1.17 to 1.42) and leather work (1.46; 95% CI 1.23 to 1.72) but not for welding (1.06; 95% CI 0.72 to 1.56). For studies of Cr(VI) production and plating, the summary RR was above 1.0 (1.25; 95% CI 0.97 to 1.60), but the 95% CI included 1.0. Summary relative risks were higher in case–control (1.55; 95% CI 1.16 to 2.07) than in cohort studies (1.26; 95% CI 1.16 to 1.37), males (1.30; 95% CI 1.20 to 1.41) than in females (1.08; 95% CI 0.65 to 1.81), and in studies of mortality (1.39; 95% CI 1.24 to 1.57) than in studies of incidence (1.17; 95% CI 1.07 to 1.29), but differences were only statistically significant when studies of incidence and mortality were compared (p=0.02). In the studies that identified Cr(VI)-associated lung cancer relative risks ≥1.5 (the proxy measure for probable higher exposure), the stomach cancer summary relative risk was 1.41 (95% CI 1.18 to 1.69; p<0.001) in all studies (figure 2) and 1.36 (95% CI 1.01 to 1.81; p=0.04) in Cr(VI) production and plating studies. The variables adjusted or stratified for in each study are shown in online supplementalary table S1. Only nine studies adjusted for some indicator of smoking, diet or socioeconomic status (SES), and the RR for these studies was 1.31 (1.01 to 1.69). Results in almost all analyses were similar regardless of whether the random effects model or the fixed effects model with the correction for between-study variability was used. For example, in the meta-analysis of all studies combined, the results using these two models were 1.28 (95% CI 1.16 to 1.41) and 1.27 (95% CI 1.18 to 1.38), respectively.

We saw no evidence of asymmetry in the funnel plot of all studies combined (figure 3), or in the funnel plots of each subgroup analysis (not shown). Egger's and Begg's tests also showed no consistent evidence of publication bias. For example, in the all studies combined analysis, the bias coefficient for Egger's test was 0.16 (p=0.55). In the analysis of all studies with lung cancer relative risks ≥1.5, the Egger's bias coefficient was 0.22 (p=0.64).

DISCUSSION

The overall summary relative risk of 1.27 (95% CI 1.18 to 1.38, p<0.001) provides evidence that Cr(VI) inhalation increases the risk of stomach cancer. The narrow CI, excluding 1.0, and the low p value provide evidence that this result is not due to chance. A major finding here is that the summary relative risk for stomach cancer was elevated in those studies in which Cr(VI)-associated lung cancer relative risks were also elevated, both in the analysis of all job categories combined (summary relative risk=1.41; 1.18 to 1.69; p<0.001) and in the analysis of chromium production and plating studies (summary relative risk=1.36; 1.01 to 1.81; p=0.04). Since Cr(VI) exposures, in general, are likely to be higher in those studies where increases in lung cancer were found, the presence of a positive lung cancer finding may be a valid surrogate for high Cr(VI) exposure. As such, these latter findings provide additional evidence that the positive findings seen in this meta-analysis are due to Cr(VI).

Statistically significant heterogeneity was seen in the meta-analysis of all studies combined (χ^2=139.6, p<0.001), and the CIs of several studies did not include the summary relative risk. However, we did not see statistically significant heterogeneity in most other analyses performed, including the analyses of studies with elevated lung cancer risks (χ^2=22.6, p=0.31). In observational epidemiology, study designs, populations, methods of assessing exposure and outcome, and statistical analyses are rarely, if ever, the same. As such, some variation across study results is expected. The fact that statistical heterogeneity

Table 1 Results of the meta-analysis of Cr(VI) exposure and stomach cancer

	No. of cases	No. of results*	Fixed effects model			Shore adjusted CI		Random effects model			Heterogeneity		
			RRs	CI_L	CI_U	CI_L	CI_U	RRs	CI_L	CI_U	χ^2	p Value	I^2 (%)
All studies	1399	74	1.27	1.20	1.35	1.18	1.38	1.28	1.16	1.41	139.6	<0.001	47.7
Job type													
Production or plating	113	18	1.25	1.02	1.53	0.97	1.60	1.25	0.95	1.65	25.9	0.08	34.4
Cement work	903	23	1.29	1.20	1.38	1.17	1.42	1.37	1.21	1.54	42.7	0.005	48.4
Leather work	237	17	1.46	1.27	1.67	1.23	1.72	1.33	1.08	1.64	23.6	0.10	32.1
Welding	31	4	1.06	0.72	1.55	0.72	1.56	1.08	0.72	1.56	3.0	0.39	0.8
All other	115	12	0.96	0.79	1.17	0.69	1.33	1.12	0.78	1.60	31.7	<0.001	65.3
Study design													
Case–control	130	11	1.55	1.16	2.07	NA	NA	NA	NA	NA	8.2	0.61	NA
Cohort	1269	63	1.26	1.19	1.34	1.16	1.37	1.25	1.13	1.39	129.6	<0.001	52.2
PMR studies	353	10	1.60	1.43	1.78	1.43	1.78	1.60	1.43	1.79	9.3	0.41	2.9
SMR studies	293	32	1.14	1.00	1.29	0.95	1.36	1.17	0.96	1.43	61.5	<0.001	49.6
Other	623	21	1.16	1.07	1.26	1.04	1.29	1.17	1.03	1.34	33.6	0.03	40.4
Incidence vs mortality													
Incidence studies	738	30	1.17	1.09	1.27	1.07	1.29	1.21	1.07	1.36	41.1	0.07	29.4
Mortality studies	661	44	1.39	1.28	1.51	1.24	1.57	1.32	1.14	1.53	89.8	<0.001	52.1
Gender													
Males only	1258	59	1.30	1.22	1.38	1.20	1.41	1.33	1.19	1.47	112.8	<0.001	48.6
Females only	23	6	1.08	0.72	1.63	0.65	1.81	1.14	0.61	2.11	8.0	0.16	37.4
Lung cancer RR ≥1.5													
All studies	170	21	1.41	1.19	1.67	1.18	1.69	1.41	1.16	1.71	22.6	0.31	11.4
Production or plating	78	13	1.36	1.06	1.73	1.01	1.81	1.31	0.96	1.80	16.9	0.15	29.0
Country, region													
Europe	859	48	1.16	1.08	1.25	1.06	1.27	1.20	1.06	1.35	78.2	0.003	39.9
North America	419	16	1.50	1.36	1.66	1.31	1.72	1.47	1.24	1.75	27.9	0.02	46.3
Asia	121	10	1.34	1.10	1.62	1.03	1.74	1.31	0.94	1.81	16.7	0.05	46.1

*Some publications provided two or more results that met the inclusion criteria but did not involve overlapping populations (eg, separate results for males and females).
CI_L, lower 95% CI; CI_U, upper 95% CI; I^2, the percentage of total variation across studies due to heterogeneity rather than chance; NA, not applicable (Shore adjusted CI (applied to the fixed effects RR) and the random effects model are only used when the χ^2 heterogeneity statistic is greater than the number of individual study results minus one); PMR, proportionate mortality ratio; RR, relative risk estimate; RRs, summary relative risk; SMR, standardised mortality ratio; χ^2, χ^2 heterogeneity statistic.

was not present in most of the subgroup analyses we performed highlights the overall consistency in many of these results. This consistency is supported by the fact that the large majority of individual RR estimates are >1.0. For example, in the analysis of all studies combined, 52 of 74 RR estimates are >1.0. The probability that this would occur by chance alone is 0.0002.

In this meta-analysis, as in almost all meta-analyses of epidemiological data, studies using different exposure metrics (eg, average exposure, exposure duration) were combined. The use of different metrics can potentially affect summary relative risks, but the likely direction is towards the null, not towards a false positive result. The reason for this is that if Cr(VI) is truly associated with stomach cancer, some metrics are likely to be more strongly associated with stomach cancer than others, and including less relevant metrics would dilute summary relative risks towards 1.0. If every study had reported data on the same single metric that was most strongly associated with stomach cancer, it is likely that the true summary relative risks would be even higher than those reported here. A similar effect could have resulted from our including studies with different levels of Cr (VI) exposure or different forms of Cr(VI). That is, if a true association exists, the inclusion of studies in which Cr(VI) exposures were relatively low would most likely bias results towards a summary relative risk of 1.0, not towards a false association. Previous research suggests that the absorption fraction is higher for soluble chromium compounds than for insoluble forms.[15] Few of the studies used in this meta-analysis provided details on Cr(VI) solubility. If less soluble forms are less carcinogenic, including studies involving these less soluble forms would dilute any associations due to soluble Cr(VI) to the null. It is most likely that all studies had at least some errors in assessing exposure. However, since they all assessed exposure using the same methods in people with and without cancer, this misclassification was most likely non-differential and also most likely biased findings towards the null.

Another factor that can potentially impact results is confounding. Most studies controlled for age and sex, but few adjusted for other factors (see online supplementalary table S1). The known risk factors for stomach cancer include older age; male sex; chronic gastritis and polyps; *Helicobacter pylori* infection, certain genetic abnormalities; lifestyle factors such as smoking, alcohol and diet (low fruit and vegetable intake or high intake of salted, smoked or nitrate-preserved foods); and coal mining, nickel refining, rubber and timber processing, and possibly exposure to asbestos.[16] Importantly, confounding factors must typically be associated with both Cr(VI) and stomach cancer, and these associations must be fairly strong to cause important confounding.[17] Some factors are most likely too rare (eg, genetic disorders, family history) or not associated strongly enough with Cr(VI) exposure (eg, *Helicobacter pylori,* a major risk factor for stomach cancer) to cause important confounding. Some cement products contain asbestos.[18] Although

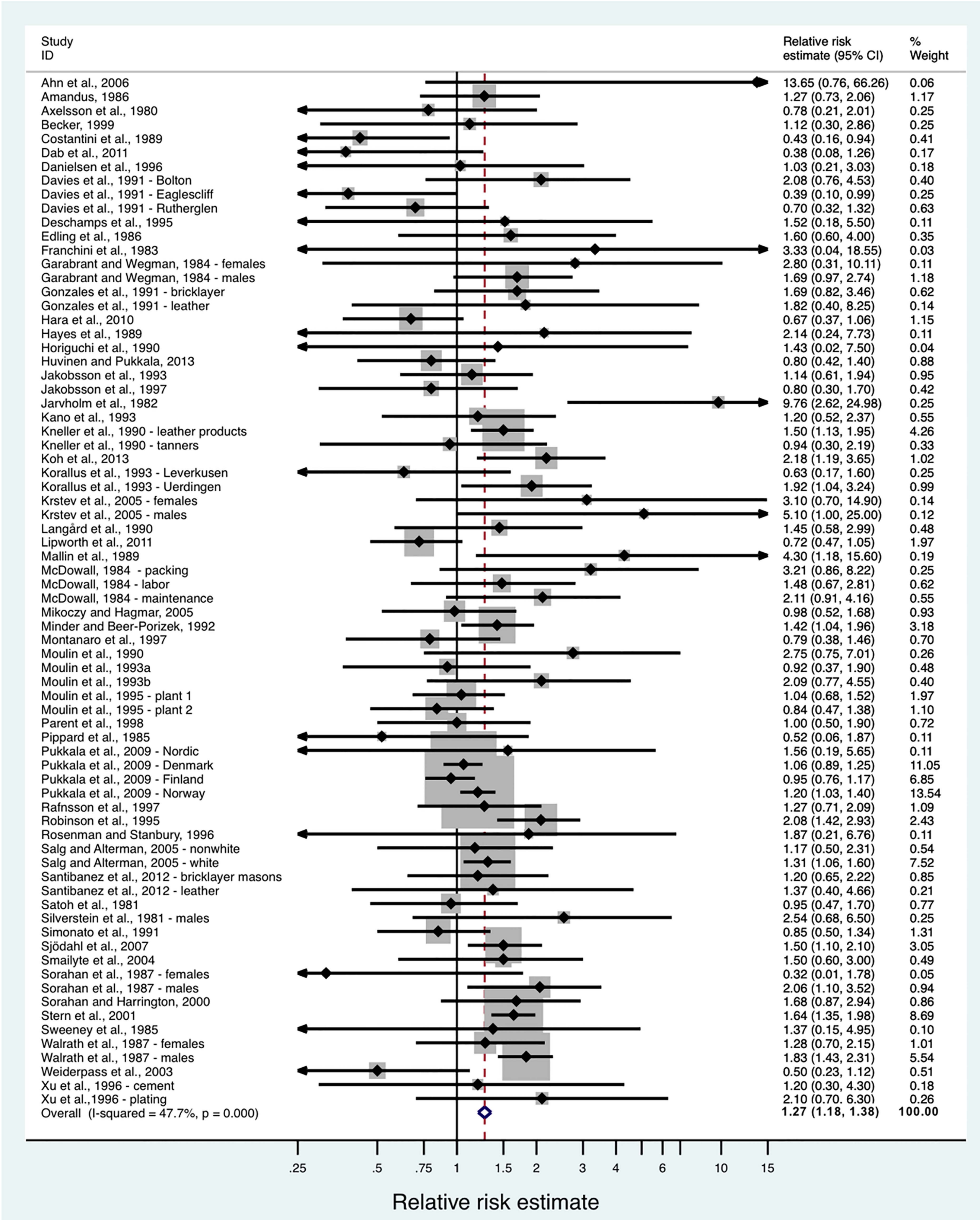


Figure 1 Forest plot of studies included in the meta-analysis of Cr(VI) and stomach cancer: all studies combined.

this could have potentially confounded results in cement workers, we excluded studies specifically in asbestos cement workers. In addition, high asbestos exposures were not known to have occurred in the other occupational categories assessed and summary relative risk estimates in cement workers were similar to those in several other job categories. A few studies adjusted for smoking, diet or SES, but the impacts of these adjustments are inconsistent, with an increase in relative risk

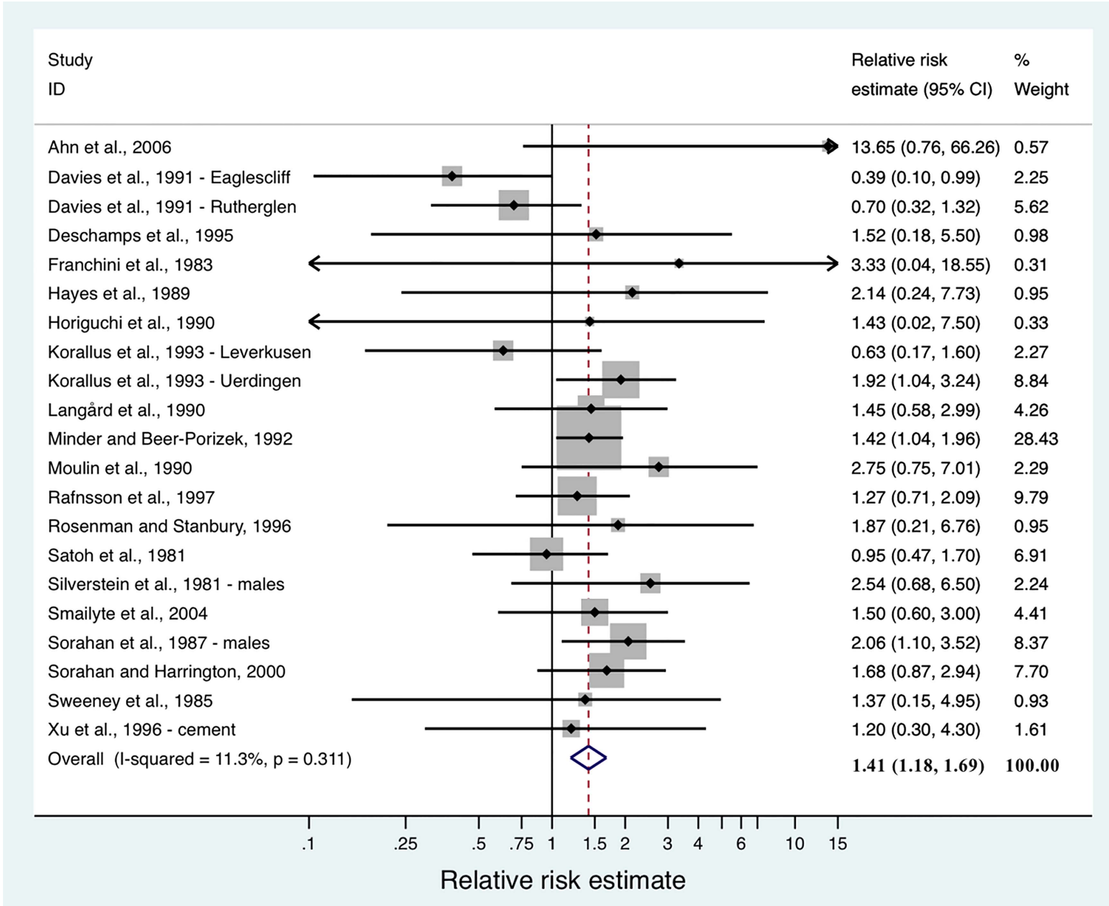
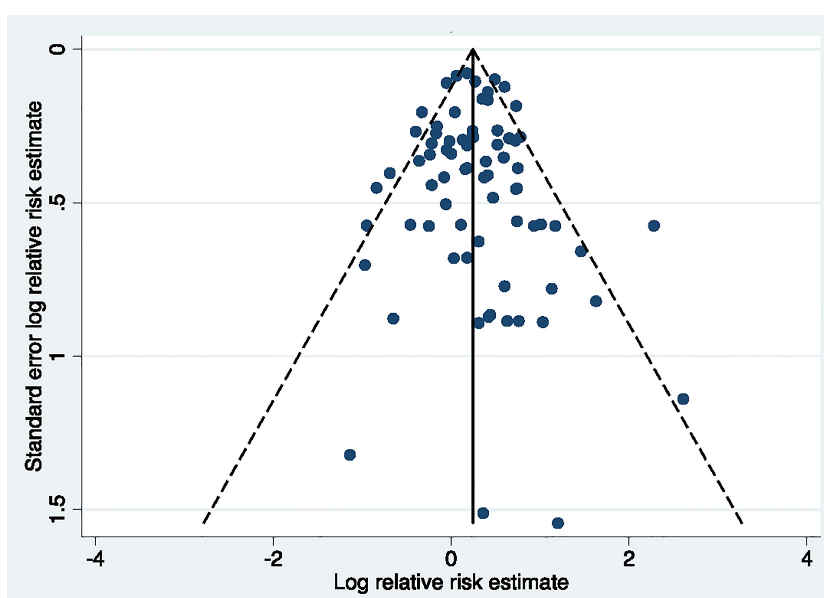


Figure 2 Forest plot of studies included in the meta-analysis of Cr(VI) and stomach cancer: only studies with lung cancer relative risk estimates ≥1.5.

estimates in some studies but a decrease in others. Axelson has shown that confounding by smoking may cause relative risks as high as 1.5 for lung cancer in occupational studies.[17] However, smoking-associated relative risks for stomach cancer are much lower than those for lung cancer, so the impact of smoking as a confounder is likely to be much less in studies of stomach cancer than in studies of lung cancer. Using the Axelson methods, and data on smoking-stomach cancer relative risks (about 1.5),[19] we estimated that confounding by smoking is unlikely to cause a relative risk >1.1 in occupational studies of stomach cancer.

The higher summary relative risks we identified for studies with positive lung cancer findings may indicate higher Cr(VI) exposure or it may indicate greater confounding by smoking. However, in a meta-analysis of those studies with lung cancer relative risk estimates ≥1.5 that provided data on non-malignant

Figure 3 Funnel plot of studies included in the meta-analysis of Cr(VI) and stomach cancer: all studies combined.



respiratory disease (which is also caused by smoking), the summary RR for non-malignant respiratory disease was not elevated (RR=1.00; 95% CI 0.71 to 1.40; n=9; median relative risk estimate=0.91), providing evidence that smoking did not confound our results.

Other potential biases include the healthy worker effect and biases related to the inclusion of case-control studies (eg, recall bias or biased selection of controls). Although the summary relative risk for case-control studies was higher than that for cohort studies, the difference between these two was not statistically significant (p=0.18). The healthy worker effect would primarily affect studies comparing exposed workers to the general population (eg, SMRs) and this effect would most likely bias SMRs downwards. Although the extent of this bias here is unknown, evidence of the healthy worker effect has been reported for several different cancer types and in a number of different occupational settings.[20–22]

In this meta-analysis, neither visual inspection of the funnel plot nor Egger's or Begg's test showed evidence of publication bias, although the funnel plots are open to subjective interpretation, and Egger's and Begg's tests can be affected by factors other than this bias. Overall, while we did not see clear evidence of this bias, it is potentially an issue in any meta-analysis.

Two previous meta-analyses of Cr(VI) and stomach cancer have been published. In Gatto *et al*,[23] the summary relative risk involving 29 studies was 1.09 (95% CI 0.93 to 1.28). Similar to our meta-analysis, the Gatto *et al* meta-analysis included studies of chromium production, cement and leather workers (see online supplementalary table S3), but the individual study results are presented only in figure form, making direct comparisons with our meta-analysis difficult. One clear difference is our inclusion of many more results (74 vs 29), particularly from cement and leather workers, but also from studies of stainless steel and chromium plating workers. The summary relative risk using the individual RR estimates we abstracted for the 29 studies used by Gallo *et al* was somewhat lower than our meta-analysis of all 74 studies (1.22; 95% CI 1.05 to 1.41 vs 1.27; 95% CI 1.18 to 1.38). Another difference may have been our use of RR estimates from subgroups that are more likely to be highly exposed (eg, exposure duration ≥10 years), although direct comparisons are difficult for the reason given above. We also excluded five studies used by Gatto *et al* because they were unpublished, involved painters or foundry workers with uncertain exposure,[24 25] or overlapped with the already included studies.[26 27] However, adding these five excluded studies to our meta-analysis of all studies caused little change (1.27; 95% CI 1.18 to 1.37) since most of these studies only received a small amount of the total weighting. In a meta-analysis by Cole and Rodu, the authors reported that the summary relative risk between Cr(VI) and stomach cancer was lower in studies that adjusted for SES than in studies that did not adjust for this variable (RR=0.82 95% CI 0.69 to 0.96 vs RR=1.37; 95% CI 1.23 to 1.53), and concluded that SES was responsible for any apparent association seen between chromium exposure and stomach cancer.[28] However, one of the authors' criteria for these analyses was that studies "that were negative or essentially negative with respect to chrome exposure were included with the papers that were controlled [for SES]." In our evaluation of the studies used by these authors in their SES-controlled analysis, we were unable to find any mention of adjustments for SES (or any related variable) in 13 of the 14 studies (93%) included. Thus, the subgroup analysis titled 'SES-controlled' appears to be a misnomer, and instead reflects their criterion of studies that were 'negative or essentially negative with respect to chrome exposure.'

A variety of data support the biological plausibility of our results. Cr(VI) is a well-documented human lung carcinogen, and there is abundant evidence that airborne Cr(VI) is systemically absorbed. For example, studies in a variety of occupational settings have shown that Cr(VI) exposed workers have elevated blood or urine chromium levels compared to unexposed controls.[29 30] These data show that airborne Cr(VI) not only reaches the lungs, but that at least some of it is also internally absorbed and therefore most likely distributed to other organs. This systemic absorption may occur directly through the lungs, or particulates containing Cr(VI) that settle in the trachea and bronchi may be cleared by mucociliary action and then swallowed.[31] This swallowed Cr(VI) would come into direct contact with the stomach mucosa. Once in the stomach, ingested Cr(VI) is reduced by the acidic environment of the stomach to Cr(III), which is poorly absorbed. However, this reduction may not be complete, and most studies suggest that at least some ingested Cr(VI) escapes gastric reduction and is absorbed.[32] In studies in rodents, administration of Cr(VI) in drinking water has resulted in statistically significant increases in benign and malignant stomach tumours (combined),[31 33] papillomas or carcinomas (combined) of the oral cavity, and adenomas or carcinomas (combined) of the small intestine.[34] In humans, Beaumont *et al*[35] reported a RR of 1.82 (95% CI 1.11 to 2.91) for stomach cancer mortality in an area where Cr(VI) pollution from a ferrochromium factory caused widespread Cr(VI) contamination of nearby drinking water sources, although issues of dose–response and other potential biases have been debated.[36 37] In an ecological study in a province in Greece with Cr-contaminated water, SMRs were elevated for liver (SMR=11.0; 95% CI 4.05 to 24.0) and lung cancer (SMR=1.45; 95% CI 1.00 to 2.03).[38] The SMR for stomach cancer was above 1.0 but was not statistically significant (SMR=1.21; 95% CI 0.44 to 2.63).

The exact mechanisms by which Cr(VI) causes cancer are unknown, but evidence for several possible mechanisms exists. These include indirect and direct effects on DNA, epigenetic effects, gene regulation effects and direct cytotoxicity. Cr(VI) readily enters cells via active transport through anion channels and intracellular reduction follows, producing reactive intermediate Cr valences, Cr(V) and Cr(IV) and ultimately Cr(III), which is DNA-reactive. Reactive oxygen species, oxygen radicals and other reactive molecules generated during this reduction process are postulated to have genotoxic effects as well.[39–46] In vitro studies have revealed that Cr(VI)-induced mutations can be generated through different types of DNA damage such as interstrand crosslinks, DNA-protein crosslinks and DNA adducts, as well as single-strand and double-strand DNA breaks.[41 47 48] Studies of Cr(VI)-exposed tannery workers show evidence of genotoxic effects including chromosomal aberration, micronuclei formation, DNA breaks and higher levels of DNA damage in lymphocytes as determined by a comet assay.[49–52] In a study of chrome plating workers, chromium-induced DNA damage as measured by three comet assay components was significantly increased in exposed workers.[29] As a whole, these studies, along with the positive animal bioassays discussed above,[34] all provide biological plausibility for the findings of this meta-analysis.

CONCLUSIONS

The results of this meta-analysis suggest that Cr(VI) exposure is associated with increased risks of stomach cancer. An important feature of this study is that summary relative risks were elevated in a number of different occupational settings and in the subgroup of studies in which lung cancer risks were also elevated. As with almost all meta-analyses, confounding and publication bias cannot be entirely ruled out. Few studies adjusted for some of the known risk factors of stomach cancer, including smoking, although an analysis of the potential magnitude of confounding from smoking suggests that this was unlikely to have caused the associations we observed. The exact relevance of our findings to Cr(VI) in drinking water is unknown. Differences in reduction and absorption patterns across the different routes of exposure could potentially impact toxicity. For example, the acidic environment of the stomach converts some ingested Cr(VI) to the poorly absorbed Cr(III), although several studies have shown that this process is not complete and some ingested Cr(VI) is absorbed.[53 54] Another difference is that drinking water exposures are generally much lower than occupational exposures, and this meta-analysis cannot be used to define exact dose–response relationships or low exposure risks. However, owing to the difficulties associated with studying lower exposures in human populations (a greater probability of bias, confounding and insufficient power),[6 37 55] chemical risk assessments and regulatory standards are frequently based on higher exposure occupational studies like the ones used here.[56] Another consideration is that drinking water exposures may cause greater toxicity because they can take place over the long term (eg, lifetime) and are more likely to occur at particularly susceptible life stages (eg, in fetuses, children and pregnant women) than exposures occurring at work. Thus, despite the different route and magnitude of exposure, our findings could have some relevance to efforts to regulate Cr(VI) in water in that they provide evidence that Cr(VI) is a cause of cancer in the human gastrointestinal tract and support the animal and limited human data linking ingested Cr(VI) to stomach cancer. US EPA and some states are considering regulating Cr(VI) in drinking water based on its potential carcinogenicity in the gastrointestinal tract, and California has recently established the first drinking water standard for Cr(VI) in the USA. The results of this study support such efforts.

Contributors CS, JJB, RW and GVA conceptualised the project and designed the overall study methods; CS and RW performed the literature searches and the statistical analyses; CS, JJB, RW, SJP and GVA assisted in the interpretation of results and writing.

Disclaimer The views expressed are those of the authors and do not necessarily represent those of the Office of Environmental Health Hazard Assessment, the California Environmental Protection Agency or the state of California.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplemental Table 1. Studies included in the meta-analysis of Cr(VI) and stomach cancer

Author	Location	Number of cases[a]	Study design	Effect measure	Industry or occupation	Relative risk estimate (95% CI)	Adjustments other than age and sex
Ahn et al., 2006[1]	Korea	2	Cohort	SRR	Iron and steel production; stainless steel production work, 10-35 years duration	13.65 (0.76-66.26)	Employment duration, and work in other processes
Amandus, 1986[2]	US	16	Cohort	SMR	Non-asbestos cement plants; > 20 years tenure in cement plant, ≥ 20 years latency	1.27 (0.73-2.06)	
Axelsson et al., 1980[3]	Sweden	4	Cohort	SMR	Ferrochromium production	0.78 (0.21-2.01)	
Becker, 1999[4]	Germany	4	Cohort	SMR	Arc welders; effective welding period > 25% of work day	1.12 (0.30-2.86)	
Costantini et al., 1989[5]	Italy: Tuscany	6	Cohort	SMR	Leather tanning; male tanners	0.43 (0.16-0.94)	
Dab et al., 2011[6]	France	3	Cohort	SMR	Cement production; employed ≥ 1 year from 1990 to 2005	0.38 (0.08-1.26)	
Danielsen et al., 1996[7]	Norway	3	Cohort	SIR	Boiler welders; ever welding on stainless steel	1.03 (0.21-3.03)	
Davies et al., 1991[8]	UK: Bolton	6	Cohort	SMR	Chromate production; early and pre-process change workers	2.08 (0.76-4.53)	Social class and area
Davies et al., 1991[8]	UK: Eaglescliff	4	Cohort	SMR	Chromate production; early and pre-process change workers	0.39 (0.10-0.99)	Social class and area
Davies et al., 1991[8]	UK: Rutherglen	9	Cohort	SMR	Chromate production; early and pre-process change workers	0.70 (0.32-1.32)	Social class and area
Deschamps et al., 1995[9]	France	2	Cohort	SMR	Chromate pigment production	1.52 (0.18-5.50)	
Edling et al., 1986[10]	Sweden	6	Case-control	OR	Leather tanning; occupation "tanner" or "tannery worker"	1.6 (0.6-4.0)	
Franchini et al., 1983[11]	Italy	1	Cohort	SMR	Metal plating; "hard" plating workers	3.33 (0.04-18.55)	
Garabrant & Wegman, 1984[12]	US: Massachusetts	2	Cohort	PMR	Leather workers; female	2.80 (0.31-10.11)	
Garabrant & Wegman, 1984[12]	US: Massachusetts	16	Cohort	PMR	Leather workers; male	1.69 (0.97-2.74)	

Gonzalez et al., 1991[13]	Spain: Catalonia	41	Case-control	OR	Brick masons; exposed to dust	1.69 (0.82-3.46)	Education, SES, and fruit and vegetable intake
Gonzalez et al., 1991[13]	Spain: Catalonia	5	Case-control	OR	Leather workers; exposed to dust	1.82 (0.40-8.25)	Education, SES, and fruit and vegetable intake
Hara et al., 2010[14]	Japan: Tokyo	14	Cohort	SMR	Chrome plating; male platers, mean age at baseline = 49.5 years	0.67 (0.37-1.06)	
Hayes et al., 1989[15]	New Jersey	2	Cohort	SMR	Chromate pigment production; ≥ 10 years of exposure to chromate dusts	2.14 (0.24-7.73)	Race
Horiguchi et al., 1990[16]	Japan: Osaka	2	Cohort	SMR	Chrome plating; workers employed ≥ 10 years	1.43 (0.02-7.50)	
Huvinen & Pukkala, 2013[17]	Finland	12	Cohort	SIR	Ferrochromium and stainless steel production workers; chromite mine workers	0.80 (0.42-1.40)	
Jakobsson et al., 1993[18]	Sweden	13	Cohort	SIR	Cement production; men employed ≥ 1 year, ≥ 15 years since start of employment	1.14 (0.61-1.94)	
Jakobsson et al., 1997[19]	Sweden	8	Cohort	SIR	Stainless steel grinding; workers diagnosed ≥ 15 years after start of employment	0.8 (0.3-1.7)	
Jarvholm et al., 1982[20]	Sweden	4	Cohort	SMR	Steel polishing; men who had worked ≥ 5 years as polishers, latency period ≥ 10 years	9.76 (2.62-25.0)	
Kano et al., 1993[21]	Japan	8	Cohort	SMR	Chromate pigment production	1.20 (0.52-2.37)	
Kneller et al., 1990[22]	China: Shanghai	55	Cohort	SIR	Leather products workers	1.50 (1.13-1.95)	
Kneller et al., 1990[22]	China: Shanghai	5	Cohort	SIR	Leather tanning; tanners, feltmongers, and pelt dressers	0.94 (0.30-2.19)	
Koh et al., 2013[23]	Korea	14	Cohort	SIR	Cement industry workers; high exposure group	2.18 (1.19-3.65)	
Korallus et al., 1993[24]	Germany: Leverkusen	4	Cohort	SMR	Chromate production; workers exposed ≥ 1 year	0.63 (0.17-1.60)	
Korallus et al., 1993[24]	Germany: Uerdingen	12	Cohort	SMR	Chromate production; workers exposed ≥ 1 year	1.92 (1.04-3.24)	
Krstev et al., 2005[25]	Poland: Warsaw	4	Case-control	OR	Leather workers; females	3.10 (0.70-14.9)	Education, smoking, and number of jobs

Krstev et al., 2005[25]	Poland: Warsaw	8	Case-control	OR	Leather workers; males	5.10 (1.0-25.0)	Education, smoking, and number of jobs
Langård et al., 1990[26]	Norway	7	Cohort	SIR	Ferrochromium production; workers first employed before 1960	1.45 (0.58-2.99)	
Lipworth et al., 2011[27]	US: California	26	Cohort	SMR	Aircraft manufacturing workers; exposed to chromates	0.72 (0.47-1.05)	Race
Mallin et al., 1989[28]	US: Illinois	9	Case-control	OR	Brickmasons and stonemasons; white males	4.30 (1.18-15.6)	Blue vs. white collar job
McDowall, 1984[29]	UK: North Kent	4	Cohort	SMR	Cement production-packing; employed in 1939 in occupation identified as cement manufacture	3.21 (0.86-8.22)	
McDowall, 1984[29]	UK: North Kent	9	Cohort	SMR	Cement production-other laborers; employed in 1939 in occupation identified as cement manufacture	1.48 (0.67-2.81)	
McDowall, 1984[29]	UK: North Kent	8	Cohort	SMR	Cement production-maintenance; employed in 1939 in occupation identified as cement manufacture	2.11 (0.91-4.16)	
Mikoczy & Hagmar, 2005[30]	Sweden	13	Cohort	SIR	Leather tanning; workers employed ≥ 1 year, 20 year latency period	0.98 (0.52-1.68)	
Minder & Beer-Porizek, 1992[31]	Switzerland	52	Cohort	SMR	Masons; males, mortality 1979-1982	1.42 (1.04-1.96)	
Montanaro et al., 1997[32]	Italy: Genoa	10	Cohort	SMR	Leather tanning; male and female workers employed ≥ 6 months, employed 1955-1988	0.79 (0.38-1.46)	
Moulin et al., 1990[33]	France	4	Cohort	SMR	Ferrochromium and stainless steel production; workers employed ≥ 1 year in ferrochromium or stainless steel workshops	2.75 (0.75-7.01)	
Moulin et al., 1993a[34]	France	7	Cohort	SMR	Ferrochromium and stainless steel production; workers employed ≥ 3 years in production workforce	0.92 (0.37-1.90)	
Moulin et al., 1993b[35]	France	6	Cohort	SMR	Stainless steel and mild steel welding; men employed as welders ≥ 1 year	2.09 (0.77-4.55)	
Moulin et al., 1995[36]	France: Plant 1	26	Cohort	SMR	Stainless steel production; males	1.04 (0.68-1.52)	
Moulin et al., 1995[36]	France: Plant 2	15	Cohort	SMR	Stainless steel production; males	0.84 (0.47-1.38)	
Parent et al., 1998[37]	Canada: Montreal	11	Case-control	OR	Leather workers; employed ≥ 10 years	1.0 (0.5-1.9)	Birthplace, education, smoking, and proxy interview

Pippard et al., 1985 [38]	UK	2	Cohort	SMR	Leather tanning; male chrome tanners	0.52 (0.06-1.87)	
Pukkala et al., 2009[39]	Denmark	140	Cohort	SIR	Bricklayers; males, 1961-2005	1.06 (0.89-1.25)	
Pukkala et al., 2009[39]	Finland	89	Cohort	SIR	Bricklayers; males, 1961-2005	0.95 (0.76-1.17)	
Pukkala et al., 2009[39]	Norway	168	Cohort	SIR	Bricklayers; males, 1961-2005	1.20 (1.03-1.40)	
Pukkala et al., 2009[39]	Scandinavia	2	Cohort	SIR	Bricklayers; females, 1961-2005	1.56 (0.19-5.65)	
Rafnsson et al., 1997[40]	Iceland	15	Cohort	SIR	Masons; men with a 30 year lag between finishing vocational training and counting person-years	1.27 (0.71-2.09)	
Robinson et al., 1995[41]	US	32	Cohort	PMR	Brickmasons; white men	2.08 (1.42-2.93)	
Rosenman & Stanbury, 1996[42]	US: New Jersey	2	Cohort	PMR	Chromium smelter; former workers employed > 20 years	1.87 (0.21-6.76)	
Salg & Alterman, 2005[43]	US	8	Cohort	PMR	Bricklayers: non-white; male union members who died between 1986 and 1991	1.17 (0.50-2.31)	
Salg & Alterman, 2005[43]	US	94	Cohort	PMR	Bricklayers: white; male union members who died between 1986 and 1991	1.31 (1.06-1.60)	
Santibañez et al., 2012[44]	Spain: Alicante	29	Case-control	OR	Bricklayers and stonemasons; men who worked ≥ 1 year in the same occupation	1.20 (0.65-2.22)	Province, education, alcohol, smoking, fruit and vegetable intake, and total energy intake
Santibañez et al., 2012[44]	Spain: Alicante	7	Case-control	OR	Pelt, leather, shoemaking; men who worked ≥ 1 year in the same occupation	1.37 (0.40-4.66)	Province, education, alcohol, smoking, fruit and vegetable intake, and total energy intake
Satoh et al., 1981[45]	Japan: Tokyo	11	Cohort	SMR	Chromium production; men employed ≥ 1 year between 1918 and 1975	0.95 (0.47-1.70)	
Silverstein et al., 1981[46]	US: Michigan	4	Cohort	PMR	Die casting and electroplating including chrome plating; white males, employees and retirees with ≥ 10 years of service in the plant	2.54 (0.68-6.50)	
Simonato et al., 1991[47]	Scandinavia	18	Cohort	SIR	Stainless steel welding; cohort included mild steel, stainless steel and shipyard welders	0.85 (0.50-1.34)	
Sjödahl et al., 2007[48]	Sweden	37	Cohort	IRR	Construction workers; males, high exposure to cement dust	1.5 (1.1-2.1)	Smoking and body mass

Smailyte et al., 2004[49]	Lithuania	6	Cohort	SIR	Cement production; workers with cumulative exposure > 130.2 mg/m^3 cement dust	1.5 (0.6-3.0)	
Sorahan et al., 1987[50]	UK: Midlands	1	Cohort	SMR	Chrome plating: females; first employment in chrome bath work	0.32 (0.01-1.78)	
Sorahan et al., 1987[50]	UK: Midlands	13	Cohort	SMR	Chrome plating: males; first employment in chrome bath work	2.06 (1.10-3.52)	
Sorahan & Harrington, 2000[51]	UK: Yorkshire, 54 plants	12	Cohort	SMR	Chrome plating; male platers and others exposed to chromic acid, employed ≥ 3 consecutive months	1.68 (0.87-2.94)	
Stern et al., 2001[52]	US	110	Cohort	PMR	Cement masons; members of Operative Plasterers' and Cement Masons' International Association	1.64 (1.35-1.98)	Race
Sweeney et al., 1985[53]	US: New York City	2	Cohort	SMR	Leather tanning; white male and female retired fur dressers	1.37 (0.15-4.95)	
Walrath et al., 1987[54]	US: New York State	14	Cohort	PMR	Leather workers; female	1.28 (0.70-2.15)	Race
Walrath et al., 1987[54]	US: New York State	71	Cohort	PMR	Leather workers; male	1.83 (1.43-2.31)	Race
Weiderpass et al., 2003[55]	Finland	unknown	Cohort	RR	All occupations; women, workers with medium to high levels of exposure to chromium	0.50 (0.23-1.12)	Stratified by social class and adjusted for job turnover rate
Xu et al., 1996[56]	China	4	Case-control	OR	Cement workers; employed at plant ≥ 15 years	1.2 (0.3-4.3)	Smoking, education, fruit and vegetable intake, stomach disease, and family history
Xu et al., 1996[56]	China	6	Case-control	OR	Metal plating (includes chromium exposure); employed at plant ≥ 15 years	2.1 (0.7-6.3)	Smoking, education, fruit and vegetable intake, stomach disease, and family history

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; PMR, proportional mortality ratio; RR, relative risk; SES, socioeconomic status; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio

[a] The number of exposed cases of stomach cancer

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Supplemental Table 2. Studies excluded from the meta-analysis

Author(s)	Publication year	Reference	Occupation/exposure	Reason for exclusion
Acquavella & Lee	1991	*J Occup Med* **33**(8):896-900	Metal components manufacturing	Refers to stainless steel, but Cr(VI) exposure is unclear.
Ahn et al.	2010	*J Korean Med Sci* **25**(12):1733-41	Foundry workers	Unclear Cr(VI) exposure.
Alderson et al.	1981	*Br J Ind Med* **38**(2):117-24	UK chromate producers	Overlap with more recent Davies et al., 1991.
Andersen et al.	1999	*Scand J Work Environ Health* **25 Suppl 2**:1-116	Bricklayers	Overlap with more recent Pukkala et al., 2009.
Aragones et al.	2002	*Occup Environ Med* **59**(5):329-37	Metal plating	Unclear Cr(VI) exposure.
Beaumont & Weiss	1980	*Am J Epidemiol* **112**(6):775-86	Welders, shipbuilders	No relative risk (RR) estimate for stomach cancer.
Becker et al.	1985	*Scand J Work Environ Health* **11**(2):75-82.	Arc welders	Overlap with more recent Becker, 1999.
Becker et al.	1991	*Br J Ind Med* **48**(10):675-83	Arc welders	Overlap with more recent Becker, 1999.
Bidstrup	1951	*Br J Ind Med* **8**(4):302-5	Chromate production workers	Overlap with more recent Davies et al., 1991.
Bidstrup & Case	1956	*Br J Ind Med* **13**(4):260-4	Chromate production workers	Overlap with more recent Davies et al., 1991.
Birk et al.	2006	*J Occup Environ Med* **48**(4):426-33	Chromate production workers	Overlap with Korallus et al., 1993, but follow-up only since conversion to process with lower Cr(VI) exposure.
Blair & Mason	1980	*Arch Environ Health* **35**(2):92-4	Metal polishers and metal platers	Unclear Cr(VI) exposure.
Boice et al.	1999	*Occup Environ Med* **56**(9):581-97	Aircraft workers	Overlap with more recent Lipworth et al., 2011.
Brinton et al.	1952	*Public Health Rep* **67**(9):835-47	Chromate workers	No RR estimate for stomach cancer.
Cammarano et al.	1984	*Scand J Work Environ Health* **10**(4):259-61	Power plant workers	Unclear Cr(VI) exposure.
Cammarano et al.	1986	*Scand J Work Environ Health* **12**(6):631-2	Power plant workers	Unclear Cr(VI) exposure.

Chow et al.	1994	*Am J Ind Med* **26**(4):511-20	All Sweden	Other Swedish studies give more specific exposure categories.
Cocco et al.	1994	*Cancer Causes Control* **5**(3):241-8	Shoe and leather workers	Unclear Cr(VI) exposure.
Cocco et al.	1998	*J Occup Environ Med* **40**(10):855-61	US death certificate study	Some overlap with Robinson et al., 1995, but includes only cancer of the gastric cardia.
Cocco et al.	1999	*Occup Environ Med* **56**(11):781-7	Concrete workers	Gives percentage of cases and controls for concrete workers but no RR estimate.
Coggon et al.	1990	*Br J Ind Med* **47**(5):298-301	Iron and steel workers	Unclear Cr(VI) exposure.
Cornell	1984	*IARC Sci Publ* (53):65-71	Stainless steel workers	No RR estimate for stomach cancer.
Cox et al.	1981	*Br J Ind Med* **38**(3):235-9	Nickel alloy plant	No RR estimate for stomach cancer.
Dalager et al.	1980	*J Occup Med* **22**(1):25-9	Zinc chromate paints	All digestive organs combined.
Danielsen et al.	1993	*Br J Ind Med* **50**(12):1097-103	Mild steel welders	Unclear Cr(VI) exposure.
Decoufle	1979	*Arch Environ Health* **34**(1):33-7	Leather workers	No RR estimate for stomach cancer.
Decoufle & Walrath	1983	*Am J Ind Med* **4**(4):523-32	US union shoemakers	Unclear Cr(VI) exposure.
Dunn & Weir	1968	*Arch Environ Health* **17**(1):71-6	Several occupations (unspecified)	No RR estimate for stomach cancer. Special emphasis on lung cancer and asbestos.
Ekstrom et al.	1999	*Cancer Res* **59**(23):5932-7	All Sweden	More specific exposure categories are given in other Swedish studies.
Engel et al.	2002	*Am J Ind Med* **42**(1):11-22	Leather workers	No odds ratio (OR) calculated for leather work. Other job categories are too broad.
Enterline	1974	*J Occup Med* **16**(8):523-6	Chromate workers	No RR estimate for stomach cancer.
Finkelstein & Wilk	1990	*Am J Ind Med* **17**(4):483-91	Steel manufacturer	All digestive organs combined.
Finkelstein et al.	1991	*Am J Ind Med* **19**(2):183-94	Steel manufacturer	Cr(VI) exposure documented in the melting area but with a wide range.
Firth et al.	1996	*Int J Epidemiol* **25**(1):14-21	Multiple occupations	No RR estimate for stomach cancer.

Firth et al.	1999	*Occup Environ Med* **56**(2):134-8	Foundry and other workers	No RR estimate for stomach cancer.
Frentzel-Beyme	1983	*J Cancer Res Clin Oncol* **105**(2):183-8	Chromate pigment workers	No RR estimate for stomach cancer.
Fu et al.	1996	*Occup Environ Med* **53**(6):394-8	Shoe manufacturing	Unclear Cr(VI) exposure.
Gibb et al.	2000	*Am J Ind Med* **38**(2):115-26	Chromium chemical production	No RR estimate for stomach cancer.
Guay & Siemiatycki	1987	*Am J Ind Med* **12**(2):181-93	Fur industry	No stomach cancer RR given for dressers (tanners). No cases in all fur workers.
Guberan et al.	1989	*Br J Ind Med* **46**(1):16-23	Painters and electricians	Only has RR estimates for painters and electricians. Unclear Cr(VI) exposure.
Haguenoer et al.	1990	*Br J Ind Med* **47**(6):380-3	Chromate pigment workers	Overlap with more recent Deschamps et al., 1995.
Hansen et al.	1996	*Am J Ind Med* **30**(4):373-82	Stainless steel welders	All digestive organs combined.
Hayes et al.	1979	*Int J Epidemiol* **8**(4):365-74	Chromate production plant	All digestive organs combined.
Hughes et al.	1987	*Br J Ind Med* **44**(3):161-74	Asbestos cement manufacturing	Cr(VI) exposure unclear. Asbestos exposure emphasized.
Iaia et al.	2002	*Med Lav* **93**(2):95-107	Leather tanners	Overlap with more recent Iaia et al., 2006.
Iaia et al.	2006	*Am J Ind Med* **49**(6):452-9	Leather tanners	Overlap with Costantini et al., 1989, which has more cases.
Itoh et al.	1996	*J UOEH* **18**(1):7-18	Chrome platers	Overlap with more recent Hara et al., 2010.
Jakobsson et al.	1990	*Arch Occup Environ Health* **62**(4):337-40	Cement workers	Combined stomach and esophageal cancer.
Jeong et al.	2011	*Am J Ind Med* 54(9):719-25	Shipbuilding	Unclear Cr(VI) exposure.
Ji & Hemminki	2006	*Eur J Cancer Prev* **15**(5):391-7	All Sweden	Other Swedish studies have more specific exposure categories
Kang et al.	1997	*Am J Ind Med* **31**(6):713-8	Asbestos related occupations	Unclear Cr(VI) exposure.
Keller & Howe	1993	*Am J Ind Med* **24**(2):223-30	Cement workers	Unclear Cr(VI) exposure. Unusual control selection - controls may include lung cancer cases.

Kjuus et al.	1986	*Br J Ind Med* **43**(4):227-36	Ferrosilicon and ferromanganese plants	No specific chromium data; exposure to polyaromatic hydrocarbons and asbestos emphasized.
Knutsson et al.	2000	*Occup Environ Med* **57**(4):264-7	All Sweden	Other Swedish studies have more specific exposure categories.
Kraus et al.	1957	*Am J Public Health Nations Health* **47**(8):961-70	Various occupations	Only very broad exposures, i.e. iron and grain dust. Unclear Cr(VI) exposure.
Kusiak et al.	1993	*Br J Ind Med* **50**(2):117-26	Uranium miners	Exposure based on Cr(VI) levels in rocks.
Langård & Norseth	1975	*Br J Ind Med* **32**(1):62-5	Chromate pigment workers	Only 133 workers in cohort, no stomach cancer cases.
Langård & Norseth	1979	*Ark hig rada toksikol* **30**:301-4	Chromate pigment workers	All gastrointestinal cancers combined.
Langård et al.	1980	*Br J Ind Med* **37**(2):114-20	Ferrosilicon and ferrochromium workers	Overlap with more recent Langård et al., 1990.
Langård & Vigander	1983	*Br J Ind Med* **40**(1):71-4	Chromate pigment workers	Only lung cancer. Overlap with Langård & Norseth, 1975 and 1979.
Lloyd et al.	1970	*J Occup Med* **12**(5):151-7	Steelworkers	All malignant neoplasms combined.
Luippold et al.	2005	*J Occup Environ Med* **47**(4):381-5.	Chromate production workers	Low-level Cr(VI) exposure only. RR estimate for cancers of all digestive organs combined.
Machle & Gregorius	1948	*Public Health Rep* **63**(35):1114-27	Chromate production	All digestive tract cancers combined.
McMillan & Pethybridge	1983	*J Soc Occup Med* **33**(2):75-84	Shipyard welders	Unclear Cr(VI) exposure.
Melkild et al.	1989	*Scand J Work Environ Health* **15**(6):387-94	Welders and shipyard workers	No stainless steel until 1973; follow-up ended in 1977.
Merlo et al.	1989	*J UOEH* **11 Suppl**:302-15	Welders	Unclear Cr(VI) exposure.
Mikoczy et al.	1994	*Occup Environ Med* **51**(8):530-5	Leather tanners	Overlap with more recent Mikoczy & Hagmar, 2005.
Mikoczy et al.	1996	*Occup Environ Med* **53**(7):463-7	Leather tanners	Overlap with more recent Mikoczy & Hagmar, 2005.
Okubo & Tsuchiya	1977	*Keio J Med* **26**(3):171-7	Chrome platers	Overlap with more recent Hara et al., 2010.
Okubo et al.	1985	*Jpn J Clin Oncol* **15 Suppl 1**:243-53	Chrome platers	Overlap with more recent Hara et al., 2010.

Pang et al.	1996	*Occup Environ Med* **53**(10):714-7	Nickel plating	Chromium platers were excluded.
Park et al.	2005	*Am J Ind Med* **48**(3):194-204	Stainless steel production	Overlap with more recent Ahn et al., 2006.
Pippard & Acheson	1985b	*Scand J Work Environ Health* **11**(4):249-55	Shoe and boot makers	Leather tanning unclear.
Polednak	1981	*Arch Environ Health* **36**(5):235-42	Welders	All digestive cancers combined.
Puntoni et al.	1979	*Ann N Y Acad Sci* **330**:353-77	Shipyard workers	Gives stomach cancer SMRs for several shipyard jobs, but Cr(VI) exposure is unclear.
Puntoni et al.	1984	*Med Lav* **75**(6):471-7	Leather tanners	Overlap with more recent Montanaro et al., 1997.
Puntoni et al.	2001	*Am J Ind Med* **40**(4):363-70	Shipyard workers	Stomach cancer data for all shipyard workers. Unclear Cr(VI) exposure.
Raffn et al.	1989	*Br J Ind Med* **46**(2):90-6	Asbestos cement industry	Asbestos exposure only.
Rafnsson & Johannesdottir	1986	*Br J Ind Med* **43**(8):522-5	Masons	Overlap with more recent Rafnsson et al. 1997.
Redmond et al.	1975	*J Occup Med* **17**(1):40-3	Steelworkers	Stomach and duodenal cancers combined.
Redmond et al.	1979	*J Environ Pathol Toxicol* **2**(5):75-96	Steelworkers	Unclear Cr(VI) exposure.
Robinson et al.	1995	*Am J Ind Med* **28**(1):49-70	Concrete/terazzo finishers	Unclear exposure in this subgroup. Data on bricklayers are included in this meta-analysis.
Rockette & Redmond	1976	*J Occup Med* **18**(8):541-5	Steelworkers and masons	All digestive organs combined.
Rosenman & Stanbury	1996	*Am J Ind Med* **29**(5):491-500	Chromium smelter workers: black workers	No cases. Data for white male workers are included in this meta-analysis.
Royle	1975a	*Environ Res* **10**(1):39-53	Chrome platers	Overlap with more recent Sorahan & Harrington 2000
Royle	1975b	*Environ Res* **10**(1):141-163	Chrome platers	Overlap with more recent Sorahan & Harrington 2000
Sheffet et al.	1982	*Arch Environ Health* **37**(1):44-52	Chromate pigment workers	Overlap with more recent Hayes et al. 1989.
Siemiatycki et al.	1982	*Teratog Carcinog Mutagen* **2**(2):169-77	Fur and leather workers	No RR estimate for stomach cancer.

Siemiatycki et al.	1986	*Am J Epidemiol* **123**(2):235-49	Population based case-control study	Only gives RR for broad categories of dust exposure.
Siemiatycki et al.	1989	*Am J Ind Med* **16**(5):547-67	Cement workers	No RR estimate for stomach cancer.
Silverstein et al.	1981	*Scand J Work Environ Health* **7 Suppl 4**:156-65	Metal plating: females	No cases. Data on male platers are included in this meta-analysis.
Silverstein et al.	1986	*Am J Ind Med* **10**(1):27-43	Iron foundry	Unclear Cr(VI) exposure.
Simpson et al.	1999	*Am J Ind Med* **36**(1):172-85	Various occupations	Unclear Cr(VI) exposure.
Sjögren	1980	*Scand J Work Environ Health* **6**(3):197-200	Welders	No RR estimate for stomach cancer.
Sjögren et al.	1987	*Scand J Work Environ Health* **13**(3):247-51	Welders	Only gives stomach cancer RR in a low Cr(VI) exposure group.
Sorahan & Cooke	1989	*Br J Ind Med* **46**(2):74-81	Foundry workers	Unclear Cr(VI) exposure.
Sorahan et al.	1994	*Occup Environ Med* **51**(5):316-22	Steel foundry workers	Unclear Cr(VI) exposure.
Stern et al.	1987	*Scand J Work Environ Health* **13**(2):108-17	Leather tanners	Overlap with more recent Stern 2003, all digestive organ cancers combined.
Stern	2003	*Am J Ind Med* **44**(2):197-206	Leather tanners	All digestive organ cancers combined.
Svensson et al.	1989	*Am J Ind Med* **15**(1):51-9	Cement workers	Overlap with more recent Jakobsson et al., 1997.
Takahashi & Okubo	1990	*Arch Environ Health* **45**(2):107-11	Chrome platers	Overlap with more recent Hara et al., 2010
Taylor	1966	*Am J Public Health Nations Health* **56**(2):218-29	Chromate workers	Only respiratory and all other cancers. Overlap with more recent Enterline 1974.
Tola et al.	1988	*Br J Ind Med* **45**(4):209-18	Platers and welders in shipyards and machine shops	States that welders had no Cr exposure. Platers' exposure unclear.
Tsuda et al.	2001	*Am J Ind Med* **39**(1):52-7	Brick and quarry work	Unclear Cr(VI) exposure.
Urbaneja-Arrue et al.	1995	*Gac Sanit* **9**(50):287-94	Steel workers	Unclear Cr(VI) exposure.
Versluys	1949	*Br J Cancer* **3**(2):161-85	Shoemakers and masons	Unclear Cr(VI) exposure. Mortality given only for 1931-1935.

Vestbo et al.	1991	*Br J Ind Med* **48**(12):803-7	Cement workers	No exposed cases.
Ward et al.	1994	*J Occup Med* **36**(11):1222-7	All deaths	Overlap with more recent Cocco et al., 1998. Some overlap with more recent Robinson et al., 1995. Includes only cancer of the gastric cardia.
Wright et al.	1988	*Am J Epidemiol* **128**(1):64-73	Dusty jobs	Unclear Cr(VI) exposure. RRs only for broad categories of dust exposure.
Wu et al.	2013	*Am J Ind Med* **56**(1):701-8	Shipbreaking workers	Cr(VI) exposure unclear for occupations listed.
Xu et al.	1996b	*Am J Ind Med* **30**(1):1-6	Steel and iron workers	Overlap with Xu et al., 1996a, which provides ORs rather than PMRs.

Supplemental Table 3. Comparison of the current meta-analysis to the previous meta-analyses by Gatto *et al.* (2010)[1] and Cole and Rodu (2005)[2]

Current meta-analysis						Gatto et al., (2010)			Cole and Rodu (2005)		
Author	**Year**	**Location**	**Number of cases**	**Industry or occupation; exposure group if more than one**	**RR (95% CI)**	**Used**	**RR (95% CI)**	**Notes**	**Used**	**RR (95% CI)**	**Notes**
Axelsson et al., 1980[3]		Sweden	4	Ferrochromium production; ≥ 15 years employment	0.78 (0.21-2.01)	Yes	Near 1.0[a]		Yes	0.91 (0.45-1.63)	Combined multiple job types
Becker, 1999[4]		Germany	4	Arc welders; effective welding period > 25% of work day	1.12 (0.30-2.86)	Yes	<1.0[a]		Yes	0.65 (0.21-1.51)	Used all welders regardless of time spent welding
Davies et al., 1991[5]		UK: Bolton	6	Chromate production; early and pre-process change workers	2.08 (0.76-4.53)	Yes	Same[b]		Yes	Same[b]	
Davies et al., 1991[5]		UK: Rutherglen	9	Chromate production; early and pre-process change workers	0.70 (0.32-1.32)	Yes	Same[b]		Yes	Same[b]	
Davies et al., 1991[5]		UK: Eaglescliff	4	Chromate production; early and pre-process change workers	0.39 (0.10-0.99)	Yes	Same[b]		Yes	Same[b]	
Gibb et al., 2000[6]		US	NA	Chromate production workers	Not used	Yes	<1.0[a]	Unpublished	Yes	0.40 (0.08-1.17)	Unpublished
Luippold et al., 2003[7]		US	NA	Chromate production	Not used	Yes	<1.0[a]	Unpublished	Yes	0.47 (0.01-2.62)	Unpublished
Pippard et al., 1985[8]		UK	2	Leather tanning; male chrome tanners.	0.52 (0.06-1.87)	Yes	Same[b]		Yes	0.51 (0.06-1.84)	Calculated SMR and CI based on O and E, we used the SMR presented by authors.
Simonato et al., 1991[9]		4 Scandinavian countries	18	Stainless steel welding; cohort included mild steel, stainless steel and shipyard welders. Incidence data.	0.85 (0.50-1.34)	Yes	0.96 (0.63-1.40)	Used mortality rather than incidence data	Yes	0.96 (0.63-1.41)	Used mortality rather than incidence data
Sorahan & Harrington, 2000[10]		UK: Yorkshire, 54 plants	12	Chrome plating; male platers and others exposed to chromic acid, employed ≥ 3 consecutive months.	1.68 (0.87-2.94)	Yes	Same[b]		Yes	1.56 (0.81-2.73)	Includes men and women

Boice et al., 1999[11]	California	11	Aircraft manufacturing; workers with potential exposure to chromate	Not used	Yes	Near 1.0[a]		No
Costantini et al., 1989[12]	Italy: Tuscany	6	Leather tanning; male tanners	0.43 (0.16-0.94)	Yes	Same[b]		No
Deschamps et al., 1995[13]	France	2	Chromate production; chromate pigment workers	1.52 (0.18-5.50)	Yes	Same[b]		No
Franchini et al., 1983[14]	Italy	1	Chrome plating; "hard" plating workers	3.33 (0.04-18.55)	Yes	Same[b]		No
Guberan et al., 1989[15]	Geneva, Switzerland	5	Painters	Not used	Yes	0.24 (0.01-1.16)	Painters	No
Hara et al., 2010[16]	Japan: Tokyo	14	Chrome plating; male platers, mean age at baseline = 49.5 years	0.67 (0.37-1.06)	Yes	Same[b]	Labeled as Hara 2009	No
Hayes et al., 1989[17]	New Jersey	2	Chromate pigment production; 10+ years of exposure to chromate dusts	2.14 (0.24-7.73)	Yes	>1.0[a]	SMR appears <2.14	No
Horiguchi et al., 1990[18]	Japan: Osaka	2	Chrome plating; workers employed 10 or more years	1.43 (0.02-7.50)	Yes	1.23 (0.25-3.58)	May not have incorporated duration	No
Iaia et al., 2006[19]	Tuscany, Italy	1	Leather tanners	Not used	Yes	0.27 (0.01-1.26)	Overlap with Constantini et al., 1989 (which had more cases)	No
Kano et al., 1993[20]	Japan	8	Chromate pigment production	1.20 (0.52-2.37)	Yes	Same[b]		No
Korallus et al., 1993[21]	Germany: Uerdingen	12	Chromate production; workers exposed ≥ 1 year.	1.92 (1.04-3.24)	Yes	Same[b]	Different plants were combined	No
Korallus et al., 1993[21]	Germany: Leverkusen	4	Chromate production; workers exposed ≥ 1 year.	0.63 (0.17-1.60)	Yes	Same[b]		No
Langård et al., 1990[22]	Norway	7	Ferrochromium production; workers first employed before 1960.	1.45 (0.58-2.99)	Yes	Same[b]		No
Montanaro et al., 1997[23]	Italy: Genoa	10	Leather tanning; male and female workers employed ≥ 6 months between 1/1/1955 and 5/12/1988.	0.79 (0.38-1.46)	Yes	Same[b]		No
Moulin et al., 1990[24]	France	4	Ferrochromium and stainless steel production; workers employed ≥ 1 year in ferrochromium or stainless steel workshops.	2.75 (0.75-7.01)	Yes	Same[b]		No

Moulin et al., 1993b[25]	France	6	Stainless steel and mild steel welding; men employed as welders ≥ 1 year at beginning of follow up period.	2.09 (0.77-4.55)	Yes	Same[b]		No		
Rafnsson et al., 1997[26]	Iceland	15	Masons; men with a 30 year lag between finishing vocational training and counting person-years.	1.27 (0.71-2.09)	Yes	Near 1.0	May not have used latency data	No		
Rosenman & Stanbury, 1996[27]	US: New Jersey	2	Chromium smelter; former workers employed > 20 years.	1.87 (0.21-6.76)	Yes	>1.0		No		
Satoh et al., 1981[28]	Japan: Tokyo	11	Chromium production; men employed ≥ one year between 1918 and 1975.	0.95 (0.47-1.70)	Yes	Same[b]		No		
Silverstein et al., 1981[29]	US: Michigan	4	Chrome plating: males; employees and retirees with ≥ 10 years of service in the plant.	2.54 (0.68-6.50)	Yes	Same[b]		No		
Sorahan et al., 1994[30]	UK: nine foundries	124	Steel foundry workers	Not used	Yes	1.34 (1.11-1.60)	Foundry workers	No		
Sorahan et al., 1987[31]	UK: Midlands, 1 plant	13	Chrome plating: males; first employment chrome bath work.	2.06 (1.10-3.52)	Yes	> 1.0	Combined males and females	No		
Sorahan et al., 1987[31]	UK: Midlands, 1 plant	1	Chrome plating: females; first employment chrome bath work.	0.32 (0.01-1.78)	Yes	See above	Combined males and females	No		
Jakobsson et al., 1997[32]	Sweden	8	Stainless steel grinding; workers diagnosed ≥ 15 years after start of employment	0.8 (0.3-1.7)	No			Yes	0.83 (0.36-1.64)	Minor differences in calculations
Takahashi et al., 1990[33]	Tokyo, Japan	7	Chrome plating	Not used	No			Yes	0.92 (0.37-1.90)	Overlap with Hara et al., , 2010
Zhang et al., 1997[34]	China		Drinking water contamination	Not used	No			Yes	0.75 (0.44-1.20)	Drinking water exposure
Ahn et al., 2006[35]	Korea	2	Iron and steel production; stainless steel production work, 10-35 years duration	13.65 (0.76-66.26)	No			No		
Amandus, 1986[36]	US	16	Non-asbestos cement plants; > 20 years tenure in cement plant, ≥ 20 years latency	1.27 (0.73-2.06)	No			No		
Dab et al., 2011[37]	France	3	Cement production; employed ≥ one year from 1990 to 2005	0.38 (0.08-1.26)	No			No		

Danielsen et al., 1996[38]	Norway	3	Boiler welders ever welding on stainless steel	1.03 (0.21-3.03)	No	No
Edling et al., 1986[39]	Sweden	6	Leather tanning; occupation "tanner" or "tannery worker"	1.6 (0.6-4.0)	No	No
Garabrant & Wegman, 1984[40]	US: Massachusetts	2	Leather workers: female	2.80 (0.31-10.11)	No	No
Garabrant & Wegman, 1984[40]	US: Massachusetts	16	Leather workers: male	1.69 (0.97-2.74)	No	No
Gonzalez et al., 1991[41]	Spain: Catalonia	5	Leather workers; exposed to dust	1.82 (0.40-8.25)	No	No
Gonzalez et al., 1991[41]	Spain: Catalonia	41	Brick masons; exposed to dust	1.69 (0.82-3.46)	No	No
Huvinen & Pukkala, 2013[42]	Finland	12	Ferrochromium and stainless steel production workers; chromite mine workers	0.80 (0.42-1.40)	No	No
Jakobsson et al., 1993[43]	Sweden	13	Cement production; men employed ≥ 1 year, ≥ 15 years since start of employment	1.14 (0.61-1.94)	No	No
Jarvholm et al., 1982[44]	Sweden	4	Steel polishing; men who had worked ≥ 5 years as polishers	9.76 (2.62-25.0)	No	No
Kneller et al., 1990[45]	China: Shanghai	55	Leather products workers	1.50 (1.13-1.95)	No	No
Kneller et al., 1990[45]	China: Shanghai	5	Leather tanning; tanners, feltmongers, and pelt dressers	0.94 (0.30-2.19)	No	No
Koh et al., 2013[46]	Korea	14	Cement industry workers; high exposure group	2.18 (1.19-3.65)	No	No
Krstev et al., 2005[47]	Poland: Warsaw	8	Leather workers: male; newly diagnosed cases, aged 21-79, 3/1/1994 to 4/30/1996.	5.10 (1.0-25.0)	No	No
Krstev et al., 2005[47]	Poland: Warsaw	4	Leather workers: female; newly diagnosed cases, aged 21-79, 3/1/1994 to 4/30/1996.	3.10 (0.70-14.9)	No	No
Lipworth et al., 2011[48]	US: California	26	Aircraft manufacturing workers; exposed to chromates	0.72 (0.47-1.05)	No	No
Mallin et al., 1989[49]	US: Illinois	9	Bricklayers; white males, aged 35 to 74.	4.30 (1.18-15.6)	No	No

McDowall, 1984[50]	UK: North Kent	4	Cement production-packing; employed in 1939 in occupation identified as cement manufacture.	3.21 (0.86-8.22)	No	No
McDowall, 1984[50]	UK: North Kent	8	Cement production-maintenance; employed in 1939 in occupation identified as cement manufacture.	2.11 (0.91-4.16)	No	No
McDowall, 1984[50]	UK: North Kent	9	Cement production-laborers; employed in 1939 in occupation identified as cement manufacture.	1.48 (0.67-2.81)	No	No
Mikoczy & Hagmar, 2005[51]	Sweden	13	Leather tanning; workers employed ≥ 1 year, 20 year latency period.	0.98 (0.52-1.68)	No	No
Minder & Beer-Porizek, 1992[52]	Switzerland	52	Masons; men aged 30 years and over, 1979-1982.	1.42 (1.04-1.96)	No	No
Moulin et al., 1993a[53]	France	7	Ferrochromium and stainless steel production; workers employed ≥ 3 years in production workforce.	0.92 (0.37-1.90)	No	No
Moulin et al., 1995[54]	France: plant 1	26	Stainless steel production; male workers employed on 1/1/1960 or hired before 5/31/1989	1.04 (0.68-1.52)	No	No
Moulin et al., 1995[54]	France: plant 2	15	Stainless steel production; male workers employed on 1/1/1960 or before 12/31/1990	0.84 (0.47-1.38)	No	No
Parent et al., 1998	Canada: Montreal	11	Leather workers; employed ≥ 10 years.	1.0 (0.5-1.9)	No	No
Pukkala et al., 2009[55]	Denmark	140	Bricklayers; males, 1961-2005	1.06 (0.89-1.25)	No	No
Pukkala et al., 2009[55]	Finland	89	Bricklayers; males, 1961-2005	0.95 (0.76-1.17)	No	No
Pukkala et al., 2009[55]	Norway	168	Bricklayers; males, 1961-2005	1.20 (1.03-1.40)	No	No
Pukkala et al., 2009[55]	Scandinavia	2	Bricklayers; females, 1961-2005	1.56 (0.19-5.65)	No	No

Robinson et al., 1995[56]	US	32	Brickmasons; white men, aged 20 and over.	2.08 (1.42-2.93)	No	No
Salg & Alterman, 2005[57]	US	94	Bricklayers: white; male union members who died between 1986 and 1991	1.31 (1.06-1.60)	No	No
Salg & Alterman, 2005[57]	US	8	Bricklayers: non-white; male union members who died between 1986 and 1991	1.17 (0.50-2.31)	No	No
Santibañez et al., 2012[58]	Spain: Alicante	7	Leather workers; men who worked ≥ 1 year in the same occupation.	1.37 (0.40-4.66)	No	No
Santibañez et al., 2012[58]	Spain: Alicante	29	Bricklayers and stonemasons; men who worked ≥ 1 year in the same occupation.	1.20 (0.65-2.22)	No	No
Sjödahl et al., 2007[59]	Sweden	37	Construction workers; high exposure to cement dust.	1.5 (1.1-2.1)	No	No
Smailyte et al., 2004[60]	Lithuania	6	Cement production; workers with cumulative exposure > 130.2 mg/m^3 cement dust	1.5 (0.6-3.0)	No	No
Stern et al., 2001[61]	US	110	Cement masons; members of Operative Plasterers' and Cement Finishers' International Association.	1.64 (1.35-1.98)	No	No
Sweeney et al., 1985[62]	US	2	Leather tanning; white male and female retired fur dressers.	1.37 (0.15-4.95)	No	No
Walrath et al., 1987[63]	US: New York	71	Leather workers: male.	1.83 (1.43-2.31)	No	No
Walrath et al., 1987[63]	US: New York	14	Leather workers: female.	1.28 (0.70-2.15)	No	No
Weiderpass et al., 2003[64]	Finland	unknown	All occupations: women; workers with medium to high levels of exposure to chromium.	0.50 (0.23-1.12)	No	No
Xu et al., 1996[65]	China	6	Chrome plating; employed at plant ≥ 15 years.	2.1 (0.7-6.3)	No	No
Xu et al., 1996[65]	China	4	Cement workers; employed at plant ≥ 15 years.	1.2 (0.3-4.3)	No	No

Abbreviations: CI, confidence interval; E, expected number of cases; O, observed number of cases; RR, relative risk estimate; SMR, standardized mortality ratio.
[a]Gatto presents data in figure form only. The terms “near 1.0”, “<1.0” or “>1.0” indicates that the relative risk estimate used by Gatto et al. (2010) could not be determined by us but is near 1.0, <1.0 or >1.0 based on its appearance in the figure.
[b]The relative risk in the figure presented by Gatto et al., (2010) appears to be the same as the relative risk used in this meta-analysis.
The studies listed under Cole and Rodu (2006) include only those identified as the authors as higher quality and controlled for socioeconomic status.

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