Department for Work and Pensions

Department for Work and Pensions Social Security Administration Act 1992

Chromium and sino-nasal cancer

Report by the Industrial Injuries Advisory Council in accordance with Section 171 of the Social Security Administration Act 1992 considering prescription for chromium and sino-nasal cancer.

Presented to Parliament by the Secretary of State for Work and Pensions
By Command of Her Majesty
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INDUSTRIAL INJURIES ADVISORY COUNCIL

Secretary of State for Work and Pensions

Dear Secretary of State,

REVIEW OF CHROMIUM AND SINO-NASAL CANCER

We present our report which considers prescription for sino-nasal cancer due to exposure to chromium. The metal chromium can exist in several different reactive forms, known as oxidation states, which are used in a variety of industries. Among these, compounds of hexavalent chromium (chromium VI) are known to be carcinogenic under some circumstances. In April 2008 you asked the Council to consider the case for prescription of sino-nasal cancer in relation to chromium exposure.

Sino-nasal cancer is a rare disease, comprising cancers of the inside of the nose and of the paranasal sinuses. During the course of our investigation we have reviewed relevant research papers and found evidence of a greater than doubled risk of sino-nasal cancer in workers exposed to chromium VI in the processes of chromate production and chrome plating. The rarity of the disease means that relatively few cases occurred in the studies on which this report depends; but in these industries, findings were consistent and persuasive.

We recommend that sino-nasal cancer due to work involving hexavalent chrome plating or the manufacture of inorganic chromates should be added to the list of prescribed diseases.

Yours sincerely,

Professor K Palmer

Chairman
December 2009

Summary

1. Sino-nasal cancer, which encompasses cancers of the inside of the nose and of the paranasal sinuses, is a rare disease in the UK. The disease is currently prescribed in relation to exposure to wood dust and leather working, for which there is strong evidence of an increased risk. In 2008 Lord McKenzie, Parliamentary Under-Secretary of State, asked the Council to consider the case for prescription of sino-nasal cancer in relation to chromium exposure. His request was prompted by a letter received from an MP regarding a constituent.

2. Following processing, the metal chromium exists in several forms, principally metallic chromium (chromium 0), trivalent chromium (chromium III), and hexavalent chromium (chromium VI). The Council considered a body of evidence relating to a number of industries in which exposure to these different forms of chromium occurred, namely chromate production, chrome plating, chromium pigment production, stainless steel welding and the leather and tanning industries.

3. Evidence from a number of studies provided support for an association between sino-nasal cancers and chromium VI in certain industries. Positive associations, in which the risk was more than doubled, were most clearly evident in workers involved in chromate production and chrome plating.

4. By contrast a number of studies involving exposure to chromium VI in chromium pigment production and in stainless steel welding failed to provide evidence of an increased risk in these groups of workers. Similarly, the results of studies involving exposure to metallic and trivalent chromium (notably the leather tanning industry) were not strongly suggestive of an association with sino-nasal cancers.

5. In chrome plating, cases were reported after quite short durations of exposure (1 to 2 years), but comparative information for the chromate industry was lacking. It was decided, therefore, that there was insufficient evidence to indicate a required duration of exposure.

6. It was also noted that process changes introduced into chromate production by 1960 may have reduced exposures. The Council considered, therefore, whether to apply a cut-off date to the prescription recommended in respect of work in chromate production. However, given the high relative risks of sino-nasal cancer before 1960, and the limited research evidence afterwards, the Council decided that such a restriction would not be well supported by the evidence and should not be applied.

7. The Council recommends, therefore, that sino-nasal cancer be added to the list of diseases for which Industrial Injuries Disablement Benefit is payable, for those who have worked in (1) hexavalent chrome plating; or in (2) the manufacture of inorganic chromates.

This report contains some technical terms, the meanings of which are explained in a concluding glossary.

Introduction

8. In April 2008, Lord McKenzie, Parliamentary Under-Secretary of State, asked the Council to consider the case for prescription of sino-nasal cancer associated with chromium exposure. His request was prompted by a letter received from an MP regarding a constituent. The Council carried out a preliminary literature search and subsequently a full review of the evidence in relation to this matter. This paper describes the findings of this review and the Council's recommendations relating to prescription.

The Industrial Injuries Disablement Benefit Scheme

9. The Industrial Injuries Advisory Council (IIAC) is an independent statutory body that advises the Secretary of State for Work and Pensions in Great Britain and the Department for Social Development in Northern Ireland on matters relating to the Industrial Injuries Scheme. The major part of the Council's time is spent considering whether the list of prescribed diseases for which benefit may be paid should be enlarged or amended.

10. The Industrial Injuries Disablement Benefit (IIDB) Scheme provides a benefit that can be paid to an employed earner because of an industrial accident or Prescribed Disease.

The legal requirements for prescription

11. The Social Security Contributions and Benefits Act 1992 states that the Secretary of State may prescribe a disease where he is satisfied that the disease:

a) ought to be treated, having regard to its causes and incidence and any other relevant considerations, as a risk of the occupation and not as a risk common to all persons; and

b) is such that, in the absence of special circumstances, the attribution of particular cases to the nature of the employment can be established or presumed with reasonable certainty.

12. In other words, a disease may only be prescribed if there is a recognised risk to workers in an occupation, and the link between disease and occupation can be established or reasonably presumed in individual cases.

13. In seeking to address the question of prescription for any particular condition, the Council first looks for a workable definition of the disease. It then searches for a practical way to demonstrate in the individual case that the disease can be attributed to occupational exposure with reasonable confidence. For this purpose, reasonable confidence is interpreted as being based on the balance of probabilities according to available scientific evidence.

14. Within the legal requirements of prescription it may be possible to ascribe a disease to a particular occupational exposure in two ways – from specific clinical features of the disease or from epidemiological evidence that the risk of disease is at least doubled by the relevant occupational exposure.

Clinical features

15. For some diseases attribution to occupation may be possible from specific clinical features of the individual case. For example, the proof that an individual's dermatitis is caused by his/her occupation may lie in its improvement when s/he is on holiday, and regression when they return to work, and in the demonstration that they are allergic to a specific substance with which they come into contact only at work. It can be that the disease *only* occurs as a result of an occupational hazard (e.g. coal workers' pneumoconiosis).

Doubling of risk

16. Other diseases are not uniquely occupational, and when caused by occupation, are indistinguishable from the same disease occurring in someone who has not been exposed to a hazard at work. In these circumstances, attribution to occupation on the balance of probabilities depends on epidemiological evidence that work in the prescribed job, or with the prescribed occupational exposure, increases the risk of developing the disease by a factor of two or more.

17. The requirement for, at least, a doubling of risk follows from the fact that if a hazardous exposure doubles risk, for every 50 cases that would normally occur in an unexposed population, an additional 50 would be expected if the population were exposed to the hazard. Thus, out of every 100 cases that occurred in an exposed population, 50 would do so only as a consequence of their exposure while the other 50 would have been expected to develop the disease, even in the absence of the exposure. Therefore, for any individual case occurring in the exposed population, there would be a 50% chance that the disease resulted from exposure to the hazard, and a 50% chance that it would have occurred even without the exposure. Below the threshold of a doubling of risk only a minority of cases in an exposed population would be caused by the hazard and individual cases therefore could not be attributed to exposure on the balance of probabilities; above it, they may be.

18. The epidemiological evidence required should ideally be drawn from several independent studies, and be sufficiently robust that further research at a later date would be unlikely to overturn it.

19. Sino-nasal cancer is not exclusively occupational and does not have unique clinical features when it occurs in an occupational context. The case for prescription, therefore, rests on reliable evidence of a doubling or more of risk in workers with a history of exposure to a putative occupational risk factor, in the case of this enquiry, chromium and/or compounds of chromium.

Sino-nasal cancer

20. The term sino-nasal cancer encompasses cancers of the inside of the nose and of the paranasal sinuses. The paranasal sinuses are spaces within the bones, behind the nose and cheeks. Each space, or sinus, is lined with cells that produce mucus to prevent the lining of the nose from drying out and to moisten the air that we breathe.The most common type of sino-nasal cancer, accounting for approximately 60%, is squamous cell carcinoma. Squamous cells are the flat, skin like cells that cover the lining of the mouth, nose, larynx, thyroid and throat. Adenocarcinomas, account for approximately 2% of sino-nasal cancers. Adenocarcinomas originate in mucus-producing gland cells (adenomatous cells) which are located in the surface tissues inside the nose.

21. Although relatively common in some parts of the world and among certain ethnic groups (southern Chinese and inhabitants of South East Asian and Arctic regions), sino-nasal cancer is extremely rare in the UK. About 300 cases are diagnosed a year, the annual incidence rate between 1994 and 2002 being 0.8 per 100,000 for males and 0.5 per 100,000 for females (Office of National Statistics, 2005). The five year survival rate from diagnosis is approximately 50%, although prognosis varies depending on the histological type of cancer.

22. There is strong evidence that exposures to wood dust and leather working increase the risk of nasal cancer and significantly increased rates of the disease have been observed in carpenters, cabinet makers and wood machinists as well as in shoemakers. There has also been suggestive evidence of an association with certain chemical exposures, including nickel and chromium, and with activities involving these substances, such as welding and soldering. In addition, cases occurring in leather workers and shoemakers have sometimes been attributed to the use of chromium in leather tanning.

23. There are no well-established non-occupational risk factors for sino-nasal cancer. However, there is some evidence that smoking, and smoking and alcohol in combination, may moderately increase the risk of this disease (see paragraph 36).

Chromium

24. Chromium is a silver white metal derived from the mineral chromite. Following processing, chromium exists in several forms, also known as oxidation states.* The principal forms are metallic chromium (chromium 0), trivalent chromium (chromium III), and hexavalent chromium (chromium VI).

* The term ‘chrome’ is sometimes used to mean the metal chromium (valence sate 0). It is also used within industry, without implication as to valency, to denote a process (e.g. chrome plating) or an occupation (e.g. chrome plater) or a product of chromium (e.g. chrome yellow pigment).

25. Metallic chromium is used in the preparation of a wide range of metal alloys, being valued for its ability to confer corrosion resistance. A particular use is in the production of stainless steel, which may contain up to 36% chromium (International Agency for Research on Cancer (IARC), 1990).

26. Trivalent chromium compounds have traditionally been used in the production of dyes and paint pigments, wood preservatives and in the tanning of leather. Chromium III also occurs in chrome plating (though less often than hexavalent chromium); and in small quantities in certain foods, including processed meats, wholegrain bread and cereals and pulses and spices.

27. A major use of hexavalent chromium is in chrome plating (a technique of electroplating a thin layer of chromium on to a metal object, particularly applied in the car and aircraft industries). Exposure to chromium VI compounds may arise in a wide range of industrial processes throughout the world – for example, in the production of pigments for inks, paints and varnishes (notably as lead chromate), in leather tanning, wood preservation and textile dying (as sodium chromate), stainless steel welding, and in the production of cement.

28. Today the main occupational activities with potential exposure to compounds of chromium include stainless steel welding, cutting and grinding, and electroplating, processes that involve many thousands of workers. Smaller numbers are employed in other manufacturing processes that involve compounds of chromium. In the UK, chromate production contracted in the late 1960s and is now largely confined to a single plant employing a few hundred workers.

Health Risks

29. It is well established that exposure to certain chromium compounds may cause dermatitis and irritation of the nose and upper respiratory tract. Long-term exposure may result in ulceration of the nasal membranes and holes in the flap of tissue which separates the nostrils (nasal septum). Dermatitis and ulceration of the mucous membranes or epidermis, resulting from exposure to chromic acid, chromates or dichromates are currently prescribed (PD C30).

30. In addition, epidemiological studies carried out in a number of countries have consistently shown excess risks of lung cancer in chromium-exposed workers. These studies have involved workers exposed to different forms of chromium. However, metallic chromium and chromium III are considered to be much less toxic than chromium VI. On the basis of epidemiological evidence and corroborative animal data, including investigations of biological mechanisms, the IARC (1990, 1997) concluded that there was sufficient evidence in humans for the carcinogenicity of chromium VI, but not for the carcinogenicity of metallic chromium or chromium III compounds.

31. The IARC's conclusions related primarily to the question of whether compounds of chromium could cause lung cancer. However, the Agency also noted that studies of chromate production workers in the UK, Japan and the USA, of chrome platers in the UK and chromate pigment production workers in Norway had indicated an excess of sino-nasal tumours associated with exposure to chromium VI. The IARC concluded in 1997 that the evidence of an association between chromium VI exposure and sino-nasal cancer was "suggestive" rather than "strong", and repeated this view in 2009.

32. In its 1990 monograph, the IARC found that there was "sufficient evidence" that the hexavalent compounds calcium chromate, zinc chromate, strontium chromate and lead chromate are carcinogenic to laboratory animals. Limited evidence was found that the hexavalent chromium compounds, chromium trioxide (chromic acid) and sodium dichromate also cause cancer in laboratory animals, but inadequate evidence in relation to metallic chromium, barium chromate, trivalent chromium compounds and welding fumes.

33. Primary carcinoma of the lung is currently prescribed under the scheme in relation to certain of these agents, namely zinc chromate, calcium chromate, or strontium chromate in their pure forms (PD D10).

34. Since the publication of the IARC monographs, several new epidemiological studies relevant to risks of sino-nasal cancer in chromium workers have been published. The Council elected therefore to carry out a review of the current evidence and to consider the case for prescription.

Consideration of the evidence

35. The Council conducted a search of the literature relating to occupational exposure to chromium and cancers of the nose and paranasal sinuses. The relevant evidence identified included both cohort studies and case-control studies. In relation to the cohort studies considered in this review two points are important to note. First, the majority of cohort studies discussed here were investigations of mortality. Since current 5-year survival rates for sino-nasal cancer are approximately 50%, more recent mortality studies will not have included every case of the disease. This might bias estimates of relative risk in exposed versus unexposed populations, although only if exposures selectively caused non-fatal patterns of disease. Second, even large cohort studies may accumulate few cases if the disease in question is very rare, as is the case here.

36. A further consideration is that several of the mortality and incidence studies considered here lacked information on alcohol consumption and smoking. The association between smoking and sino-nasal cancer is uncertain. IARC (2004) reviewed nine studies and found that when all histological types of sino-nasal cancer were considered there was no statistically significant increased risk in smokers. However, in seven studies which considered dose-

response relationships, five showed a significant positive trend with increasing numbers of cigarettes smoked (Brinton *et al*, 1984; Hayes *et al*, 1986; Fukuda and Shibata, 1990; Zheng *et al*, 1992; Caplan *et al*, 2000). Zheng *et al* also showed a decreasing residual risk following smoking cessation. Other studies have shown that smoking significantly increases the risk for squamous cell carcinomas of the sino-nasal area, but not for adenocarcinomas (Brinton *et al*, 1984; Hayes *et al*, 1987; Strader *et al*, 1988; Zheng *et al*, 1992). On balance, the evidence suggests that smoking represents a moderate risk factor for sino-nasal cancer, particularly squamous cell carcinoma. By contrast, most studies have failed to find an association between alcohol consumption and nasal cancers (Brinton *et al*, 1984; Hayes *et al* 1987). However, one study (Strader *et al*, 1988) identified a three-fold increased risk of squamous cell carcinomas of the nasal cavities in those who consumed more than 21 alcoholic drinks per week. Moreover, further analysis suggested that smoking adds to the effect of drinking, such that, in those who consumed more than 21 alcoholic drinks per week, the relative risk increased from 2.4 in non-smokers, to 3.5 associated with smoking 20 pack-years, and 5.3 with smoking 40 pack-years.

37. In addition to an early review on the topic (paragraph 38), the Council identified a number of more recent studies with data on the association between sino-nasal cancer and exposure to chromium and its compounds. These cover the major sources of exposure to chromium VI, namely the production of chromium and chromium compounds, chrome plating, and the production of chromium-containing paints and pigments. Other reports related to exposure to chromium III and chromium metal, in leather tanning and in the use of chromium tanned leather. Finally, the Council has considered a number of papers which investigated the risk of sino-nasal cancer in stainless steel welders.

Studies involving exposure to hexavalent chromium (Chromium VI)

Chromate production

38. Some early data on chromium VI and cancer were contained in a review of the health risks associated with chromium exposure carried out by Enterline in 1974. The studies quoted in Enterline's review involved workers who were predominantly exposed to hexavalent chromium. In particular, an early study by Machle and Gregorius (1948) reports excess deaths from cancer of the nose and pharynx in three chromate plants. Cancer mortality rates (per 100,000/year) for male chromate workers in six US plants between 1930 and 1937 were compared with those of oil refinery workers over a similar period (1930-8). Over five times as many cancers of the 'oral region' were found in the chromate workers (27 versus 5). Enterline also reported a survey of employees of a chromate plant employed for at least one year between 1931 and 1936 (Mancuso *et al*, 1951). One of the 152 deaths which occurred during this period was from sinus cancer, which was considered to be high for this size of group.

39. In the UK, Alderson *et al* (1981) followed a cohort of 2715 men who had been employed for at least one year between 1948 and 1977 at one of three plants producing hexavalent chromium compounds. The process involved the conversion of insoluble chromium III to soluble chromium VI compounds (sodium chromate and calcium chromate) and thus carried the potential for exposure to both forms of chromium. This study represented a further update of a study originally reported by Bidstrup (1951) and Bidstrup and Case (1956), where an excess of lung cancer had been identified. Comparing rates with national mortality rates, Alderson *et al* similarly identified an increased risk of lung cancer but also a significant excess of nasal cancer at one site (observed 2, expected 0.15; p=0.03).

40. A further follow-up of this cohort was reported by Davies *et al* (1991), covering 2298 workers employed between 1950 and 1976, and focussing, in particular, on possible reductions in risk following major plant and process changes which took place between 1958 and 1960. The revised process involves lime-free conversion of chromite ore, thus eliminating the formation of calcium chromate, which has been demonstrated to be carcinogenic in animal experiments. At the two largest factories, among the 1422 men who started work before the process changes, there was a significant excess of lung cancer and also of nasal cancers (observed 4, expected 0.26; SMR 1538, equating to a Relative Risk (RR) of 15.38*). The four cases all had at least 20 years employment at the plant. In two cases tumours developed after a latency period of 54 years and 44 years and in two cases after latencies of nearly 30 years. In view of these very long latencies the authors questioned whether these might represent chance occurrences unrelated to chromium exposure. However, an excess risk would still apply, even with the removal of these two cases from the analysis. There was no excess risk of nasal cancers among those who started work following completion of the process changes, no further deaths from nasal cancer after 1983 and no excess at the other smaller plant.

41. A German study (Korallus *et al*, 1993) also focussed on investigating alterations in risk following a similar process change in two chromate producing plants. The data indicated a reduction in the risk of lung cancer and in the incidence of nasal septum perforation in those first exposed following process change. In this study, however, there were no reported deaths from nasal cancer throughout the 40 year period of follow-up, which included workers first exposed pre- and post-process change.

42. A mortality study carried out at four chromium smelting plants in the USA (Rosenman and Stanbury, 1996) involved 3408 workers ever employed there between 1937 and 1971. Exposure was to both hexavalent and trivalent chromium. Proportional Cancer Mortality Rates (PCMRs) were calculated for

* Certain estimates of relative risk are, by convention, and in the original publications, expressed after multiplying by 100; for ease of interpretation, in this summary they are not. The concluding glossary gives a fuller explanation

different cancers using US population data. There was a significantly increased PCMR for lung cancer. In addition, there was a significant excess of nasal cavity/sinus cancer (PCMR 5.18; 95% Confidence Interval (CI) 2.37-11.30) based on six cases, all in white males. The tumours were at different nasal sites (2 nasal cavity, 2 maxillary sinus, 1 nasal cavity/middle ear, 1 accessory sinuses undetermined). The increase in PCMR for white men occurred in all durations of work >1 year and all four worksites studied. All cases occurred within 20 years of leaving employment.

43. Also in the United States, Luippold *et al* (2003) investigated mortality in 493 former workers of a chromate production plant, employed for at least one year between 1940 and 1972. Workers were followed until 1997. Two cancer-related deaths for 'other parts of the respiratory system' were found (0.2 expected), of which one involved the maximillary sinuses (much above the expected rate in the general population).

Chrome plating

44. In the UK, Sorahan *et al* (1987) studied 2689 platers, exposed to hexavalent chromium and employed between 1946 and 1983. Chrome plating at the factory involved a process of electro-deposition using chromic acid. Cancer mortality rates were compared with general population rates for England and Wales. There were significant excesses for a number of cancers and a significant excess of cancer of the nasal cavity. This was based on three cases observed versus 0.3 expected (SMR 10.0; $p<0.05$). Separate analysis of mortality rates in those exposed only to nickel (an established carcinogen) indicated that this exposure was not significantly associated with an increased cancer risk in this group of workers. The three cases of nasal cancer occurred at least 10 years after first employment. There was no evidence for an association with two markers of chromium VI exposure (total duration of employment in chrome plating; years spent in chromium bath work). It was noted that chromium bath workers were the most heavily exposed group and there were significant increases in lung cancer and nasal ulceration in those employed in this particular type of work (confirmed at later follow-up; Sorahan *et al* 1998). All three cases of nasal cancer had some experience of this type of work. However, this was of relatively short duration. One case had two years employment with chromium bath work and two cases each had one year of this work.

45. A further mortality study of chrome platers (Sorahan and Harrington, 2000) involved a cohort of 1087 platers (920 men and 167 women), exposed to hexavalent chromium, from 54 plants in the UK. These workers were investigated for the period between 1972 and 1997. The focus of the paper was the investigation of lung cancer. However, one death from nasal cancer was observed (0.15 expected), giving an SMR of 6.87 although 95% CIs were wide (0.17-38.3). During the same period no deaths from nasal cancer were reported (0.17 expected) in a comparison group of 1163 workers with no exposure to chromium.

Chromium pigment production

46. In a small study, Langård *et al* (1975, 1983) followed 133 men employed during 1948-72 in a Norwegian plant producing chromium pigments. By 1980 there was one case of cancer of the nasal cavity. No relative risk was given, although the occurrence of a case of such a rare tumour in this small cohort is likely to be well above expectations. The authors note that this case occurred in a worker with only three months exposure, death occurring three years following first exposure.

47. A mortality study of workers producing hexavalent lead chromate and zinc chromate pigments at three plants in the UK was reported by Davies (1984). The study covered all male workers (1152) completing at least one year's unbroken service by June 1975, starting from 1933 which represented the earliest date for which records were available. The results indicated a significantly increased risk of lung cancer associated with medium or heavy exposure to zinc chromate. There was one recorded death from sino-nasal cancer which occurred in a fitter with access to all departments of the plant and therefore categorised as having medium exposure to zinc chromate. Exposure duration was two years and death occurred seven years following first exposure. Although the author considered a single case to be of doubtful significance, based on national death rates only 0.2 cases were expected.

48. A mortality study involving chromium pigment manufacturers in the United States, also exposed to hexavalent lead chromate and zinc chromate, was carried out by Hayes *et al* (1989). This study followed mortality in 1737 workers employed between 1940 and 1982. There was an excess of lung cancer which was associated with increasing duration of employment. However, there was no increase in deaths from other cancers. Nasal cancers were not mentioned, presumably due to an absence of cases. (The extremely low incidence of the disease in the general population is such that only very large studies can confidently exclude the possibility of an increased risk, however.)

Stainless steel welding

49. A number of cohort studies relating to stainless steel welding, carried out in diverse occupational and geographical settings, were identified. In addition, 5 case-control studies were found (summarised in paragraphs 68-73), of which two (Hernberg, 1983; d'Errico 2009), identified an increased risk associated with welding. The cohort studies were consistent in reporting no increased risk of sino-nasal cancer. The majority of studies examined the risk of a range of cancers and few made any reference to cases of sino-nasal cancer. It is assumed, therefore, that such cases were either absent or not in noteworthy excess. These studies are summarised briefly below.

50. Sjögren (1980) carried out a retrospective mortality study among 234 welders from eight different companies in Sweden employed for more than five

years between 1950 and 1965. Follow-up was until 1977. No cases of sino-nasal cancer were reported. In an extension of this study (Sjögren *et al*, 1987) compared two cohorts of welders considered to have high and low exposure to hexavalent chromium, which were followed until 1984. No cases were reported in either group. Further follow-up to 1992 (Milatou-Smith *et al*, 1997) confirmed these results.

51. Beaumont and Weiss (1980) carried out a prospective cohort study of 8679 members of the metal trades union in the Seattle area of the US, who had been employed for at least three years between January 1st 1950 and December 31st 1973. Follow-up was until 1977. There were no reported cases of sino-nasal cancer. Tumours of the buccal cavity (mouth) and pharynx, were reported for the group as a whole, and were not in excess of expectations.

52. Puntoni *et al* (1984) carried out a prospective cohort study on shipyard workers in Genoa, Italy who were employed or retired on January 1st 1960, and who were followed until December 31st 1975. Relative risks for different diseases in a range of occupations were calculated in relation to the general population of Genoa. There were no reported cases of sino-nasal cancer in welders.

53. Lam and Tan (1984) studied death rates for nasopharyngeal cancer among different occupational groups in Hong Kong between 1976 and 1981. The authors note that deaths from this cause in this region are among the highest in the world. There were 18 such deaths in plumbers and welders, giving a proportional mortality rate of 2.2, relative to the total population of Hong Kong. However, the authors cautioned that occupations given on death certificates refer only to the last occupation and that, in addition, death certificates in Hong Kong do not record the occupation of retired persons, both factors which complicate interpretation of the data. It should also be noted that these results related to plumbers and welders combined in an area of the world where this disease is unusually common.

54. Zheng *et al* (1992) studied occupational risks for nasopharyngeal cancer in Shanghai, where rates of this disease are similarly very high. The results did not support an increased risk in welders. Occupational data obtained from 996 patients diagnosed between 1980 and 1984 and compared with that for the general population, indicated a Standard Incidence Rate (SIR) of 0.72, based on 11 cases, for a broad grouping of workers which included welders, but also plumbers, sheet metal preparers and erectors.

55. Becker *et al* (1985) carried out a retrospective cohort study among 1224 welders and 1694 turners, first employed before 1970 at 25 German factories manufacturing sanitary installations, power plants and boilers. Follow-up was until 1983. No sino-nasal tumours were reported. Two subsequent follow-ups, to 1988 and to 1995 (Becker *et al*, 1991; Becker 1999), similarly reported no cases.

56. Newhouse *et al* (1985) studied the records of 1027 welders and other workers employed in a UK shipyard between 1940 and 1968. Follow-up was until 1982. No cases of sino-nasal cancer were reported.

57. Simonato *et al* (1991) carried out a multi-centre mortality and incidence study of 11,092 welders from 135 companies located in nine European countries. Death and incidence rates for various causes were calculated with reference to national rates. There were no reported cases of sino-nasal cancer. Over the whole study population, cases of cancer of the buccal cavity and pharynx were less common than expected.

58. Melkild *et al* (1989) investigated the incidence of cancer in 4778 Norwegian shipyard workers, including 783 steel welders, who had been employed for at least three months between January 1st 1946 and March 31st 1977. Follow-up was from 1953 to 1986. However, it was noted that stainless steel welding had only been carried out since 1974, previously work involving only mild steel welding. In shipyard workers as a whole there were two cases of nasal cancer, (SIR 2.11; 95% CI 0.21-7.58). However, there were no cases recorded in welders.

59. Hansen *et al* (1996) investigated cancer incidence in 10,059 Danish metal workers employed between 1964 and 1984. No cases of sino-nasal cancer were recorded in welders but there were four cases of buccal cavity tumours (below the number expected).

60. Apart from the investigation carried out in Hong Kong by Lam and Tan, only one study reported an increased risk of sino-nasal cancer in welders. Danielsen *et al* (1996) in Norway investigated cancer incidence amongst 2957 welders who were entered on the National Register of Boiler Welders, of whom 606 were stainless steel welders. Subjects were studied from the year of registration until 1992. The SIR for nasal cancer in welders as a whole, calculated by reference to rates in Norwegian men, was 3.33 (95% CI 0.66-9.78), based on three cases. However, separate analysis of the sub cohort of 606 welders registered for stainless steel welding showed no cases of nasal cancer.

Studies involving exposures to chromium III and chromium metal

Ferrochromium production

61. Axelsson *et al* (1980) carried out a mortality and incidence study among workers at a ferrochromium plant in Sweden. Exposures were to metallic and trivalent chromium. All men employed for at least one year between 1930 and 1975 (1876 workers) were included. Expected mortality and incidence rates for those resident in the county where the factory was situated were computed based on rates for that county. A 15 year latency was assumed for cancer incidence. The total number of deaths from all cancers was less than expected (69 versus 76.7 expected) and no increased mortality or incidence in respect

of any specific cancer was reported. Sino-nasal cancer was not mentioned, presumably because there were no cases.

62. A further study by Langård *et al* (1990) investigated cancer incidence among ferro-chromium and ferro-silicon workers in Norway. The study populations were selected because of their predominant exposure to chromium III; but 11-13% of the chromium measured in the work environment was water soluble and presumed to be in the hexavalent state. Workers were first employed between 1928 and 1964, although production of ferro-chromium did not begin until 1934, terminating in 1982. The observation period was from January 1953 to December 1985. For all cancers, incidence in ferro-chromium workers was slightly raised, (SIR 1.24; 95% CI 0.88-1.51; 56 observed, 48.3 expected) and there was an excess of lung cancer, (SIR 1.88; 95% CI 0.74-2.82; 10 observed, 6.5 expected). No mention is made by the authors of any cases of nasal cancer.

Leather and tanning industries

63. There have been several studies concerning work in leather tanning and sino-nasal cancer. Interpretation of the findings in relation to chromium III may be complicated by the potential for co-exposure to leather dust, itself an established and already prescribed occupational cause of the disease (PD D6). However, Pippard (paragraph 64) comments that exposure to leather dust in the tanning process is considered to be low since this is a wet process involving few dusty operations.

64. There have been three mortality studies involving the leather tanning industry. In the UK Pippard *et al* (1985) studied 833 male tannery workers employed between 1939 and 1982, of whom 573 were tanning using vegetable extracts and 260 were employed in chromium tanning. Death rates were compared with rates for England and Wales. One death was reported for nasal cancer (0.21 expected; SMR 4.76, 95% CI 0.12-26.53) which was not statistically significant. This death occurred in a vegetable tanner. No excess of deaths for other cancers was observed in either group.

65. Stern *et al* (1987) followed 9352 US chromium leather and tannery workers employed between 1940 and 1979. Workers were exposed to trivalent chromium sulphate, although they were also exposed to numerous other chemicals, including formaldehyde which has also been suspected as a risk factor for nasal cancer. Deaths from all causes were lower than expected when compared with general or local population rates. For all cancers the SMR was 0.79 (95% CI 0.70-0.89). However, there was one death from nasal cancer (0.4 expected) in an employee with more than 18 years employment in the finishing department of the tannery. The finishing process did not involve chromium exposure, although it did involve some exposure to formaldehyde. This study was subsequently updated (Stern, 2003) to include a further 11 years of follow-up, when a further 1153 deaths occurred. Ninety-two different causes of death were analysed. No further deaths from nasal cancer were observed.

66. Iaia *et al* (2006) carried out a mortality study involving 4874 workers at 92 Italian leather tanneries, employed between 1970 and 1998. Of these 972 were chromium tanners. The workers were exposed to numerous chemicals, including trivalent chromium. Overall mortality and cancer mortality rates for chromium tanners were below expected when compared with regional mortality rates. There was one death from nasal cancer, compared with 0.2 expected. The study included both chromium and vegetable tanners and it was not clear whether this death occurred in a chromium tanner.

67. In addition to the above mortality studies, Acheson *et al* (1982) carried out an incidence survey of men and women employed in the boot and shoe making industry in the UK, employed between 1950 and 1979. The average annual incidence rate for nasal cancer (all histological types) for males employed in the industry during the period was 55.4 per million compared with 12.2 per million for other men resident in the same area. However, nasal tumours only occurred in those employed in the finishing and preparation of soles and heels, a process which involved vegetable-based tanned leather. No cases were observed in those involved in the finishing and preparation of shoe uppers where leather is tanned using trivalent chromium compounds.

Case-control studies

68. In contrast to the previously described occupational cohorts, several investigators conducted case-control studies in which samples of hospital-assembled cases were compared with suitable non-cases (controls) in terms of their work exposures and experience. This approach has the advantage of identifying relatively large numbers of cases of a rare disease, but the potential disadvantage that exposures would be characterised more crudely (by patients' self-reports), and from a general population sample, among whom levels of exposures may be relatively light.

69. Hernberg *et al* (1983) collected all cases of nasal and sino-nasal cancer, diagnosed between 1977 and 1980, from the cancer registries of Finland and Sweden and from the hospital records of Denmark. Cases (167) were matched for age and sex with cases of colonic or rectal cancer. In an attempt to control for potential bias in exposure recollection, both groups were informed that their condition was the one under study. For exposure to chromium the Odds Ratio (OR) was 2.7 (95% CI 1.1-6.6). For welding, flame cutting and soldering the OR was 2.8 (95% CI 1.2-6.9), and where these activities involved chromium and/or nickel exposure it was 3.3 (95% CI 1.1-9.4). Since most workers were exposed to both chromium and nickel these cases could not be separated in the analysis. None of the workers had been involved in chrome production.

70. Brinton *et al* (1984) studied 160 patients in two US States, diagnosed between 1970 and 1980, matched with hospital and community based controls. Exposure to chromates was associated with a significantly increased

risk amongst males only (RR 5.09). However, exposure was predominantly as a result of exposure to products and paints in the building industry and the nature and range of other exposures could not be determined. A significant association with smoking was also noted with a two-fold increase in risk for males and 1.5 for females. In addition, more than 50 years smoking was associated with a three-fold risk. These risks appeared to be associated specifically with squamous cell carcinomas. The authors report that associations with occupational exposures were unaffected by control for use of tobacco products.

71. Comba *et al* (1992) identified all 78 cases of sino-nasal cancer diagnosed in five hospitals in Italy between 1982 and 1987. Age and sex matched controls (254) were drawn from hospital admissions for other conditions. A significantly increased risk was identified for leather workers who had been involved with shoemaking (OR 8.3, 95% CI 1.9-36) and for leather tanners who had not worked as shoemakers (OR 5.0 based on 2 cases; 95% CI 0.92-28), although it was not stated whether the shoemakers were involved in the processing of chromium tanned or vegetable tanned leather, or whether the tanners were involved in chromium or vegetable tanning. In this study an OR associated with smoking of 2.0 for males, and 0.83 for females was reported although, despite these findings, risk estimates for exposure to chromium III did not include adjustment for smoking.

72. Luce *et al* (1993) carried out a case-control study in France, involving all cases (207) diagnosed between January 1986 and February 1988 at 27 participating hospitals. They were matched for age and sex with hospital controls diagnosed with other forms of cancer and with controls derived from lists of friends and acquaintances of cases. For squamous cell carcinomas and adenocarcinomas ORs for 'probable or definite' exposure to chromium VI were 0.7 and 0.4 respectively. For other types of nasal tumours the OR was 2.4, although this was not statistically significant (95% CI 0.8-7.1). The authors concluded that there was no increased risk of sino-nasal cancer associated with chromium exposure. They noted that chromium exposures reported related mainly to stainless steel welding and spray painting of metals, and that consequently exposures might have been relatively low compared to those encountered among chromate production workers. Adjustment for smoking and alcohol consumption reportedly did not affect their results.

73. d'Errico *et al* (2009) collected all cases in the Piedmont region of Italy between 1996 and 2000. 113 cases were matched to 336 hospital based controls recruited from ear, nose and throat and orthopaedic departments, matched by age, sex and residence location. The study investigated a range of putative occupational risk factors and different histological types of sino-nasal cancer. A latency period (interval between exposure and disease) of 10 years was assumed and therefore any exposure occurring within 10 years of diagnosis

was excluded. The OR for all histological types with reported exposure to chromium VI was 2.8 (95% CI 0.55-14.06), for adenocarcinoma 2.1 (95% CI 0.22-21.1), and for other histological types of sino-nasal cancer 9.2 (95% CI 1.40-60.13). Of these only the last was statistically significant. There were no cases of squamous cell carcinoma associated with chromium VI exposure. Exposure to welding fume was considered separately. The adjusted OR for welding fume for all cases was 2.0 (95% CI 1.0-3.82), for adenocarcinoma was 1.3 (95% CI 0.52-3.52) and for squamous cell carcinoma was 4.1 (95% CI 1.66-10.13). However, it was noted that none of the nine cases of sino-nasal exposed to welding fume had been involved in stainless steel welding. Age, sex and smoking were not shown to be significant risk factors for sino-nasal cancer in this dataset, after accounting for occupational exposures.

Case series

74. A study by Lund (1991) constituted a case series, in which 50 patients diagnosed with sino-nasal cancer were interviewed about previous exposures. The most common exposure was to wood dust. No-one reported exposure to chromium compounds.

75. However, other cases of nasal carcinoma, possibly associated with chromium exposure, have been reported in the literature. Satoh *et al* (1994) described four cases who had worked in the same chromate factory in Japan for between 19 and 32 years.

Conclusions

76. Data from the mortality studies described in paragraphs 38 to 48 provide support for an association between sino-nasal cancers and exposure to chromium VI. This cancer is rare, posing a challenge to investigators seeking to demonstrate a significant excess risk. Absolute numbers of cases were small. Nonetheless, relative risks in the range of five to fifteen-fold have been reported in the studies quoted by Enterline (1974), and those by Langård *et al* (1975, 1983), Alderson *et al* (1981), Davies (1984), Sorahan *et al* (1987), Davies *et al* (1991), Rosenman and Stanbury (1996), Sorahan and Harrington (2000), and Luippold *et al* (2003). Set against this are two studies in which no reported cases have occurred (Hayes *et al*, 1989), Korallus *et al* (1993).

77. Positive reports have been most clearly linked with workers involved in chromate production (Enterline, 1974; Langård *et al* 1975, 1983; Alderson *et al* 1981; Luippold *et al* 2003) and chrome plating in the UK (Sorahan *et al* 1987; Sorahan and Harrington 2000). Data on chromium pigment production are more limited and less compelling.

78. In the chromate production and chrome plating industries latencies have generally exceeded 10 years, sometimes by a considerable margin. Most

investigations considered only workers with a minimum employment of one year. In chrome plating, cases were reported after quite short durations of exposure (1 to 2 years), but comparative information for the chromate industry is lacking.

79. Case-control studies are more limited in their capacity to assess exposure to chromium, and to determine the form of chromium involved as well as the contribution of other potentially relevant exposures. However, the findings by Hernberg *et al* (1983), Brinton *et al* (1984), Luce *et al* (1993) and d'Errico *et al* (2009) are consistent with the possibility that hexavalent chromium more than doubles the risk of certain types of sino-nasal cancer. Associations with chromates also featured in one of these reports.

80. The case-control study by Hernberg *et al* highlighted welders as a group who appeared to be at increased risk of sino-nasal tumours. By contrast, a number of cohort studies involving exposure to chromium VI in stainless steel welding have failed to provide any corroborating evidence of an increased risk. Overall, therefore the data are insufficient to support a case for prescription in welders.

81. Similarly, the results of studies involving exposure to metallic and trivalent chromium (paragraphs 61 to 67) are not strongly suggestive of an association with sino-nasal cancer. There were no cases reported in ferro-chromium production plants in Sweden and Norway; in four studies in tanneries, few cases were recorded, and with the exception of one case where the specific job was unclear, all occurred in workers who were not exposed to chromium III.

82. The findings described in this report are consistent with the known carcinogenic potential of hexavalent chromium in animal experiments and its classification as a carcinogen by the IARC and several other scientific bodies (including the US Environmental Protection Agency, the US National Toxicology Program Report on Carcinogenesis and the American Conference of Industrial Hygienists).

83. One study from the UK indicates that risks in chromate production predated the process changes introduced by 1960 and were not found later (paragraph 40). A second study in Germany confirmed a reduction in exposure around this time, without providing data on risks of sino-nasal cancer (paragraph 41). The Council has considered, therefore, whether to apply a cut-off date to the prescription recommended in respect of work in chromate production. However, given the high relative risks of sino-nasal cancer before 1960, and the limited research evidence afterwards, the Council has decided that such a restriction would not be well supported by the evidence and should not be applied.

84. *On the balance of evidence the Council recommends that sino-nasal cancer be added to the list of diseases for which IIDB is payable, for those who have worked in (1) hexavalent chromium plating; or in (2) the manufacture of inorganic chromates*. Due to the limited evidence about hexavalent chromium exposure in welders and chromate pigment workers the Council has been unable to prescribe for these occupational categories, but will monitor future evidence and would encourage research activities in this area.

Prescribed disease	Occupation
C32 Sino-nasal cancer	Work involving (1) hexavalent chrome plating; or (2) the manufacture of inorganic chromates

Prevention

85. The Control of Substances Hazardous to Health Regulations 2002 (as amended) (COSHH) apply to work with chromium. These regulations require that work is not carried out with any substance liable to be hazardous to health unless a suitable and sufficient assessment has been made of the risks created by the work and measures are taken to prevent exposure as far as is reasonably practicable. Where it is not reasonably practicable to prevent exposures by elimination or substitution with a safer substance or total enclosure, exposure must be adequately controlled by the use of appropriate work processes, systems and engineering controls and measures, including local ventilation systems, to control exposures at source. Suitable respiratory protective equipment may be used in addition, where adequate control cannot otherwise be achieved. Those working with chromium need to be informed of the hazards/risks and be provided with appropriate training. In addition COSHH may require employers to arrange appropriate health surveillance, for instance where its use may give rise to an identified health risk.

Diversity and equality

86. IIAC is aware of issues of equality and diversity and seeks to promote as part of its values. The Council has resolved to seek to avoid unjustified discrimination on equality grounds, including age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender and sexual orientation. During the course of the review of chromium and sino-nasal cancer, no diversity and equality issues were apparent.

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Glossary of terms used in this report

Types of study

Case series: A study which assembles or follows a group of people who have the same exposure or the same disease. Case series can provide descriptive information on the characteristics or outcomes of certain groups of people; but they do not provide information, for example, on how rates of disease compare with those expected in the absence of exposure.

Case-control study: A study which compares people who have a given disease (cases) with people who do not (controls) in terms of exposure to one or more risk factors of interest. Have cases been exposed more than non-cases? The outcome is expressed as an **Odds Ratio**, a form of **Relative Risk**.

Cohort study: A study which follows those with an exposure of interest (usually over a period of years), and compares their incidence of disease or mortality with a second group, who are unexposed or exposed at a lower level. Is the incidence rate higher in the exposed workers than the unexposed/ less exposed group? Sometimes the cohort is followed forwards in time ('prospective' cohort study), but sometimes the experience of the cohort is reconstructed from historic records ('retrospective' or 'historic' cohort study). The ratio of risk in the exposed relative to the unexposed can be expressed in various ways, such as a **Relative Risk** or **Standardised Mortality Ratio**.

Measures of association

Statistical significance: This refers to the probability that a result as large as that observed, or more extreme still, could have arisen simply by chance. The smaller the probability, the less likely it is that the findings arise by chance and the more likely they are to be 'true'. A 'statistically significant' result is one for which the chance alone probability is suitably small, as judged by reference to a pre-defined cut-point. (Conventionally, this is often less than 5% ($p<0.05$)).

Relative Risk (RR): A measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. *A value greater than 1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or **confounding**.)

Odds Ratio (OR): A measure of the strength of association between exposure and disease. It is the odds of exposure in those with disease relative to the odds of exposure in those without disease, expressed as a ratio. For rare exposures, odds and risks are numerically very similar, so the OR can be thought of as a **Relative Risk**. *A value greater than 1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or **confounding**.)

Standardised Mortality Ratio (SMR): A measure of the strength of association between exposure and mortality; a form of **Relative Risk (RR)** in which the outcome is death. The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard).

By convention, SMRs (and proportional cancer mortality rates (PCMR) and standardised incidence rates (SIR) as described below) are usually multiplied by 100. Thus, an SMR (or PCMR or SIR) of 200 corresponds to a RR of 2.0. For ease of understanding in this report, SMRs (or PCMR or SIRs) are quoted as if RRs, and are not multiplied by 100. Thus, *a value greater than 1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or **confounding**.)

Proportional cancer mortality rates (PCMRs): The proportional cancer mortality ratio is the proportion of deaths in the study population attributable to a specific type of cancer divided by the proportion of deaths in the general population attributable to that same specific type of cancer.

Standardised incidence rate (SIR): An SIR is the ratio of the observed number of cases of disease (e.g. cancer) to the expected number of cases, multiplied by 100. The ratio is usually adjusted to take account of differences in the population evaluated with the comparison or "normal population", due to age, gender, calendar year, and sometimes geographical region or socioeconomic status.

Other epidemiological terms

Confidence Interval (CI): The **Relative Risk** reported in a study is only an *estimate* of the true value in the underlying population; a different sample may give a somewhat different estimate. The CI defines a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. The commonly chosen 95%CIs give a range in which there is a 95% chance that the true value will be found (in the absence of bias and confounding). *Small studies generate much uncertainty and a wide range, whereas very large studies provide a narrower band of compatible values.*

Confounding: Arises when the association between exposure and disease is explained in whole or part by a third factor (confounder), itself a cause of the disease, that occurs to a different extent in the groups being compared.

For example, smoking is a cause of lung cancer and tends to be more common in blue-collar jobs. An apparent association between work in the job and lung cancer could arise because of differences in smoking habit, rather than a noxious work agent. Studies often try to mitigate the effects of ('control for')

confounding in various ways such as: restriction (e.g. only studying smokers); matching (analyzing groups with similar smoking habits); stratification (considering the findings separately for smokers and non-smokers); and mathematical modelling (statistical adjustment).

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