

Industrial Injuries Advisory Council Information Note

CANCERS OF THE LARYNX OR OVARY AND WORK WITH ASBESTOS

February 2015

Background

1. Following a request from the Asbestos Victims Support Groups' Forum, the Council has reviewed the possible associations between asbestos exposure and non-lung cancers. The request was prompted by the publication of Monograph 100c by the International Agency for Research on Cancer (IARC). The monograph addresses the risks of a wide variety of cancers and concludes (p.294) that there is sufficient evidence in humans that asbestos causes mesothelioma and cancer of the lung, larynx, and ovary; while positive associations have been observed for cancers in other sites, IARC did not consider the available evidence strong enough for asbestos to be classified as a probable cause of these health end-points.

2. Since mesothelioma and lung cancer from work with asbestos are already prescribed within the Scheme, the Council has restricted attention to cancers of the larynx and ovary. This report summarises the available evidence and the Council's views on prescription.

Cancer of the larynx

3. Each year there are around 2,500 new cases of laryngeal cancer in the UK, more than 75% of them in men. Most cases are recognised in people aged over 60 years. Smoking and heavy alcohol consumption are important risk factors; in research studies where these have not been considered it can be difficult to establish an independent effect of occupational factors. Since laryngeal cancer can often be treated successfully (60% of patients live for more than 10 years after diagnosis) studies that rely on mortality statistics alone will underestimate the true incidence of the disease.

4. The IARC monograph relied largely on a review of cancers and asbestos exposure published by the US National Academy of Science (NAS) in 2006; only one subsequent report (Musk *et al.*, 2008) was included.

5. IIAC last reviewed asbestos and cancer of the larynx in Position Paper 22 published in 2008; this too was based on the NAS review (of 29 cohort and 18 case-control studies) but included also four additional investigations, three of them of cohort design. The NAS review estimated a combined relative risk of about 1.4, with

some reports indicating risks higher than this and some lower. At that time, the Council concluded that while the data suggest an association between laryngeal cancer and asbestos exposure, they do not provide strong, consistent evidence of a doubling of risk (the threshold normally applied in recommending prescription within the Scheme), particularly given the possibility of confounding by smoking and alcohol; but that the topic should be revisited after publication of the IARC monograph.

6. In 2014 the Council reviewed the latest IARC report and undertook a new search of the published literature (from 2008 onwards) which revealed six additional cohort and two case control studies; these are summarised in the table below.

Table. Laryngeal cancer: summary table of evidence from cohort and case control studies.

Cohort studies					
	Setting	Period of exposure	Numbers studied	Cases (n)	Relative risk (95% confidence interval)
Lehman <i>et al.</i> , 2008	US plumbers union	1971-1995	15,411 deaths	57 (deaths)	PMR 1.28 (0.97-1.66)
Magnani <i>et al.</i> , 2008	Italian factory workers	1950-1986	3434	15 men 1 woman	SIR 1.25 (0.70-2.06) SIR 4.81 (1.2-26.78)
Musk <i>et al.</i> , 2008	Australian asbestos miners	1943-1966	6943	13 (deaths)	SMR 2.57 (1.37-4.39)
Pira <i>et al.</i> , 2009	Italian asbestos miners	1930-1990	1056	8 (deaths)	SMR 1.82 (0.78-3.59)
Strand <i>et al.</i> , 2010	Norwegian Navy (asbestos exposure assumed)	1950-1989	28,345	28	SIR 0.85 (0.56-1.82) On-ship workers ≥2 years, SIR 0.73
Wang <i>et al.</i> , 2012	Chinese asbestos textile workers	1972-2008	586 (men)	2 (deaths)	SMR 4.26 (1.17-15.52)
Case-control studies					
	Setting	Numbers studied (source of controls)		Adjusted OR* (95% confidence interval)	
Ramroth <i>et al.</i> 2011	Germany	257 cases 769 controls (population)		Various, depending on exposure measure. RRs<2.0 except in the highest category of 'isolation' (sic) work in which there were 6 cases: OR=2.5 (0.63-9.6)	
Langevin <i>et al.</i> , 2011	Boston, US	118 cases 857 controls (population)		1.04 (0.64 to 1.67)	

* for smoking and alcohol consumption.

Key: PMR = proportionate mortality ratio; SIR = standards incidence ratio; SMR = standardised mortality ratio.

7. Three of these more recent cohort studies report risk estimates that were more than doubled. The first (Musk *et al.*, 2008) derived from a study of men who worked in a blue asbestos (crocidolite) mine and mill in Western Australia. Thirteen deaths from cancer of the larynx were recorded, a figure 2.57 times higher than would be expected. The report provides no information on the levels of exposure in

relation to this risk; and no account was taken of either smoking or alcohol consumption.

8. A study of asbestos textile workers in China (Wang *et al.*, 2012) reported, on the basis of two deaths, that the risk of laryngeal cancer was increased by more than four-fold; again no information was provided on exposure levels or smoking and alcohol as risk factors.

9. A third study (Magnani *et al.*, 2008) reported, in a study of women working in an Italian textile factory, an incidence of laryngeal cancer that was more than four-fold higher than expected; this however was derived from a single case and may have been a chance finding. There was no corresponding increase in risk among men from the same factory.

10. The other cohort studies, of plumbers in the US, asbestos miners in Italy, and Norwegian mariners, all reported a less than doubling of risks.

11. None of these cohort studies could account for the confounding effects of smoking and alcohol consumption. This was possible in the two case-control studies summarised in the table. In one, of 257 cases of laryngeal cancer in German men and women (Ramroth *et al.*, 2011), an odds ratio of 2.5 was reported in association with the highest category of 'isolation' (probably insulation) work. This estimate, however, may readily have arisen by chance and was not replicated in another case control study from the US (Langevin *et al.*, 2011).

12. On the basis of this review and the body of evidence previously considered the Council has concluded, as it did in 2009, that the evidence of a doubling of risk of laryngeal cancer associated with asbestos exposure remains inconsistent. While some studies denote higher risks, perhaps in more highly exposed workers, such reports are generally based on small numbers of cases with little or no information on the levels of exposure that would incur such a risk; several studies relate to exposures that would not be incurred in the UK. Thus, the Council continues to believe that the evidence is not sufficiently robust, compelling and detailed to recommend prescription.

Cancer of the ovary

13. The Council has not previously reviewed the question of cancer of the ovary and asbestos exposure.

14. In the UK there are around 7,000 new cases of ovarian cancer each year. The disease is more common in older women, three quarters of cases occurring over the age of 55 years and a third in women over 75. There is only a weak relationship with smoking. About a third of women with cancer of the ovary survive for 10 years or more after diagnosis.

15. As with laryngeal cancer, the IARC monograph relied heavily on the NAS review and a few extra studies, including a total of eight occupational cohorts. The

Council has considered this evidence carefully and conducted an additional review of the published literature.

16. A systematic review of occupational exposures (Camargo *et al.*, 2011) included 18 cohort studies whose findings were published up to March 2010; they include all those reviewed by IARC. Elevated risks were found in the majority of studies. The summary, estimated relative risk (RR) from this review was 1.77. A sensitivity analysis, whereby an arbitrary 20% of ovarian cancer diagnoses were assumed instead to be peritoneal mesothelioma, resulted in a lower RR estimate of 1.42.

17. This last analysis was conducted because there can be difficulty in distinguishing between cancer of the ovary and other abdominal malignancies, including mesothelioma of the peritoneum which is known to be strongly associated with asbestos exposure. Such misdiagnosis could lead to the true risk of ovarian cancer being overestimated. As Acheson *et al.* commented in one report, "The question must arise whether the excess number of deaths that have been attributed to ovarian cancer have been correctly classified, or whether they represent cases of peritoneal mesothelioma. From the earliest descriptions of peritoneal mesothelioma the difficulties of the differential diagnosis vis-a-vis ovarian cancer have been emphasised. The clinical picture of secondary carcinomatosis of the peritoneum and of peritoneal mesothelioma is similar, and clinicians may be forgiven if the possibility of a rare industry related tumour does not come to mind, particularly in a female patient" (Acheson *et al.*, 1982).

18. Ideally, to overcome the concern raised in the previous paragraph, cases of ovarian cancer would be corroborated by histological inspection of tissues. In many of the reports identified by IARC and summarised by Camargo *et al.*, such information was not available, and for the remainder it was in only a limited and incomplete way. (The report by IARC stated that "three of the [cited] studies...specifically examined the possibility that there were misdiagnosed cases of peritoneal mesothelioma, and all failed to find sufficient numbers of misclassified cases", but in practice a review of the key reports indicates that relevant data were often missing). This remains a limitation in interpreting the evidence base.

19. Camargo *et al.*, conducted an analysis of risks by industry (military gas mask manufacture, work with asbestos textiles, work with asbestos cements, mining of asbestos) and a separate but overlapping analysis of six populations 'highly exposed' to asbestos. With the above caveat in mind, elevated risks were estimated across all of these industries, including British investigations of gas mask workers and textile workers (described below).

20. Among workers deemed to be at highest exposure, the summary estimate of RR was 2.78 (95% confidence interval (95% CI) 1.36 to 5.66). The Council has carefully examined the four studies of so-exposed cohorts in which the risks of ovarian cancer were more than doubled:

- a. Wignall and Fox, 1982: This was a follow-up study of women who were exposed to blue asbestos in the manufacture of military gas masks in Nottingham during and after the Second World War. Six subsequently died from ovarian cancer, a

rate 2.13 times higher than expected; one case was subsequently attributed to peritoneal mesothelioma, reducing the RR below 2.0, (there is no indication that all of the remaining cases were histologically confirmed). The reported increase in risk was not statistically significant. Exposures to asbestos were probably very high but were not quantified either by concentration or by duration of employment.

- b. Berry *et al.*, 2000: A study of women who started work between 1936 and 1942 in an asbestos textile factory in east London reported, by 1980, that there had been nine deaths from cancer of the ovary, a rate 2.53 (95% CI 1.16 to 4.80) times higher than expected. A statistically significant excess risk was found only for those who had worked for more than two years at 'severe' levels of exposure. This category included workers involved in sectional pipe making, the manufacture of insulating material with a high asbestos content, workers in the textile and mattress sections, openers, disintegrators, and those employed in the disposal of asbestos dust. Only 28% of deaths were subject to histological scrutiny and the findings in relation to cases of ovarian cancer were not separately described.
- c. Pira *et al.*, 2005: This was a follow-up study of women who worked in an asbestos textile factory in Italy. On the basis of three deaths, the risk of ovarian cancer in those with 10 or more years of employment was more than five times higher than expected, an estimate that was not statistically significant at the normal 5% level.
- d. Magnani *et al.*, 2008: This was a study of workers in an asbestos cement factory in Italy. Increased risks (by 2.7–3.0 fold) of mortality from ovarian cancer were reported in those with more than 10 years of exposure, although these estimates were based on a small number of cases (8) and none of them was statistically significant; nor were they clearly related to the duration of employment in the plant. Cases of ovarian cancer were not confirmed histologically, in distinction to cases of peritoneal mesothelioma, which were. Mortality from the latter in the women cement workers was more than 25 times higher than expected from regional mortality rates, illustrating the potency of asbestos to affect the RR of this rare tumour, and hence the concern over diagnostic misclassification.

21. A second systematic review, published in 2011 (Reid *et al.*, 2011), included studies published up to 2008. Fourteen cohort (one para-occupational) and two case-control studies were identified, four of which were new from the review by Camargo *et al.* The summary estimate of RR for the 16 studies was 1.75 (95% CI 1.45 to 2.10). This fell to 1.54 (95% CI 1.22 to 1.95) when only studies believed by the authors to involve histologically confirmed ovarian cancer were included.

22. These reviews did not include a cohort study of Chinese textile workers (Wang *et al.*, 2013). On the basis of a single case, an odds ratio (OR) of 7.69 (95% CI 1.36 to 43.58) was reported. No related estimate of exposure was provided.

23. On the basis of the evidence summarised here, the Council has concluded that exposures to asbestos probably increase the risk of ovarian cancer and may do so by more than two-fold if very high. One uncertainty in the evidence base, however, is the extent to which risks have been overestimated by misdiagnosing cases of peritoneal mesothelioma as ovarian cancer. Furthermore, considering the case for prescription in British populations, only workers in asbestos textiles would

now stand to benefit from prescription (given the time elapsed since the studies by Acheson *et al.*, 1982 and Wignall *et al.*, 1982), and the case in textile workers is supported only by one study (Berry *et al.*, 2000) in which the circumstances of 'severe' exposure are insufficiently defined to enable an occupational prescription to be defined. The Council does not therefore recommend prescription for cancer of the ovary in relation to asbestos exposure.

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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 (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**.

Measures of association

Statistical significance and P values: Statistical significance 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**.)

Proportional mortality ratio (PMR): The proportional mortality ratio is the proportion of deaths in the study population from a specific disease divided by the proportion of deaths in the general population from that same specific disease.

Standardised incidence ratio (SIR): A measure of the rate of cancer incidence for a particular type of cancer in a working population compared with the general population, with adjustment for age, gender, calendar year and sometimes socio-economic status. The SIR is the ratio of the observed number of cancer cases (due to a given cancer arising from exposure to a given 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 cancer incidence as the general population (the standard).

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**.)

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).

Meta-analysis: A statistical process of pooling quantitative information across studies to produce an overall estimate of Relative Risk (meta-RR), taking account of their differing sizes.