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THE INDUSTRIAL INJURIES ADVISORY COUNCIL

POSITION PAPER 27

Beryllium and Lung Cancer

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Beryllium and lung cancer

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Summary

1. The association between lung cancer and occupational exposure to beryllium was brought to the Council's attention following a review on the burden of occupational cancer, commissioned by the Health and Safety Executive (HSE). The report highlighted risks of a number of cancers following occupational exposures to chemical agents. The Council carried out a preliminary literature search and subsequently a full review of the evidence in relation to beryllium and lung cancer. This paper describes the review and considers the case for adding this condition to the list of diseases (referred to in this paper as prescribed diseases) for which people can claim Industrial Injuries Disablement Benefit (IIDB).

2. Beryllium is a very light, but hard metal. These properties, together with its good electrical and thermal conductance and resistance to erosion, render it a useful stable alloy component. Copper-beryllium alloys are used extensively in the aerospace, telecommunications, computer, vehicle, and oil and gas industries.

3. In the US, the National Institute for Occupational Safety and Health (NIOSH) has estimated that 44,000 workers were exposed to beryllium dust or fumes in the early 1980s. In contrast, information from the HSE suggests far more limited industrial use of beryllium in the UK, with few exposed workers currently, but with the potential for numbers to increase in time.

4. Known toxic effects of beryllium compounds include dermatitis, berylliosis (an acute lung inflammation) and chronic beryllium disease (a form of pneumoconiosis). Beryllium has also been shown to be carcinogenic in animal studies.

5. Chronic beryllium disease caused by inhalation of beryllium or a beryllium compound is already in the list of diseases prescribed for the purposes of IIDB.

6. The main epidemiological evidence on occupational risks of lung cancer in beryllium-exposed workers derives from large US studies of beryllium process workers and of a US national register of beryllium workers. Although there have been several research reports, the evidence base is restricted to only a few cohorts with relevant data. The Council found no UK-relevant studies to inform its inquiries.

7. The available data suggest an increased risk of lung cancer following beryllium exposure, but generally less than a doubling of risk (the threshold the Council normally applies in recommending on the prescription of diseases that lack occupationally distinctive features).

8. The Council identified one study in which a more than doubling of risks was found among workers who had suffered the very rare acute form of disease, berylliosis; and one re-analysis that reported higher risks with allowance for the latency (delayed onset) of disease. These findings, which have not been independently replicated, relate to historically high levels of exposure.

9. The Council has concluded that at present there is insufficient evidence to recommend that lung cancer in relation to beryllium should be added to the list of prescribed diseases. However, it will continue to monitor the research literature in case new evidence emerges, sufficient to prompt reconsideration.

A glossary of terms found in this report is included as a concluding appendix.

Introduction

The Role of the Industrial Injuries Advisory Council

10. 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.

11. IIDB provides compensation that can be paid to an employed earner because of the effects 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

12. This topic was brought to the Council's attention following a review commissioned by the HSE, on the burden of occupational cancer. The report highlighted risks of a number of cancers following occupational exposures to chemical agents, including an association between beryllium and lung cancer. The Council carried out a preliminary literature search and subsequently a full review of the evidence on this topic. This paper describes this review and considers the case for prescription.

13. Beryllium is a very light, but hard metal with a high melting point. Its good electrical and thermal conductance and its resistance to corrosion render it useful as a stable, lightweight alloy component. Copper-beryllium alloys are used extensively in the aerospace, nuclear, telecommunications, computer, vehicle and oil/gas industries. Beryllium oxide is incorporated into a ceramic which is used in electronic circuitry, ignition systems and microwave ovens. Potential for exposure arises in the refining of beryllium metal and melting of beryllium-containing alloys, the manufacturing of electronic devices, and the handling of other beryllium-containing material.

14. In the US, NIOSH has estimated that 44,000 workers were exposed to beryllium dust or fumes in the early 1980s, and pockets of exposure continue to the present time. By contrast, data provided to the Council by the HSE suggest far more limited industrial use of beryllium in the UK. There is no production of beryllium, its alloys or compounds in the UK. Beryllium metal, beryllium alloys and beryllium oxide are all imported. In 2006, only one company was known to be using beryllium oxide in the manufacture of an electronic product, while an estimated 51 British companies were engaged in the manufacture or machining of products containing beryllium as an alloy. The HSE's expectation however, is that future use of beryllium alloys in the UK will increase, given a proliferation in the industrial uses of beryllium.

15. Only limited information exists on the level to which beryllium workers have been exposed. In the US, the present Occupational Safety and Health Administration (OSHA) permissible exposure limit of 2 $\mu g/m^3$ TWA (time weighted average over an 8-hour shift) was introduced in 1949, prior to which one study in a US beryllium-alloy plant found considerably higher exposure levels, ranging from 411 $\mu g/m^3$ in the general air surrounding mixing operations to 43,000 $\mu g/m^3$ in the breathing zone of alloy operations.
16. In the UK, the HSE holds limited monitoring data on exposures in four of the British firms surveyed in 2006 (12 samples). In general exposure levels were less than 0.1 $\mu g/m^3$, substantially below the workplace exposure limit (WEL) of 2 $\mu g/m^3$. The highest recorded value, in a worker wearing air-fed respiratory protective equipment, was 5.5 $\mu g/m^3$. Higher levels of exposure may have occurred historically, as implied by well described cases of chronic beryllium disease (a slow acting inflammatory lung disease which seems to be immunologically mediated); but these directly measured exposures are markedly lower than in American studies from which estimates of health risk in this report derive.

17. Toxic effects from beryllium compounds have been known for decades. These include dermatitis, berylliosis (an acute lung inflammation resembling pneumonia, caused by inhaling beryllium-containing dust or fumes), and chronic beryllium disease. Acute

berylliosis is associated with high levels of exposure (e.g. greater than 100 µg/m^3), and is thus rarely seen nowadays. Chronic beryllium disease and beryllium sensitisation arise at lower levels, and there have been calls to tighten and reduce the current control standard.

18. According to data supplied by the occupational surveillance reporting scheme THOR (The Health and Occupational Reporting network), University of Manchester,* one case of suspected beryllium disease was reported during the period from 2002 to 2008, in a man classified as working in the manufacture of basic metals industry (Standard Industrial Classification (SIC) 27).

19. Beryllium has also been shown to be carcinogenic in animals in studies extending back more than half a century. Suspicions that it might cause lung cancer in humans arose because of the evidence of carcinogenicity in animals, because the main route of exposure is inhalation and because other pneumoconioses, such as silicosis have been linked with risk of lung cancer.

20. The topic has proved controversial. In a 1980 review, the International Agency for Research on Cancer (IARC, 1980) concluded that there was sufficient evidence that beryllium metal and several beryllium compounds were lung carcinogens in rats and monkeys, but that there was insufficient evidence in humans. However, when IARC revisited the question (IARC, 1993) more published data had accrued and it adopted a precautionary stance, deeming the evidence sufficient to classify beryllium as arcinogenic to humans. IARC's position was restated in 2009 (Straif *et al.*, 2009). This conclusion has been subject to scientific challenge, as described below.

* http://www.medicine.manchester.ac.uk/coeh/thor

The legal requirements for prescription

21. 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.

22. 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.

23. 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.

24. 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

25. 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

26. 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. Lung cancer, the topic of this review, is such a disease. 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 (in this case lung cancer) by a factor of two or more.

27. 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.

28. 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.

29. Lung 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, beryllium. Cigarette smoking is a common non-occupational determinant of lung cancer in the general population. Thus, any apparent association with occupation should not arise simply as a result of the greater propensity of workers in certain occupations to smoke. More generally, the potential for confounding to create spurious relationships should be considered in weighing the case for prescription.

Consideration of the evidence

30. The main epidemiological evidence on beryllium and lung cancer derives from studies of a large US cohort of beryllium process workers and of a US national register of beryllium workers. These populations shared some workers in common and have been the subject of repeated reports and reanalyses, as well as some debate.

31. One of the major cohort studies concerned 9,225 men employed for at least 2 days between 1940 and 1969 at any of seven US beryllium production or processing plants. The cohort was followed until 1988 (Ward *et al.*, 1992). Vital status was ascertained for 97% of the cohort and life table analyses used to compare observed deaths with the US general population rates by age, gender, place and time period. Smoking data were available for a minority (16%) of the cohort, who reported on their smoking habits in 1968. 280 deaths were observed *vs.* 222 expected (standardised mortality ratio (SMR) 1.26, 95% confidence interval (CI) 1.12 to 1.42).

32. Significantly increased risks were found only for workers in the two oldest plants; and in the whole cohort were increased somewhat with latency (interval from first exposure) of ≥30 years and in those employed before 1950 when exposures had been higher. After adjustment for the available smoking data, the SMR for the whole cohort fell to 1.12. Beyond duration of employment, no exposure data were available for this analysis; but a higher risk (SMR 3.33, 95% CI 1.66-5.95) was found in employees with a history of acute beryllium disease at one of the beryllium processing facilities with historically very high exposures (up to 4700 $\mu g/m^3$).

33. The second influential cohort mortality study (Steenland and Ward, 1991) was based on patients listed by a US beryllium case registry (set up by a ***Massachusetts*** hospital). Initially, 421 registry cases were followed, but this study was then enlarged by 13 more years of follow-up (until 1988) and by including data from women employees. Eventually, 689 patients were studied. A life table technique was used to compare mortality rates in the cohort with rates in the US population, stratified by age, race, gender, and calendar time. Exposure data were confined to first and last exposure to beryllium, but used to specify the latency period. In this study, smoking habits were available (as of 1965) for 32% of workers. 95% of the cohort was traced, including 418 subjects with death certificates (almost 14,000 person-years at risk).

34. The 70 deaths from cancer included 28 from lung cancer. Overall, the SMR for lung cancer among beryllium registry workers was 2.00 (95% CI 1.33-2.89) and no trend was found by duration of exposure or time since first exposure. However, those with acute beryllium disease – which requires a high level of exposure – had a higher risk of lung cancer (SMR 2.32, 95% CI 1.35-3.78) than those with chronic beryllium disease (SMR 1.57, 95% CI 0.75-2.89). Attempted adjustment for smoking did not alter the results.

35. The studies by Ward and Steenland persuaded IARC to change its classification of beryllium (IARC, 1993). However, amid much debate, critical commentary by the Beryllium Industry Scientific Advisory Committee and by scientists commissioned by this

body, continued to appear in the scientific press. It was suggested that selection bias had arisen in assembling the registry members (Steenland study), that the confounding effects of smoking had been inadequately addressed, and that the findings in Ward *et al.* were confounded by co-carcinogens (acid mists) in the processing plant with very high rates of disease. Critics also highlighted an apparent lack of relation to duration of exposure and latency.

36. To address these concerns and provide quantitative dose-response estimates, Steenland and co-workers (in Sanderson *et al.*, 2001) conducted a nested case-control study based upon one of the beryllium alloy production plants with sufficient historic exposure data (not the one with very high rates of disease). Each of 142 lung cancer cases was age race-matched to five controls. Calendar-time specific beryllium exposure estimates were made for every job in the plant and used to estimate worker's cumulative, average and maximum exposures.

37. In assessing exposure-response relationships, cancer studies often invoke the use of a "lag" period – that is, they suppress from analysis exposures close to diagnosis, as biological models for carcinogenesis assume that recent exposures cannot have contributed to disease occurrence. Ten or 20 year lag periods are commonly used and were in this case-control study (Sanderson *et al.* 2001). Little relation was found between beryllium exposure and lung cancer in the absence of lagged analysis, but odds ratios were higher after lagging for most exposure metrics and more likely to show exposure-response relationships, although most of these were non-linear. Among workers exposed to average levels above 2 $\mu g/m^3$, odds ratios were increased 4.1-4.2 fold with a 10 year lag period and 2.2 to 2.3 fold for a 20 year period; where the maximum exposure was greater than 2 $\mu g/m^3$, odds ratios were increased 3.9 to 4.6 fold with a 10 year lag period, and 2.1 to 2.3 fold with a 20 year lag period. Smoking data were only available on a minority of those analysed, but no apparent differences were found in smoking patterns by level of beryllium exposure (this internal analysis was restricted to exposed workers and any confounding effect by smoking would

require that smoking patterns varied by level of beryllium exposure – this was not found.)

38. Further debate ensued, this time focusing on the potential for selection bias in case and control recruitment and confounding by age at hire and birth year, but a reanalysis (Schubauer-Berigan *et al.* 2008) did not materially alter the findings. One major qualification, however, is that risks appeared to be increased in those born before 1900 and were not much in evidence in those born later on.

Potential for Prescription

39. Although there have been several reports on lung cancer and occupational exposure to beryllium, the evidence base is restricted to only a few cohorts with relevant data. Interpretation of these findings has been contentious, although more generally the IARC classifies beryllium as a human carcinogen. In the main, risks of lung cancer have not been as much as doubled – the threshold the Council normally applies in recommending on the prescription of diseases that lack occupationally distinctive features (see paragraphs 26 and 27).

40. Limited evidence for a doubling or more of risk exists in workers with the very rare acute berylliosis, and in those with historically high levels of exposure, assuming a latency of 10 or more years. Such findings are restricted to a single study and have not been independently replicated.

Conclusions

41. The Council has concluded that at present there is insufficient evidence to recommend that lung cancer in relation to beryllium should be added to the list of prescribed diseases. However, it will continue to monitor the research literature in case new evidence emerges, sufficient to prompt reconsideration.

Prevention

42. Beryllium is known to be hazardous to health and work with it is limited and controlled. The Control of Substances Hazardous to Health Regulations 2002 (as amended) (COSHH) apply to work with the agent. 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 beryllium 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

43. The Industrial Injuries Advisory Council is aware of issues of equality and diversity and seeks to promote them 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 beryllium and lung cancer, no diversity and equality issues became apparent.

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Appendix: A glossary of terms used in this report

Types of study

Case-control study: A study which compares people who have a given disease (cases) with people who do not have that disease (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 in 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**.

Nested case-control study: A special form of **case-control study** in which the cases and controls all come from within a well-defined cohort. (Paragraph 36 in this report concerns such a study.)

Measures of association

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, the figure is usually multiplied by 100. Thus, an SMR of 200 corresponds to a RR of 2.0. For easy of understanding in this report, SMRs 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**.)

The study described in Paragraphs 31 to 34 of this report used this measure of association.

Other research terms and concepts in this report

Confidence Interval (CI): The **Relative Risk** reported in a study is only an *estimate* of the true value in the population; another study, involving a different sample of people, 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).

Other technical terms in this report

Time-weighted average (TWA): A calculation used in the measurement of concentrations of substances in the air, whereby occupational exposures in any 24-hour period are expressed as a single uniform exposure over a specified reference period (usually 8 hours).

Workplace exposure limits (WEL): An occupational exposure limit set under the Control of Substances Hazardous to Health (COSHH) Regulations in order to help protect the health of workers. WELs are concentrations of hazardous substances in the air, averaged over a specified reference period (usually 8 hours) referred to as a time-weighted average (TWA).

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