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Research into Malignant and Non-malignant Respiratory Disease Prescriptions: Report for Chromium VI and Lung Cancer

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1 Introduction

This report is part of Phase 2 of this project and contains an evaluation of more detailed research focussing on elements which require more attention from the Phase 1 report.

In Phase 2, IOM undertook to carry out more in-depth searches, after piloting, for relevant epidemiological evidence for the chosen exposure-disease combinations. It was intended that IOM screen, extract and tabulate the epidemiological evidence for these priority occupational circumstances, giving due focus to the exposure circumstances potentially associated with a doubling of the relative risks. IIAC are to be consulted on their views on the report, before it is finalised. This report contains an evaluation of the quality and robustness of the epidemiological evidence, including the relevance and practicality of exposure measures used.

This report therefore contains the findings for chromium VI (CrVI) and lung cancer and is the fifth of six high-priority occupational exposure-disease combinations that were identified with IIAC as being of highest priority for consideration in Phase 2 of this project.

This report contains a commentary on the extracted data for relevant occupational epidemiological studies and is meant to be read in conjunction with the associated spreadsheets containing the data extraction from these studies (Appendix 1). The data contain those studies reported in the most recent IARC Monograph (IARC Working Group, 2012), together with those identified from literature searches by the IOM research team (and the bibliographies of) more recent publications.

It is worth noting that exposure to CrVI may occur by inhalation and skin contact. Inhalation is probably the most important exposure route for respiratory diseases. Biological monitoring data will reflect all routes of exposure and air sampling will just reflect inhalation exposure.

2 Methods

Searches of Web of Science and NLM PubMed databases were undertaken in February 2023 using the following search string: Exposure AND ("Hexavalent chromium" OR “chromium VI” OR “CR VI” OR "chromium 6") AND (lung AND cancer). The searches were run in PubMed in the title/abstract field (no date restrictions) in ‘Advanced Search’ and in Web of Science Core Collection in the topic field (title, abstract, keywords) from 1996 to present, 1996 being the latest year for studies considered by the most recent IARC report.

Bibliographies of the studies included in the chromium and lung cancer reviews found in our earlier literature searches (see below) were searched to identify any additional individual studies that should be screened for inclusion in the tables of evidence.

3 Results

The table of results from the most recent IARC Monograph (IARC Working Group, 2012) is included at Appendix 2. This section of the report is grouped according to the industrial classification used in the IARC report, with an additional category for population-based studies.

3.1 Chromate Production

Mortality and morbidity were studied among male workers employed 1940 to 1950 who were members of sick-benefit plans at seven plants in the United States engaged in the extraction of chromates from chemical-grade chromite ore. All disabilities that ended between 1946 and 1950 were included, provided they lasted for 8 calendar days or longer. Industrial injuries and compensated cases of occupational disease were not included. For the mortality analysis only deaths of workers who were members of a sick-benefit association and died within one year after becoming disabled are included. Deaths due to industrial injuries are not included. The relative risk compared to US males was 28.9 (95% CI: 18.87 to 42.35, 26 deaths). No mention was made of exposure levels for chromates or of adjustment for smoking. (Brinton et al., 1952).

Deaths from respiratory cancer were observed by among 1,200 male chromate production workers in 3 chromate production plants (3 of those identified in the Brinton et al study) in the US employed from 1937 to 1940 and followed from 1941 to 1960. Based on 69 deaths the relative risk for lung cancer was 9.43 (95% CI: 7.34 to 11.93). No mention was made of exposure levels for chromates or of adjustment for smoking (Enterline, 1974).

Mortality of 896 males was analysed. These were workers at a manufacturing plant for chromium compounds between 1918 and 1975 in Japan. Follow-up was to 1978 or death. The overall SMR (95% CI) for lung and sinonasal cancer combined was 9.23 (6.27 to 13.10, 31 deaths of which 25 were lung cancer). Broken down by duration of employment gave SMRs of 5.91 (1.37 to 9.88. 5 deaths) for 1-10 years, 7.48 (3.42 to 14.19, 9) for 11-20 years and 17.47 (10.18 to 55.19, 17) for 21+ years. The relative risk based just on the lung cancer cases was 9.5 (6.2 to 3.92, 26). No mention was made of exposures levels for chromates or of adjustment for smoking (Satoh et al., 1981).

A study of 1,150 workers at two German chromate-producing factories employed for more than one year from 1934 to 1979 gave an SMR with North Rhine Westphalia as the reference population of 2.1 (1.56 to 2.76, 51) (Korallus et al., 1982). Data from the 1983 update paper stated that high exposure in the earlier years of operation have declined steadily and has for some time been below the current technical guide concentration of 0.1 mg/m3 Cr (as CrO_3). The mean annual values were between 0.021 and 0.073 Cr/m3 recorded from 1977 to 1987. Data recorded before 1977 were thought not to correspond to the current analytical conditions. The same applies to urinalysis of Cr, which was between 8 and 21 µg Cr/g creatinine between 1980 and 1985 and between 4 and 14 before 1986 and 1990. It was stated that due to rotation of workers through all workplaces, it was not possible to estimate individual exposure (Korallus et al., 1993).

An Italian study of 540 chromate production workers employed 10 years or more and followed-up from 1948 to 1985 gave a lung cancer SMR for all workers of 2.17 (1.18 to 3.63, 14) and an SMR for high exposure to Cr VI of 4.2 (1.53 to 9.14, 6). Only an abstract was available for this study (de Marco et al., 1988).

A UK study updated a 1981 study of 2,298 workers at 3 chromate production factories exposed for more than one year before 1976 and followed up from 1950 to 1988 giving a lung cancer SMR for all workers of 1.97 (1.59 to 2.28, 175), an SMR for high chromate exposure jobs of 2.45 (2.07 to 2.87, 151) and an SMR of 1.02 (0.56 to 1.71, 14) for post-process change. Mention is made of higher and lower exposures, without any quantification. The amount of missing smoking data was too high to include in the analysis (Davies et al., 1991).

A German study updated a 1982 report on mortality at two German chromate-producing factories whose principal aim was to establish whether the change to a production process using lime-free conversion of chromite ore, thus eliminating the formation of calcium chromate, had resulted in a distinct reduction in bronchial carcinoma mortality among workers exposed for the first time after the change. All workers worked for at least one year after 1948 were followed up to the end of 1988. The lung cancer SMRs (increased by the percentage of cases with unknown causes of death) for the two plants were 1.75 (1.20 to 2.46, 32) and 2.39 (1.77 to 3.17, 43). Although no direct adjustment was made for smoking, the authors determined that smoking prevalence was 70% in the study cohort compared to 50% in the general population. The authors claimed that smoking on its own would produce an SMR of 1.35 without chromate exposure. The SMR for the two plants combined was 2.1 (1.56 to 2.76) with North Rhine Westphalia as the comparison population. See statement for earlier study regarding exposures (Korallus et al., 1993).

A study of 3,408 workers in 4 chromate production facilities was carried out in New Jersey in the US. Workers were employed during 1937 to 1971. The PMR for lung cancer for all white males was 1.95 (1.67 to 2.27, 170). For all black males the PMR was 1.88 (1.41 to 2.45, 54). For white males with 20+ years of exposure, the PMR was 2.83 (1.68 to 4.47) and for black males with 20+ years of exposure, the PMR was 6.30 (2.30 to 13.71, 6). The PMRs for lung cancer by duration of employment for white men were 1.33 (1.00 to 1.73, 55) for < 1 year, 2.37 (1.84 to 3.01, 67) for >1-19 years, 2.70 (1.82 to 3.85) for >10-20 years, and 2.83 (1.68 to 4.47) for >20 years. The equivalent PMRs for black men were 1.15 (0.68 to 1.81, 18), 1.96 (1.18 to 3.07, 19), 4.50 (2.25 to 8.05, 11), and 6.30 (2.30 to 13.71, 6) respectively. The authors were not able to examine risks by exposure estimates (and none was presented) and there was a lack of data on smoking habits (Rosenman and Stanbury, 1996).

A study of 2,357 male workers at a chromium production plant in Baltimore in the US, excluding those who began work before 1950, included followed-up from 1950-92. Exposures were estimated for each worker assigned by job title and a job-exposure matrix (JEM) based on air measurements. Smoking status was available for most workers. SMRs were calculated with Maryland rates as the reference. The SMR for lung cancer for all workers was 1.80 (1.49 to 2.14, 122). The SMR for those with a cumulative exposure of 0-0.00249 mg CrO_3.yr/m^3 was 0.96 (0.63 to 1.38, 26), for 0.0015-0.0089 was 1.42 (0.95 to 2.01, 28), for 0.009-0.0769 was 1.57 (1.07 to 2.20, 30) and for 0.077-5.25 was 2.24 (1.60 to 3.03, 38). The coefficient from Cox regression modelling was highly statistically significant after adjusting for smoking status (p = 0.0001) (Gibb et al., 2000).

A study of 482 chromate production workers in Ohio in the US included workers employed for at least one year between 1940-72 and followed-up from 1941-97. A JEM was developed from hygiene surveys and used to derive cumulative estimates of exposure. SMRs were calculated with Ohio rates as the comparator. The SMR for lung cancer for all workers was 2.41 (1.80 to 3.17, 5). For workers with a cumulative exposure of 2.70-23 mg.yr/m^3 the SMR was 4.63 (2.83 to 7.16, 20). The SMR for those hired after 1959 was 0.92 (0.34 to 2.01, 6). Only limited information was available on other potential confounders such as smoking histories or other occupational exposures and was not used in the analysis (Luippold et al., 2003).

A study of two US plants producing chromates using a low-exposure process was conducted. In plant 1, 430 men employed 1971-98 and followed-up from 1979-1998 were included. In plant 2, men employed 1979-98 and followed-up from 1980-98 were included. A detailed exposure assessment that linked individual work histories to a JEM was conducted; however, exposures were low for all work areas. Using state rates as the comparator, the SMR for lung cancer was 0.94 (0.17 to 2.44, 3). Mean cumulative exposure to hexavalent chromium (mg/m^3.y) was 1.58 SD = 2.5) for the cohort as a whole, but 3.28 (4.59) for the workers who died from lung cancer. Smoking data were available for a large proportion of the cohort (88%), but were limited in detail, and could only be used to distinguish ever- and never-smokers. Given the small number of lung cancer deaths, there was limited ability to assess smoking as a confounder (Luippold et al., 2005).

A study of 901 workers in Germany with > 1 year exposure was examined at 2 low exposure chromate-production plants. The exposure period was approximately 1960-1998 with follow-up over the same period. Detailed employment histories were reconstructed for each cohort member. An industrial hygiene survey was carried out. There were more than 12,000 urinary chromium results collected during routine medical examinations. This is a subset of the workers in the Korallus study – those with exposure post-change process. Smoking status was available for most workers. With North Rhine Westphalia and the comparator, the SMR for lung cancer for all workers was 1.48 (0.93 to 2.25, 22). Based on cumulative exposure based on urine levels of 0-39.9 µg.yr/l the SMR was 0.36 (0.01 to 2.00, 1) for 40-99.9 µg.yr/l was 0.95 (0.26 to 2,44, 4), for 100-199.9 µg.yr/l was 0.94 (0.31 to 2.20, 5) and for > 200 µg.yr/l was 2.09 (1.08 to 3.65, 12). The highest exposure category analyses with a 10-year and 20-year lag showed slightly higher SMRs, but they were not statistically significant. The SMRs for duration of exposure were 0.78 (0.16 to 2.29, 3) for 1-4 years, 1.45 (0.53 to 3.16, 6) for 5-9 years, 1.19 (0.57 to 2.19, 10) for 10-19 years and 1.79 (0.37 to 5.23, 3) for 20+ years respectively. Risk associated with either cumulative or peak exposure remained after controlling for smoking status, a strong independent risk factor for lung cancer. It is worth noting that the all-cause mortality (SMR = 0.80 (0.67 to 0.96) and so the lung cancer excess appeared against the backdrop of a healthy worker effect (Birk et al., 2006).

The exposure-response for hexavalent chromium (CrVI)-induced lung cancer among workers of the Painesville Ohio chromate production facility has been used internationally for quantitative risk assessment of environmental and occupational exposures to airborne CrVI. The mortality of 714 Painesville workers (including 198 short-term workers) was updated through December 2011, exposures were reconstructed, and exposure-response modelling was conducted using Poisson and Cox regressions to provide quantitative lung cancer risk estimates. The average length of follow-up was 34.4 years with 24,535 person-years at risk. Lung cancer was significantly increased for the cohort SMR = 186 (145 to 228), for those hired before 1959, those with >30-year tenure, and those with cumulative exposure >1.41 mg/m^3-years or highest monthly exposures >0.26 mg/m^3. Of the models assessed, the linear Cox model with unlagged cumulative exposure provided the best fit and was preferred. Smoking and age at hire were also significant predictors of lung cancer mortality. Adjusting for these variables, the occupational unit risk was 0.00166 (0.000713 to 0.00349), and the environmental unit risk was 0.00832 (0.00359 to 0.0174), which are 20% and 15% lower, respectively, than values developed in a previous study of this cohort (Proctor et al., 2016).

The mortality of 2,354 workers first employed at a Baltimore chromate production plant between 1950 and 1974. The National Death Index was used to determine vital status and cause of death. Cumulative chromium (VI) exposure and nasal and skin irritation were evaluated as risk factors for lung cancer mortality. There were 91,186 person-years of observation and 217 lung cancer deaths. The SMR for lung cancer was 1.63 (1.42 to 1.86). The relative risk for lung cancer by cumulative exposure to chromium was for: 0-0.00149 mg CrO_3/m^3-years 1.05 (0.77 to 1.41), 0.0015 to 0.0089 1.60 (1.20 to 2.08), 0.009 to 0.0768 1.44 (1.07 to 1.90) and 0.077 to 5.05 2.19 (1.70 to 2.77) (Gibb et al., 2015). A re-analysis of this same data set has been published that examined the impact of age on the previous results (Gibb et al., 2020).

3.2 Chromate Paints and Pigments

A US study of 977 spray painters using zinc chromate paints in aircraft maintenance at 2 US military bases, employed to 1959 and followed-up 1959-66. The PMR for lung cancer was 1.94 (1.14 to 2.81, 21). For <5 year's employment, the PMR was 1.41 (0.45 to 2.67, 9), for 5-9 years it was 2.00 (0.73 to 4.35, 6) and for 10+ years it was 3.00 (1.10 to 6.53, 6). No assessment of Cr VI exposures was made (Dalager et al., 1980).

An Italian study of 427 workers in a plant manufacturing paint and coatings, employed 1946-77 and followed-up 1954-78 was conducted. Exposure was to chromate pigments and there was documented co-exposure to asbestos. The SMR using local rates was 2.27 (0.98 to 4.47, 8). Only an abstract was available for this study (Bertazzi et al., 1981).

A study set in Germany and the Netherlands considered 978 workers in 5 plants manufacturing zinc and lead chromates. The dates of employment and follow-up were not clear. The SMR based on national rates was 2.0 (1.20, 3.12, 19). Exposure was classified as high, medium, low or uncertain. Smoking histories were not available for the entire cohorts (Frentzel-Beyme, 1983).

The results of a follow-up study on the incidence of lung cancer in 133 workers producing zinc chromate pigments in Norway are presented. The level of exposure was stated as being considerably reduced since 1972. By the end of 1972 three cases of lung cancer had occurred in a sub-cohort of 24 workers who had been employed for over three years. The same group of workers has now been followed up to December 1980 and three further cases of lung cancer were found. The observed/expected ratio was 44 in this group, virtually the same as at the end of 1972. Five of the six patients smoked. Only one had been exposed to chromates other than zinc chromates (Langård and Vigander, 1983).

Lung cancer mortality among 1,152 men working at three English chromate pigment factories was studied from the 1930s or 1940s until 1981. Workers at factory C were exposed only to lead chromate and experienced normal mortality (SMR = 1.09)). Workers at factories A and B were exposed to both lead and zinc chromate; mortality was normal among those who had only low exposure (SMR = 1.01). For workers with high or medium exposure lung cancer mortality was significantly raised among men remaining at least a year after entering service at factory A during 1932-54 (SMR = 2.22) and at factory B during 1948-67 (SMR = 4.4). At factory A, 1933-46 entrants staying only 3-11 months were not affected (SMR = 1.19) and 1955-63 entrants also appeared unaffected (SMR = 1.00); working conditions there improved in 1955. The hazard at factories A and B affected workers who left after one year as well as those with longer service, and latent intervals were unusually short. The results indicate that moderate or heavy exposure to zinc chromate may give rise to a severe risk of developing lung cancer, but that exposure which is relatively mild or lasts less than a year may not constitute an effective risk. The results provide no indication that lead chromate induces lung cancer in man, even under conditions conducive to lead poisoning (Davies, 1984).

A study of mortality among 1,879 male workers employed in a New Jersey chromium pigment factory was carried out, with follow-up from 1940 to 1982. Vital status of 1,737 (92%) of the eligible cohort members was determined. For the entire study group, no significant excess was observed for respiratory cancer. However, the total number of years of employment in the factory and the total number of years of exposure to chromate dusts were both statistically significantly ($p < 0.05$, for trend) associated with an increased risk for lung cancer. The excess risk for lung cancer associated with duration of exposure to chromate dusts was, however, only clearly apparent for subjects followed for 30 years or more after initial employment. For this group, the SMRs were 81, 139, 201, and 321 for the subjects with 0 years, less than 1 year, 1-9 years, and 10+ years of exposure to chromate dusts ($p < 0.01$, for trend), respectively. No quantification of exposures was carried out (Hayes et al., 1989).

In a follow-up study of 294 men who had worked for at least 6 months in a chromate-producing factory in France between 1958 and 1987, only 16 were lost to follow-up and the number of person-years in the study was 5,207. Occupational data were provided by the administration of the plant. The causes of deaths were ascertained from hospital and general practitioners' records. The observed numbers of deaths were compared with the expected numbers based on local rates with adjustment for age, sex and calendar time (standardized mortality ratio, SMR). Mortality due to lung cancer was in significant excess (SMR = 3.60, 95% CI = 2.13 to 5.68). Significantly higher lung cancer SMRs were found for workers whose duration of employment was more than 10 years. Exposure assessment was impossible to obtain for each worker, but there some idea of past exposures in some of the departments (Deschamps et al., 1995).

The mortality of 2,354 workers first employed at a Baltimore chromate production plant between 1950 and 1974 was extended. The National Death Index was used to determine vital status. Cumulative chromium VI exposure was evaluated as a risk factor for lung cancer mortality. There were 91,186 person-years of follow-up and 217 lung cancer deaths (SMR 1.63, 95% CI: 1.42 to 1.86). Cumulative exposure to chromium VI was associated with lung cancer mortality in a model that included smoking and years worked (Gibb et al., 2015).

3.3 Chromium Electro-plating

Mortality was examined among workers employed between 1974 and 1978 in a zinc die-casting and electroplating plant. A PMR analysis of 238 deaths and a case-control study were conducted. Chemical exposure included die-casting emissions and mists from chrome and nickel plating and exposures were qualitative and made from plant inspections of industrial hygienists. The chief proportionate mortality finding was a significant excess of lung cancer among both white men (PMR = 1.91) and women (PMR = 3.70). Quantitative chemical exposure profiles for departments or workers were not determined. The case-control analysis indicated a possible association between lung cancer and work in certain departments (Silverstein et al., 1981).

A retrospective cohort study was conducted in nine chrome-plating plants in Italy to examine the mortality of workers employed for at least one year during the period January 1951-December 1981. The study group totalled 178 individuals, 116 of whom were from "hard" and 62 from "bright" chrome-plating plants. Most deaths from cancer occurred among hard chromium platers, the excess against the expected rate being statistically significant (7 observed, 2.7 expected, $p = 0.02$). All deaths from lung cancer occurred in the subcohort of hard chrome-plater (3 observed, 0.7 expected, $p = 0.03$). Out of a total of 10 measurement for hard chrome plating, the air concentration of chromium average 7 (range 1 to 50) µg/m^3 as chromium trioxide near the baths and 3 (range 0 to 12) in the middle of the room (Franchini et al., 1983).

A prospective cohort study was conducted to examine the health hazards of chromium plating with a follow-up period of over sixteen years. Subjects were 1,193 male metal platers in the small-scale chromium plating plants in Tokyo. They were divided into a chromium plater subgroup (n = 623) and non-chromium plater subgroup (n = 567) and were followed up from October 1976 through December 1992. In the chromium plating subgroup, a trend toward statistical significance was seen for the risk of lung cancer (SMR 1.18; 95%CI 0.99 to 3.04). No significantly elevated risk was seen in the non-chromium plating subgroup. Only an abstract was available for this study (Itoh et al., 1996).

The mortality experienced by a cohort of 2,689 nickel/chromium platers between 1946 and 1983 has been investigated. All members of the study cohort had some period of chrome exposed employment. Overall, compared with the general population of England and Wales, statistically significant differences relating to cancer were found for cancers of the lung and bronchus (E = 48 1, O = 72). Chrome bath workers are the more heavily exposed workers, and a striking difference in SMRs was found for lung cancer among men first employed as chrome bath workers (SMR = 199) and men first employed as other chrome workers (SMR = 101). The method of regression models in life tables was used to compare the durations of chrome exposed employment of those dying from causes of interest with those of all matching survivors in the same year of follow up, while controlling for sex, and for year and age of starting employment. Data on smoking habits were not available, but the author suggested that there was no reason to believe that they would correlation with duration of chrome employment. Significant positive associations were found only for cancers of the lung and bronchus and duration of chrome bath work. Some 60 occupational hygiene measurements were carried out before 1973 and although a few high values were recorded (0.0, 1.6, 0,4 mg/m^3), the median value was “not detectable or trace”. After 1973, the vast majority of measurements were < 0.05 mg/m^3 (Sorahan et al., 1987).

Lung cancer was examined in a cohort of chrome platers, a group exposed to chromic acid. The mortality of 1,087 chrome platers (920 men, 167 women) from 54 plants situated in the West Riding of Yorkshire, United Kingdom, was investigated for the period 1972–97. All subjects were employed as chrome platers for >3 months and all were alive on 31 May 1972. Mortality data were also available for a cohort of 1,163 comparison workers with no known occupational exposure to chrome compounds (989 men, 174 women). Information on duration of chrome work and smoking habits collected for a cross-sectional survey carried out in 1969–72 were available for 916 (84.3%) of the chrome platers; smoking habits were available for 1004 (86.3%) comparison workers. Two analytical approaches were used, indirect standardisation and Poisson regression. Based on serial mortality rates for the general population of England and Wales, significantly increased mortality from lung cancer was observed in male chrome platers (observed 60, expected 32.5, SMR 185, ($p<0.001$) but not in male comparison workers (observed 47, expected 36.9, SMR 127). Positive trends were not shown for duration of employment exposed to chrome, although data on working after 1972 were not available. Exposures were not quantified in this study (Sorahan and Harrington, 2000).

A cohort of metal chrome plating workers in Italy (at least 6 month’s employment between 1968 and 1994) was examined for the presence of excess lung tumours. Follow-up was to December 2003. The population of Veneto was used as a comparison. Completeness of follow-up was greater than 95%. Only one death was identified in female subjects, due to lung cancer. In males there were 7 deaths from lung cancer, a marked excess with that based on the comparison population. The risk was greater for those working in more recent years. Only an abstract was available for this study (Roberti et al., 2006).

In a cohort of 2,991 Italian electroplaters, a proportion of whom were exposed to low levels of nickel and/or chromium, cumulative exposure to their compounds was obtained by multiplying average concentrations of the metals in each electroplating tank by duration of employment in the company. The association of exposure to compounds with mortality was assessed by multivariable Cox models. No cancer site was associated with chromium exposure controlling for nickel. The hazard ratios for lung cancer (95% CIs) for low, medium and high exposure were 0.65 (0.28 to 1.69, 0.19 (0.22 to 1.70) and 1.41 (0.70 to 2.87) respectively (Sciannameo et al., 2019).

3.4 Studies in other industries

An investigation was carried out to determine the cause of death and the incidence of tumours among 1932 workers in a ferrochromium plant in Sweden. The workers had been exposed mainly to metallic and trivalent chromium (Cr3+); hexavalent chromium (Cr6+) was also present in certain working operations. The population was defined as all men employed at the plant for at least one year during 1930-75, and were classified according to their occupation within the industry. Employees were classified into working groups with respect to Cr3+ and Cr6+ using recent exposure data and discussions with older current and former employees. The causes of death were initially obtained from parish registers. For deaths occurring between 1951 and 1975, death certificates were collected from the National Central Bureau of Statistics. Data on the incidence of cancer during 1958-75 were obtained from the Swedish National Cancer Registry. Expected death rates and incidence of tumours were calculated, based on the rates for the county in which the factory was situated. Five cases of respiratory cancer were found, against an expected 7.2. Among maintenance workers, an increased number of respiratory tumours was found. Two of the latter were mesotheliomas and could be connected with asbestos exposure. No increase was found for respiratory tumours among the heavily exposed workers at the arc-furnaces; one case of mesothelioma was found in this group (Axelsson et al., 1980).

Results were presented of a cohort study on the incidence of cancers and crude death rates in ferrochromium and ferrosilicon workers. The whole cohort was observed from 1 January 1953 to 31 December 1985. Two sets of results were presented; one restricted to workers first employed before 1960 and one to workers first employed before 1965. Concentrations of total dust in the working area near the ferrosilicon furnaces ranged from 0.8 to 5 mg/m^3 at the tapping floor, from 3 to 10 mg/m^3 during tapping and from 6 to 26 mg/m^3 during charging, whereas maintenance workers operating in an atmosphere containing between 4 and 36 mg/m^3 of mixed dust. The ferrochromium furnace operators worked in an atmosphere from 0.3 to 24 mg/m^3 general dust and from 0.04 to 0.29 mg/m^3 total chromium. The highest concentration was during packing when the concentration of mixed dust sometimes exceeded 25 mg/m^3. It was on the tapping floor that workers spent a great proportion of their active working time. At the charge floor the mean concentration of total chromium was 0.05 mg/m^3 of which 11 to 33% was water soluble. The latter cohort consists of 1,235 workers. An excess of lung cancer (SIR = 154) was observed in the ferrochromium workers employed before 1965 (Langård et al., 1990).

A multicentre cohort of 11,092 male welders from 135 companies located in nine European countries was assembled with the aim of investigating the relation of potential cancer risk, lung cancer in particular, with occupational exposure. The observation period and the criteria for inclusion of welders varied from country to country. Follow up was successful for 96.9% of the cohort and observed numbers of deaths (and for some countries incident cancer cases) were compared with expected numbers calculated from national reference rates. Mortality and cancer incidence ratios were analysed by cause category, time since first exposure, duration of employment, and estimated cumulative dose to total fumes, chromium (Cr), Cr VI, and nickel (Ni). Overall, a statistically significant excess was reported for mortality from lung cancer (116 observed vs 86.8 expected deaths, SMR = 134). When analysed by type of welding an increasing pattern with time since first exposure was present for both mild steel and stainless steel welders, which was more noticeable for the subcohort of predominantly stainless steel welders. No clear relation was apparent between mortality from lung cancer and duration of exposure to or estimated cumulative dose of Ni or Cr. Whereas the patterns of lung cancer mortality in these results suggest that the risk of lung cancer is higher for stainless steel than mild steel welders the different level of risk for these two categories of welding exposure cannot be quantified with precision (Simonato et al., 1991).

A re-analysis of this study using a JEM examined lung cancer mortality for stainless steel welders with at least 5 years of employment by cumulative exposure after 20 years since first exposure. For none of the cumulative exposure categories for chromium VI for ever stainless steel welders or predominantly stainless steel welders was the SMR significantly raised, although there were fewer than 10 cases in each exposure category (Gérin et al., 1993).

The cancer incidence in a historical cohort of 10,059 metal workers employed during the period 1964-1984 was investigated. Standardized incidence ratios (SIR) were calculated based on registry extracts from the Danish Cancer registry. Lifetime exposure data (occupational and other) were obtained by a postal questionnaire in living cohort members and interviews by proxy for deceased and emigrated subjects. The incidence of lung cancer was increased among workers ever "employed as welders" (SIR = 1.38, 95% C.I. 1.03 to 1.81). There was a significant excess risk of lung cancer among "mild steel (MS) only welders" (SIR = 1.61, 95% C.I. 1.07 to 2.33) and "nonwelders" (SIR = 1.69, 95% C.I. 1.23 to 2.26) (indicating carcinogenic exposures other than welding), a borderline significant lung cancer excess among "MS ever welders" (SIR = 1.32, 95% C.I. 0.97 to 1.76), and a nonsignificant excess risk of lung cancer among "stainless steel (SS) only welders" (SIR = 2.38, 95% C.I. 0.77-5.55) (Hansen et al., 1996).

The association between welding and lung cancer has been studied in a nested case-referent study within a cohort of 8,372 metal workers in Denmark. Lifetime exposure data on welding and other occupational exposures, as well as alcohol and smoking habits, were obtained by interviews of spouses and colleagues. Analysis was based on 439 deceased controls and 94 deceased cases. There was a 70% excess of lung cancer associated with "welding exposure ever" (OR +/- 95% C.I.: 1.68, 1.02 to 2.78). Overall OR for "mild steel (MS) welding ever" was 1.64 (95% CI, 0.99 to 2.72). The risk estimates for welding exposures showed an increasing tendency up to 15 years of exposure. The pattern of stainless steel welding resembles that of mild steel with an estimated OR of 1.65, 0.88-3.0 (Lauritsen and Hansen, 1996).

A retrospective cohort study evaluated the risk of lung cancer in aerospace workers with a minimum of 6 months' employment in jobs with chromium [VI] exposure (n = 2429). Standardized incidence ratios (SIR) estimated the risk of lung cancer by duration of employment in chromate-exposure jobs and cumulative exposure based on industrial hygiene and work-history data. Jobs were classified into categories of "high" (spray painters, decorative painters), "moderate" (sander/maskers, maintenance painters) and "low" (chrome platers, surface processors tank tenders, polishers, paint mixers) exposure. To estimate cumulative exposure, each exposure category was assigned a summary time-weighted average, based on the weighted time-weighted averages and the information from the industrial hygienists. The overall SIR for lung cancer was 0.8 (observed (Obs) = 15). Lung cancer risk was inversely related to estimates of cumulative chromate exposure and duration of employment as a painter. Although based on few cases, an elevated lung cancer risk was found in subjects who had worked for 5 or more years as a chrome plater or surface processor tank tender (Obs = 2, SIR = 1.9) and sander/masker or polisher (Obs = 3, SIR = 2.7). A clear association was not observed between chromate exposure and the risk of lung cancer in this population of workers (Alexander et al., 1996).

A cohort consisting of 233 welders working on stainless steel and exposed to high levels of chromium was selected. According to an earlier survey, the hexavalent chromium exposures of such welders are often above 20 $\mu g/m^3$. Another cohort consisting of 208 railway track welders exposed to low levels of chromium was also selected. The participants of both cohorts had welded for at least five years between 1950 and 1965 and were followed for mortality until December 1992. Among the welders exposed to high levels of chromium, six deaths due to pulmonary tumours occurred. This number is higher than the two deaths that occurred among the welders exposed to low levels of chromium and the corresponding mortality of the general population, but not significantly higher (Milatou-Smith et al., 1997).

A cohort of 1,172 male masons exposed to cement and hexavalent chromium was followed-up. The cohort was defined as those who had served their apprenticeship and were fully licensed as masons (cement finishers), were born after 1880 and were alive in 1955. The men were exposed to an aerosol of wet concrete, particularly when spraying. According to the analyses of urinary chromium the masons were exposed to hexavalent chromium. The concentration of hexavalent chromium in Icelandic cement in 1983 was 5.8 to 9.4 mg/kg. After the use of ferrous sulphate as a reduction agent began in 1992, the hexavalent chromium dropped to less than 2 mg/kg. In 1987, the mean concentration of total dust in the air, measured in personal samples from eight masons over a three day period was 16.3 mg/m^3. The highest concentration was measured while the masons were spraying. The amount of total chromium in the samples ranged from detection limits of 0.004 mg/m^3 to 0.008 mg/m^3. A computer file on masons was record linked to the Cancer Registry. The SIR for lung cancer was 1.69 in the total cohort and 1.77 when a lag of 30 years was included. The SIR for lung cancer among those born in 1920 or later was 1.86. Results from a postal questionnaire showed that fewer masons had never smoked and more masons had stopped smoking than the controls from the general population (Rafnsson et al., 1997).

A retrospective cohort mortality study was conducted of workers employed for at least 1 year at a large aircraft manufacturing facility in California on or after 1 January 1960. The workers were potentially exposed to compounds containing chromate, trichloroethylene (TCE), perchloroethylene (PCE) and mixed solvents. Individual workers were classified into categories of routine, intermittent or no likely exposure to chromate and the other exposures. A total of 3,634 (8%) of workers had potential chromate exposure. An additional 3,809 (8%) had potential for intermittent chromate exposure). The mortality experience of these workers was determined by examination of national, state, and company records to the end of 1996. The SMRs for 40 causes of death categories were computed for the total cohort and for subgroups defined by sex, race, position in the factory, work duration, year of first employment, latency, and broad occupational groups. Factory job titles were classified as to likely use of chemicals, and internal Poisson regression analyses were used to compute mortality risk ratios for categories of years of exposure to chromate, TCE, PCE, and mixed solvents, with unexposed factory workers serving as referents. The study cohort comprised 77,965 workers who accrued nearly 1.9 million person-years of follow up (mean 24.2 years). Factory workers estimated to have been routinely exposed to chromate were not at increased risk of lung cancer (SMR 1.02) (Boice et al., 1999).

The mortality of workers involved in the production of stainless and alloyed steel from 1968 to 1992 was studied, in order to investigate the risk of lung cancer due to exposure to metals, i.e. iron oxides, chromium and/or nickel compounds. The study design was a historical cohort mortality study and a nested case-control study concerning lung cancer. A panel of five experts developed a JEM of semi-quantitative estimates of exposure to metals, including chromium and/or their compounds. Intensity and frequency estimates for chromium were assigned 0 for no exposure, and 1, 2 and 3 for low, medium and high exposure. Probability was also used to estimate the accuracy of the intensity and frequency codes. SMRs were computed using regional mortality rates as an external reference for comparing observed and expected numbers of deaths. Conditional logistic regression was used to estimate odds ratios (ORs). Occupational exposure was assessed through the complete job histories of cases and controls and a specific job-exposure matrix. The cohort comprised 4,288 male and 609 female workers. No significant SMR was observed for mortality from lung cancer (54 deaths; SMR = 1.19; CI 0.88 to 1.55). The case-control study was based on 54 cases and 162 individually matched controls. Smoking habits were available for 71%. No lung cancer excess was observed for exposure to chromium and/or nickel (OR = 1.18, CI 0.62 to 2.25). Adjustments for tobacco consumption did not reveal any confounding effect from smoking (Moulin et al., 2000).

The increased occurrence of lung cancer in residents of Dolny Kubin, the North-Slovakia district with ferrochromium industry, compared to the general population of Slovakia, led the authors of this paper to study the influence of occupational and environmental exposure to chromium on the lung cancer incidence, respecting also the risk coming from cigarette smoking. Men were divided into three subgroups according to exposure: 0 – not particularly exposed to chromium,; 1 = workers of ferrochromium workers not directly exposed to chromium; and 2 workers directly exposed to chromium (smelters, tapers, crane operators). Residents of Dolny Kubin district with diagnosed lung cancer in 1984-1999 were involved in the study. The occurrence of lung cancer was significantly higher in people working in ferrochromium industry. The age at the onset of the disease in people exposed to chromium was by 5.5 years lower than in non-exposed. Smoking was an important risk factor, which has been proved particularly in the non-exposed group where 62% were smokers and the onset of the lung cancer in them occurred about 3.4 years earlier than in non-smokers. In exposed groups, no significant effect of smoking was found (Halasová et al., 2005).

A study was conducted to see if an elevated risk of lung cancer was caused by welding emissions or by confounding by smoking or asbestos exposure. Male metal workers employed for at least 1 year in Danish stainless or mild steel industrial companies between 1964 and 1984 were enrolled in a cohort. Data on occupational and smoking histories were obtained by questionnaire in 1986. A welding exposure matrix with more than 1000 workplace measurements of particulates in ambient air was used to estimate accumulated exposure to welding fume particulate until 1985 (mg/m^3.years). Welders in the cohort who started welding in 1960 or later were followed from 1968 to 2003 for cancer incidence. The SIR for lung cancer for welders was 1.35 (1.06 to 1.70). Among the stainless steel welders, the risk increased significantly with increasing cumulative welding particulate exposure, while no exposure-response was found for mild steel welders, even after adjustment for tobacco smoking and asbestos exposure (Sørensen et al., 2007).

A cohort consisted of male workers in 6 Portland cement factories in Korea was studied. Study subjects were classified into five groups by job: quarry, production, maintenance, laboratory, and office work. Cancer mortality and incidence in workers were observed from 1992 to 2007 and 1997 to 2005, respectively. Standardized mortality ratios and standardized incidence ratios were calculated according to the five job classifications and none was statistically significant. The SMRs for lung cancer were 0.00 (0.00 to 1.38), 1.36 (0.72 to 2.33), 0.28 (0.01 to 1.59), 2.60 (0.32 to 9.41) and 1.28 (0.55 to 2.52) respectively. The respective SIRs were 0.79 (0.10 to 2.85), 0.84 (0.36 to 1.66), 0.87 (0.18 to 2.56), 2.72 (0.33 to 9.84), and 1.45 (0.69 to 2.66) (Koh et al., 2011).

3.5 Population-based Studies

A pooled cases control study of 19 previous epidemiological studies of occupational chromium poisoning in 14 cities in China has been published (Yang et al., 2013). The studies were conducted between 1983 and 2010. Workers with Cr VI exposure in production workshops were considered as the exposed groups, while coworkers with no Cr VI exposure were designated as controls. The pooled odds ratio for lung cancer was 3.53 (1.97 to 6.32). It is not clear whether adjustment was made for potential confounding factors.

The risk of lung cancer after exposure to welding fumes, hexavalent chromium and nickel was examined among men from two German population-based case control studies (2,418 cases; 3,488 controls). Exposure to CrVI was assessed by substituting the original shift concentration of a welding exposure matrix (WEM) that was developed for a European cohort of welders with estimates derived from measurements at German workplaces. This WEM was linked to individual welding histories that were acquired from a welding-specific questionnaire to estimate cumulative exposure to CrVI. The combined odds ratio for chromium VI after adjusting for the other exposures under study (including smoking and other at-risk occupations) was 1.85 (1.35 to 2.54). Risk estimates increased with increasing cumulative exposure to Cr (VI) (Pesch et al., 2019).

Lung cancer risks were examined in relation to quantitative indices of occupational exposure to Cr (VI) and nickel and their interaction with smoking habits in 14 case-control studies from Europe and Canada, including 16,901 lung cancer cases and 20,965 controls. A measurement-based job-exposure matrix estimated job-year-region specific exposure levels to Cr (VI) and nickel. Due to their high correlation, the authors refrained for mutually adjusting for Cr (VI) and nickel independently. In men, ORs for the highest quartile of cumulative exposure to Cr (VI) was 1.32 (1.19 to 1.47). The analogous result for women was 1.04 (0.48 to 2.24). In men, excess lung cancer risks due to occupational Cr (VI) exposure were also observed in each stratum of never, former and current smokers (Behrens et al., 2023).

4 Synthesis and Discussion

The current prescriptions that involve hexavalent chromium and lung cancer are set out at Appendix 3. It can be seen that the prescription is restricted to specific chromate salts in the pure forms, specifically calcium chromate, zinc chromate and strontium chromate. It became prescribed in 1986[1].

Five reviews of chromium VI and lung cancer were identified in the Phase 1 report. A systematic review and quantification of respiratory cancer risk for occupational exposure to hexavalent chromium has been published. The review contains five studies of two cohorts of chromium production workers (Seidler et al., 2013).

An overview of occupational cancer in painters in Korea reported that the epidemiologic studies show a causal relationship of commercial painting and lung cancer with a meta-RR of 1.34 (95% CI: 1.23 to 1.41) (Myong et al., 2018). However, hexavalent chrome is one of a number of carcinogens that painters are potentially exposed to.

A review of the carcinogenicity of hexavalent chrome with a focus on the regulatory authorities' views on its carcinogenicity has been published (Kim et al., 2018). Occupational circumstances mentioned were chromate production and chromium plating. A question mark remained about stainless steel welding because of co-exposure to other lung carcinogens.

A 2019 meta-analysis examined hexavalent chromium and the incidence and mortality of human cancer (Deng et al., 2019). For respiratory system cancers, 44 cohort studies were included. The meta-SMR for lung cancer from the random effects meta-analysis was 1.31 (1.17 to 1.47). In subgroup analysis, the meta-SMR was significantly higher among male workers, in North America, and in Europe than in female workers and in Asia. The meta-SMRs were higher in chromate production workers, chromium platers, and welders, than in cement production workers, aircraft manufacturing workers and tanners. A review by (Alvarez et al., 2021) focussed on the full range of health effects associated with chromium VI compounds. Whilst this included cancer, their review did not focus on the size of any relative risks and nor did it focus much on the occupational circumstances giving rise to lung cancers.

For lung cancer following exposure to hexavalent chromium, the most recent IARC Monograph (IARC Working Group, 2012) stated that almost all of the relative risk estimates were greater than 1.0. Among chromate production workers, virtually all studies showed excess risks of lung cancer, except for a few estimates of risks for US workers hired since exposures were lowered (Luippold et al., 2005), but these latter analyses had few subjects and low statistical power. Similarly, studies of chromate pigment production workers tended to show elevated risks of lung cancer in nearly all the cohorts and subcohorts reported, though not every relative risk estimate was statistically significantly increased. Also, among chromium electroplating workers, there was a clear pattern of excess risk in most cohorts. Workers in other industries who may have had somewhat lower levels of chromium VI exposure than those in the previously mentioned industries, had a less convincing set of relative risk estimates, though nearly all were above 1.0. A few of the cohort studies collected high-quality data on smoking histories, and incorporated these into nested case-control analyses; these tended to show elevated risks independent of smoking, and when smoking was adjusted for the relative risk of chromium VI exposure was increased. Many of the epidemiological studies were limited by co-exposures to other occupational lung carcinogens (e.g. certain other metals, asbestos) and a lack of adjustment for these and for smoking.

[1] IIAC. Occupational Lung Cancer, 1986

There was an information note on Lung cancer and welding published in 2013[2]. It recognised that some welding fumes, such as those from stainless steel contain recognised lung carcinogens (e.g. hexavalent chromium). The information note referred to recently carried out meta-analyses (at that time) and concluded that the weight of evidence examined by the Council confirms the probable (lung) carcinogenicity of welding fume. Few, however, of the individual risk estimates, and none of those in aggregate (from the meta-analysis), reached the necessary threshold for prescription (of greater than or equal to 2).

[2] https://www.gov.uk/government/publications/lung-cancer-and-welding-iiac-information-note

5 Conclusions

Chromate production workers have been at increased relative risk of lung cancer, which are more than doubled. However, it may be possible than this risk has decreased in more recent years. It is not clear from the current prescription if exposure to "zinc chromate, calcium chromate and strontium chromate in their pure forms" adequately cover chromate production work (in the UK), particularly in the earlier years of operation. From the epidemiological evidence there is no reason to differentiate between different chromium salts or require them to be in a pure state.

There is a suggestion from the literature that the relative risks of lung cancer in this industry are reduced after a certain date potentially to a level below 2, possibly from the 1980s onwards. This could usefully be further clarified, taking into account latency, perhaps in consultation with the industry.

Smoking data were not always available and when present were highly variable, and not based on the ideal assessment of cumulative pack-years. However, where smoking was adjusted for there often remained an excess lung cancer risk due to hexavalent chromium.

IIAC has previously examined the relative risks of lung cancer (due to chromium and other exposures) in chrome plating and certain forms of welding. It may be worth revisiting these issues to see if there is now any robust evidence of a doubling of the relative risk. Another industry worth examining for historic risks is cement production, although as for chromate production, this risk may have been removed or diminished due to changes in the production process. Finally given that IARC has classified work as a painter as definitely carcinogenic, it may be useful for IIAC to see to what extent there might be an increased risk among painters who used chrome-based paints.

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Appendix 1- Data Extraction Spreadsheet and List of All the References Considered

Data extraction CrVI + lung cancer final fo

Chrome_VI_and_Lung_Cancer_All Papers.x

Appendix 2- Table for chromium and lung cancer from the most recent IARC Monograph

100C-04-Table2.1.pdf

Appendix 3- Current prescriptions for Chromium VI and Lung Cancer

Primary carcinoma of the lung.	Exposure to zinc chromate, calcium chromate or strontium chromate in their pure forms

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