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Cadmium and Genito-urinary Cancers

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Industrial Injuries Advisory Council Review of Occupational Exposure to Cadmium and Genito-urinary Cancer

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Position Paper No 24

Cadmium and Genito-urinary Cancers

Summary

1. The Council's attention was drawn by a Council member to a recent paper which suggested an association between cadmium exposure and bladder cancer. Although this paper concerned non-occupational exposure, the Council decided, in view of its positive findings, to review the occupational literature on this subject and to consider the case for prescription. Cadmium is known to accumulate in the body with long-term exposure, and to be stored principally in the liver and kidneys. High concentrations are associated with kidney disease and renal failure. However, the relationship between cadmium exposure and cancers of the renal system is unclear.

2. A literature search identified a number of papers concerning the relationship between occupational cadmium exposure and bladder cancer and, in addition, a body of evidence relating to the association between cadmium exposure and cancers of the kidney and prostate. Consequently the Council elected to extend their review to include these cancer sites. This paper therefore reviews the evidence relating to cadmium and three genito-urinary cancers (bladder, renal and prostate) and describes the Council's conclusions in relation to prescription.

3. Cadmium is often present in foods, particularly in areas of high industrial activity. However, smoking represents the single most important source of cadmium intake in the general population. Smoking has also been identified as a major risk factor for bladder cancer and for renal cancer and a possible risk factor for prostate cancer. Thus, in the relationship between occupational exposure to cadmium and genito-urinary cancers, smoking represented a potential source of non-occupational exposure, as well as a potential confounder (alternative cause of the disease).

4. Bladder, renal and prostate cancers are fairly common in the general population and are not clinically or histologically different in cadmium-exposed workers than in other patients. The case for prescription therefore depends on robust epidemiological evidence for at least a doubling of risk of each disease in those with occupational exposure, taking into account the potentially confounding effects of smoking.

5. In the case of **bladder cancer**, four mortality studies and one case-control study were identified, as set out in nine relevant reports. Evidence from the mortality studies did not support a doubling of risk in those occupationally exposed to cadmium. In the light of improvements in treatment, an excess in disease incidence could be overlooked by focussing solely on fatal outcomes; but the single incidence study was unable to identify any cases over a 32-year period. The case-control study provided weak evidence for an association between bladder cancer and cadmium, being based on small numbers. Overall, the Council considered that the evidence was insufficient to recommend prescription.

6. Seven studies were identified which investigated the relationship between **renal cancer** and occupational cadmium exposure, of which six were case-control studies and one was a cohort study, first reported on in 1979 with three later follow-up analyses. No increased risk of renal cancer was identified in the extended cohort study. Results from the case-control studies were less consistent, in that data from two suggested a doubling of risk associated with longer (at least 6 years) exposure. However, three studies did not report a doubling of risk and the remaining two failed to adjust for the effects of smoking in the analysis. The importance of taking smoking into account was underlined in one study where a relative risk of 0.8 among occupationally exposed non-smokers, increased to a relative risk of 4.4 in occupationally exposed smokers. Overall, therefore, the Council considered that the case for prescription was not sufficiently established.

7. Fifteen studies, ten cohort studies and five case-control studies were identified concerning the relationship between occupational cadmium exposure and **prostate cancer**. An early cohort study reported more than a doubling of risk in those with more than 2 years exposure, taking into account a latency of more than 20 years. However, subsequent follow-up and expansion of this cohort failed to identify any further cases. No increased risk was identified in any of the remaining cohort studies. Only one of the five case-control studies reported a doubling of risk, but this study did not control for the effects of smoking. The Council concluded therefore that there was insufficient evidence to recommend prescription.

8. Although the case for prescription in cadmium-exposed workers with these genito-urinary cancers is not presently supported, the Council undertakes to keep the position under review and to consider any new evidence which may emerge in the future.

Introduction

The Role of the Industrial Injuries Advisory Council

9. The Industrial Injuries Advisory Council (IIAC) is an independent statutory body set up in 1946 to advise the Secretary of State for Social Security on matters relating to the Industrial Injuries Scheme.

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 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.

Background to the current review

11. In November 2007 the Council's attention was drawn to a recent paper, (Kellen *et al* 2007), which suggested an association between cadmium exposure and bladder cancer. In this study blood cadmium concentration was used as a marker for cadmium exposure and was compared in 172 cases of bladder cancer and 359 controls. Mean blood cadmium concentrations were higher in cases than in controls (1.1µg/l and 0.7µg/l respectively). Cadmium concentration was positively associated with an increased risk of bladder cancer in that the odds of disease were almost six times higher in those in the highest vs. lowest group as classified by blood cadmium concentration. Analysis allowed for age, sex, smoking and other factors known to be associated with bladder cancer. It was noted that an earlier case series (Darewicz *et al* 1998), had investigated urinary cadmium levels in 10 cases of bladder cancer, reporting that 6 cases showed levels between 0.8 and 1.5µg/l, whereas in healthy individuals levels would be expected to be well below 1µg/l.

12. The body's ability to excrete cadmium is limited and thus, with long-term exposure, it tends to accumulate in certain organs. It is principally stored in the liver and kidneys and high concentrations of cadmium are known to result in kidney disease and renal failure. However, the relationship between cadmium exposure and certain cancers, including those of the bladder and renal system is less clear. Early incidental observations by Potts (1965) of an apparently high number of cancers

overall in cadmium battery workers prompted a number of epidemiological investigations into the morbidity and mortality of cadmium exposed workers. The results of some studies have been suggestive of an association between long-term exposure and certain cancers, notably cancers of the lung and of the renal system. The most recent studies of Kellen and Darewicz (noted above) were concerned with non-occupational exposures. However, given their positive findings, the Council considered that the possible association between bladder cancer and occupational cadmium exposure merited further consideration and elected to review the available occupational literature and to consider the case for prescription.

13. The literature search subsequently undertaken revealed that, in addition to a number of investigations concerning occupational cadmium exposure and bladder cancer, there existed a body of evidence relating to possible associations between cadmium exposure and renal (kidney) and prostate cancer. Consequently the Council decided to broaden the scope of the review to include consideration of these other genito-urinary cancers.

The legal requirements for prescription

14. 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:

    i. 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

    ii. 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.

15. 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.

16. 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.

17. 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

18. For some diseases attribution to occupation may be possible from specific clinical features of the form of the disease, or of the circumstances 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 s/he returns to work, or in the demonstration that s/he is allergic to a specific substance with which s/he comes 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

19. 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.

20. The requirement for, at least, a doubling of risk is not arbitrary. It 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.

21. 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.

Cadmium

22. Cadmium is a silver-white malleable metal which occurs in the environment primarily in association with zinc but also with lead. It is recovered as a by-product during the smelting of these two elements and cadmium compounds are used in a range of industrial processes including electroplating, dyeing and printing, the manufacture of cadmium alloys and the manufacture of alkaline batteries.

23. There are a number of non-occupational sources of cadmium exposure. Food (meat, fish and leafy vegetables) represents an important contribution to daily uptake, particularly in locations with high levels of industrial activity. Estimates from the United States suggest that an adult absorbs between 1 and 3 µg of cadmium per day from food sources.

24. Tobacco smoking represents the most important single source of cadmium exposure in the general population. It has been estimated that about 10% of the cadmium content of a cigarette is inhaled through smoking. The absorption of cadmium from the lungs is much more effective than from the gut, and as much as 50% of the cadmium inhaled via cigarette smoke may be absorbed. Thus, smokers may absorb 1-3 µg of cadmium for each pack of cigarettes smoked. (Agency for Toxic Substances and Disease Registry, US, 1999).

25. Smoking has been identified as an important risk factor for both bladder cancer, (Zeegars *et al* 2000) and renal cancer, (McLaughlin *et al* 1984) and is also a suspected risk factor for the development of prostate cancer, (Hiatt *et al* 1994). The fact that tobacco smoking is also an important source of cadmium intake means that, in the investigation of the association between occupational cadmium exposure and genito-urinary cancers, smoking may complicate interpretation in two ways. Firstly, if cadmium exposed workers smoke

more than the reference population, any observed effect may be due to smoking rather than to occupational exposure. Secondly, cadmium exposed workers who smoke will absorb a higher dose of cadmium than would be expected from their occupational exposure. Workplace monitoring data may not therefore accurately reflect their total exposure. In these circumstances the contribution of workplace exposures to any observed effect may be overestimated.

26. The non-carcinogenic effects of cadmium exposure on respiratory and kidney function have been well documented, (Newman –Taylor 1998). However, the carcinogenicity of cadmium is less well established. (Huff *et al* 2007).

27. Genito-urinary cancers are common in the general population and are not considered to be clinically or histologically distinct in occupationally related cases. The case for prescription for each type of cancer (bladder, renal and prostate) will therefore depend on the identification of a robust body of epidemiological evidence to support at least a doubling of risk in those with occupational exposure to cadmium. Moreover, it is necessary to demonstrate that this doubling of risk occurs independently of the effects of smoking.

Consideration of the evidence

28. The epidemiological evidence identified in this review is restricted to occupational reports and relates to two types of study, cohort studies and case-control studies, each of which has certain advantages and disadvantages. In cohort studies a group of individuals with exposure to a particular agent, in this case cadmium, are identified, and their incidence of disease or death is compared with that of unexposed comparison populations. This allows the calculation of a direct estimate of relative risk (RR) or of relative mortality (Standardised Mortality Ratio, SMR). Cohort studies often focus on specific workforces in which exposures tend to be relatively high and of long duration, often with supporting exposure measurements. Cohort studies of cancer in the occupational setting typically overcome the practical problem of long latency (the many years an investigator has to wait between exposure and cancer onset) by studying populations in retrospect using records of employment and exposure, linked with databases of cancer registry or more usually death certification. Most of the cohort studies identified in this review were of mortality. Treatment for genito-urinary cancers has improved in recent years and therefore survival rates have increased. These studies may therefore have underestimated the incidence of the disease. Moreover,

retrospective studies often lack information on the smoking habits of the workforces studied, a factor of importance in this area of investigation.

29. In case-control studies patients who have been diagnosed with a disease, in this case a genito-urinary cancer, are identified, and their past exposure to possible causal agents, including cadmium, is compared with that of controls who do not have the disease. From this an odds ratio (OR) is calculated which approximates to a relative risk. This design overcomes the problem of latency, as the starting point is a collection of established cases. Cases are also plentiful (often coming from special hospital clinics), but typically these are drawn from all walks of life, rather than from a particular industry where exposure to the substance in question is high. Exposure assessment in case-control studies is made retrospectively (usually by asking the patient) and is potentially subject to reporting bias. For example, those suffering from disease may be more likely to recall certain exposures than those without disease. However, the opportunity exists to ask also about smoking habits and so to allow for this factor in analysis.

Bladder Cancer

30. Bladder cancer is a commonly occurring tumour of the urinary system and accounts for one in every 27 new cases of cancer in the UK each year. Excluding non -melanoma skin cancer, it is the fifth most common cancer overall with some 10,100 new cases occurring annually. The disease is far more common in men than in women. It is rare below the age of 40, but the incidence increases with age thereafter. The risk is lower (at least halved) in Black and Asian than in Caucasian adults. Occupational risk factors exist, including exposure to polycyclic aromatic hydrocarbons and to aromatic amines used in dye manufacture. However, smoking is considered to be the main risk factor, (IARC 1986). On the basis of a meta-analysis of 41 epidemiological studies, Zeegars *et al* (2000) estimated that approximately half of male urinary tract cancers and one-third of female urinary tract cancers could be attributable to smoking.

31. The Council conducted a literature search to identify epidemiological studies which specifically investigated the association between occupational exposure to cadmium and morbidity or mortality due to bladder cancer. Four mortality studies and one case-control study were identified, described in nine separate reports.

32. In an early study of 269 cadmium- nickel battery workers and 94 cadmium-copper alloy workers, (Kjellstrom *et al* 1979), workers with at least 5 years cadmium exposure were followed to 1975, and compared with an internal reference group of 328 alloy workers with no exposure to cadmium. No increase in cancer mortality overall was observed, and no increased mortality due to bladder cancer, (Relative Risk, (RR), 0.93, based on one case). A subsequent follow-up of the nickel-cadmium workers to 1983 (Elinder *et al* 1985), similarly found no significantly increased risk overall for bladder cancer, (Standardised Mortality Ratio, (SMR), 181). However, analysis incorporating a 10-year latency period (interval between first exposure and disease onset) yielded an SMR of 222, and with 20 years latency an SMR of 250. Neither of these figures was statistically significant.

33. In a further extension to this study (Jarup *et al* 1998) the authors included a further 400 workers and also incorporated detailed historical exposure assessments conducted on all cohort members. Thus a total of 869 workers, employed for at least one year between 1940 and 1980, were followed up until 1992. There were 3 deaths from bladder cancer (vs. 1.7 expected on the basis of comparison with regional reference rates) between 1951 and 1992, giving an SMR of 176. No incident cases of bladder cancer were found between 1959 and 1991.

34. In a larger study, by Armstrong and Kazantzis (1983), a cohort of 6995 men exposed to cadmium for more than one year between 1942 and 1970 were followed up until 1979. Expected number of deaths was calculated on the basis of mortality rates for the population of England and Wales. There was no excess of deaths from any disease of the genito-urinary system. Further five-year follow-up (Kazantzis *et al* 1988), confirmed the finding of the initial study. There was a small non-significant excess mortality from nephritis during the follow-up period, but no excess associated with other diseases of the genito-urinary system.

35. Sorahan *et al* (1995) studied mortality in 347 copper cadmium alloy workers, 624 workers employed in the vicinity of the copper cadmium alloy work and 521 iron and brass foundry workers. The workers were followed for the period 1946-1992. The main focus of the study was to investigate the relationship between cadmium exposure and malignant and non-malignant respiratory disease. However, mortality from cancer at other sites was also recorded. There were 3 observed deaths from bladder cancer (1.80 expected on the basis of comparison with morbidity rates for the general population of England and Wales) yielding an SMR of 167.

36. Another study by Sorahan & Esman (2004) investigated mortality in a cohort of 926 male nickel cadmium battery workers, first employed and employed for at least one year between 1947 and 1975. This study originally focussed on lung cancer mortality and followed workers to 1984 (Sorahan 1987). Sorahan & Esmen carried out a further follow-up to 2000 which included investigation of other cancer sites and also exposure data derived from work histories which were available for the period 1947-1986. There were 5 deaths from bladder cancer as compared to 4.2 expected from mortality rates for England and Wales (SMR 118).

37. One case-control study (Siemiatycki *et al* 1994) compared the exposure histories of 484 confirmed cases of bladder cancer with those of 1879 cases of other cancers and 533 healthy controls. Exposure was categorised as 'substantial' where there was probable or definite exposure at a high concentration for more than 5 years, with at least 5 years having elapsed since first exposure. Initial analysis comparing those with substantial and non-substantial exposure, and adjusting statistically for age, ethnicity, socioeconomic status, smoking and tea and coffee consumption, yielded an OR of 4.0 (95% CI [1]1.0-16.3) for substantial exposure. Further analysis, which adjusted, in addition for other occupational exposures associated with bladder cancer, gave an OR of 3.2 (95% CI 0.7-13.6). However this was not statistically significant. The authors considered that these results provided only weak evidence of an association between cadmium exposure and bladder cancer and emphasised the small numbers involved in this section of the analysis.

38. In summary, the occupational epidemiological literature provides only limited evidence of a significantly increased risk of bladder cancer associated with cadmium exposure. The strongest evidence for at least a doubling of risk comes from a single case-control study in which the authors were cautious about drawing a causal interpretation. Evidence from the cohort studies does not support a doubling of risk. The majority of these studies were of mortality rather than morbidity and it is possible that, given improvements in treatment, an excess incidence of disease went undetected by a focus only on cancer deaths. However, the only incidence analysis (Jarup *et al* 1998) was unable to identify any cases over a 32-year period up to 1991. Overall, the evidence is insufficient to support prescription.

[1] CI=Confidence Interval. A 95% confidence interval (CI) represents a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. A lower confidence limit >1 suggests a positive association that is unlikely to arise simply by chance (less than 1 chance in 20).

Renal Cancer

39. Renal cancer is the 11th most common cancer diagnosed in the UK, with about 7,000 cases each year. It is rare under the age of 50, but incidence increases with age and two-thirds of those diagnosed are over the age of 65. Like bladder cancer, renal cancer is more common in men than in women. Obesity has been shown to be a risk factor, particularly among women (McLaughlin *et al* 1984).

40. A strong association between smoking and renal cancer is well-established, with several studies demonstrating at least a doubling of risk (Yu *et al,*1986; La Vecchia *et al,* 1990; Kreiger *et al,* 1993). The risk increases with the number of cigarettes smoked. For example, La Vecchia *et al* showed relative risks of 1.1, 1.9 and 2.3 for moderate, intermediate and heavy smokers respectively. McLaughlin *et al* estimated from their data that 30% of renal cancers in men and 24% in women were attributable to smoking.

41. The literature search conducted by the Council identified 10 occupational studies which investigated the association between occupational cadmium exposure and renal cancer. These included the mortality and incidence study of cadmium exposed workers, noted above, of Kjellstrom *et al* (1979), and its later follow-up in 1985 (Elinder *et al*) and in 1998 (Jarup *et al*). A nested case-control study of deaths from renal cancer by Armstrong and Kazantzis (1985) drew on data from the UK cohort study described above in (Armstrong & Kazantzis 1983). Other evidence came from two earlier cohort studies of nickel-cadmium battery workers, (Sorahan & Waterhouse, 1983; Holden, 1980) and six other case-control studies.

42. The study by Kjellstrom *et al* (1979) and its later follow up, involving cadmium-nickel battery workers, showed no increased risk for renal cancer. In the most recent follow-up to 1992 (Jarup *et al* 1998) there was one observed male death from renal cancer (expected deaths 2.5, SMR 40, 95% CI 1-224). Similarly there was one diagnosed case (expected incidence 3.63, SIR 28, 95% CI 0.7-154).

43. Armstrong and Kazantzis (1985) identified nine cases of renal cancer from the three cohorts they studied, which were matched to 27 controls. Exposure was graded as high, medium or low and ‘ever’ or ‘always’. The OR for ‘ever medium’ exposure versus ‘always low’ exposure was 0.43 (95% CI 0.07-2.49) (i.e. compatible with a protective effect, although not significantly so). Although based on very few cases, the results provide no support for an association between cadmium exposure and renal cancer.

44. An early case-control study by Kolonel (1976) compared 64 cases of renal cancer with 269 controls composed of 72 cases of colon cancer and 197 cases of non-malignant digestive diseases. Three main sources of exposure to cadmium, namely diet, smoking and occupation, were investigated. Compared to those who were non-smokers and had no occupational exposure to cadmium, an RR of 0.8 amongst occupationally exposed non-smokers was observed. By contrast the RR for occupationally exposed smokers was 4.4, emphasising the importance of smoking as a risk factor for this disease.

45. Three further large case-control studies included adjustment for smoking in the analysis. Mandel *et al* (1995) carried out a large international multicentre study involving 1732 incident cases of renal cell carcinoma and 2309 controls. A significant association with cadmium exposure was shown (OR 2.0 95% CI 1.0-3.9). In addition the OR for 1-11 years of exposure versus 12+ years of exposure was 4.3.

46. In a further multicentre study carried out in Germany, Pesch *et al* (2000) compared 935 incident cases of renal cell carcinoma with 4298 controls. The authors present data derived from two separate job exposure matrices (JEM), based on British and German methodology. Although an overall twofold risk associated with high exposure was identified using the German JEM, the smoking adjusted risk using the British JEM was less than doubled and statistically non-significant for both men and women (OR 1.3 and 1.5 respectively).

47. Hu *et al* (2002) carried out a study in Canada involving 1279 newly diagnosed cases of renal cell carcinoma and 5370 controls. The smoking adjusted ORs in respect of exposure to cadmium salts were 1.7 (95% CI 1.0-3.2) for men, and 0.7 (95% CI 0.2-3.1) for women. However, for those with at least six years exposure the ORs increased to 2.7 (95% CI 1.3-5.5) for men, and 2.4 (95% CI 1.2-5.0) for women.

48. The remaining two case-control studies did not carry out adjustment for smoking. A study in Finland (Partanen *et al* 1991) involving 338 cases of renal cell cancer diagnosed during 1977 and 1978 identified an OR of 4.37 (95% CI 0.44-43.0), contrasting high with background exposure. The results, based on 3 exposed cases, were not statistically significant and the authors considered that they provided only a suggestion of an association with cadmium exposure. McCredie and Stewart (1993) studied 489 cases of renal cell carcinoma and 147 cases of renal pelvic cancer in New South Wales, Australia.

Unadjusted ORs in respect of cadmium exposure versus non-exposure were 1.13 (95% CI 0.45-2.82) for renal cell cancer and 2.59 (95% CI 0.73-9.17) for renal pelvic cancer.

49. Overall, when the effects of smoking are taken into account, the data do not provide strongly consistent evidence of at least a doubling of risk associated with occupational cadmium exposure. The strongest evidence comes from the case-control study of Hu *et al* which indicated a more than doubling of risk following at least six years of exposure. However, this must be set against the negative findings of several other studies, in particular, those of the cohort study which has now been subject to many years of follow-up. Current evidence, therefore, does not support prescription.

Prostate Cancer

50. Prostate cancer is the most common cancer in men in the UK (excluding non-melanoma skin cancer). Nearly 35,000 cases are diagnosed each year which represents 24 out of every 100 cancers diagnosed in men. It is rare under the age of 50 but incidence increases with age and two-thirds of new cases occur in men aged 70 and over. The disease is more common in Black and Asian men than in Caucasian men but is uncommon in those of Chinese origin. Genetic factors appear to play a role in that the risk is estimated to be doubled in those with a relative diagnosed with the disease. This increases to a threefold risk in those with a brother who develops prostate cancer. (Luo & Ping, 2003). Smoking has been reported to increase the risk in some studies (Hiatt *et al,* 1994, adjusted Relative Risk 1.9), but not in others (Slattery *et al*, 1993)

51. The literature search carried out by the Council identified 15 occupational studies concerning cadmium exposure and prostate cancer, of which ten were cohort studies and five were case-control studies. The dataset included a number of studies already referred to above in relation to bladder cancer and renal cancer, namely the cohort study by Kjellstrom *et al,* (1979), which was subsequently followed up by Elinder *et al* (1985) and Jarup *et al,* (1998), the cohort study of Armstrong & Kazantzis (1983), and the subsequent nested case-control study (Armstrong and Kazantzis ,1985), and the cohort studies of Sorahan *et al* (1995) and Sorahan & Esmen (2004). In addition, Kazantzis *et al* (1988) reported a further follow-up of the study of Armstrong & Kazantzis (1983) study in respect of prostate cancer.

52. Cohort studies were largely consistent in showing no statistically significant excess in mortality from prostate cancer in cadmium-exposed workers (Kjellstrom *et al* 1979, RR 0.93; Andersson *et al* 1984, SMR 129; Elinder *et al* 1985, SMR 108; Armstrong & Kazantzis 1983, SMR 99; 1988, SMR 90; Sorahan *et al* 1995, SMR 71; Sorahan & Esmen 2004, SMR 116). Similarly no significantly increased incidence of diagnosis of prostate cancer was reported in the study of nickel-cadmium battery workers (Jarup *et al* 1998, SIR 28). In the study by Elinder *et al*, the SMR increased with increasing dose and latency (at least 5 years exposure and 10 years latency, SMR 125, at least 5 years exposure and 20 years latency, SMR 148) but these figures did not reach statistical significance. An early cohort study by Lemen *et al* (1976) of cadmium production workers in the United States, reported an SMR of 347 for those with >2 years exposure and an SMR of 452 when >20 years latency as taken into account. However, this cohort was followed up for a further five years and the population expanded to include a further 257 workers with brief (up to 23 months) employment (Thun *et al* 1985). No further deaths from prostate cancer occurred during this period

53. Findings of the case-control studies were also largely consistent. Only one of the five studies reported a doubling of risk. In a large case-control study in the Netherlands, Van der Gulden *et al* (1995) found a statistically significant excess risk for those 'frequently exposed' versus 'never exposed', (OR of 2.76 95% CI 1.05-7.27), based on seven cases. However, while control for age was included there was no control for smoking. No evidence for a doubling of risk was seen in the remaining case-control studies. These included two studies from the United States, a small study by Checkoway *et al* (1987), involving 40 cases, (OR 0.79), and a study by Platz *et al* (2002) which compared prediagnostic toenail cadmium concentrations in cases and controls. Here an OR of 0.70 was found when comparing the first and fifth levels of cadmium concentration. The nested case control study of Armstrong & Kazantzis (1985) reported an OR of 1.35, comparing 'ever high' with 'always low' exposure. In this study, in addition, an OR of 1.13 was obtained for ten years of high exposure as opposed to an OR of 1.09 for 10 years of low exposure. A further study in the United States (Elghany *et al* 1990) reported results separately for three different measures of exposure (self-reported –ever-exposed, hygiene-assessed –ever-exposed, hygiene-assessed by record linkage for longest exposed job). The results were very similar, giving ORs of 1.3, 1.0 and 1.0 respectively for all tumours and 1.5, 1.2 and 1.1 respectively for more aggressive tumours.

54. In summary, the findings of both cohort and case-control studies provide little support for an association between occupational cadmium exposure and an increased risk of prostate cancer. Positive evidence is limited to the early cohort study of Lemen *et al,* where no further deaths were noted at later follow up, and the case-control study of Van der Gulden *et al* which failed to adjust for smoking as a potential confounder.

Conclusions

55. The Council has considered separately the evidence relating to a possible association between occupational exposure to cadmium and three types of genito-urinary cancers (bladder, renal and prostate). A considerable body of evidence was examined, comprising both case-control studies and a number of large cohort studies which had been progressively extended to cover workplace exposure over many years. The Council considers that the existing evidence in respect of each of these conditions does not support prescription. However, we undertake to keep the position under review and to consider any new evidence that may emerge in this field.

Prevention

56. Cadmium is known to be hazardous to health and work with it is strictly limited and controlled.

    The Control of Substances Hazardous to Health Regulations 2002 (as amended) (COSHH) apply to work with cadmium. 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 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 cadmium 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 a risk of emphysema.

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