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POSITION PAPER 26

**Laryngeal cancer and strong inorganic
acid mists containing sulphuric acid**

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Laryngeal Cancer and strong inorganic acid mists containing sulphuric acid

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Summary

1. Twenty years ago, when reviewing the issue of cancer of the larynx and occupational exposure to asbestos, the Council noted a potential relationship with exposure to strong acid mists. At that time the available evidence was considered insufficient to support prescription. In 2009, the Council re-examined the question after a full search of the peer-reviewed literature.
2. Cancer of the larynx is moderately common in the UK; and in about half of cases is successfully treated. There are strong causal associations with smoking and with heavy alcohol consumption. Since the disease in occupationally-exposed patients is indistinguishable from 'background' disease, the case for prescription depends on robust epidemiological evidence for at least a doubling of risk in those with occupational exposure, taking into account the potentially confounding effects of tobacco and alcohol use.
3. 'Strong acid mists' frequently comprise sulphuric acid and are encountered in a wide variety of industries including primary chemical production, steel pickling and the manufacture of lead batteries, soaps and fertilisers.
4. Twenty papers relating to occupational acid mist exposures in these industries were examined. Few studies concerned UK workforces and fewer still controlled adequately for confounding exposures. An independent and more than doubled risk of laryngeal cancer was found among a cohort of US steel workers but was not replicated in other studies of similar workers. The Council found no consistent evidence for such a risk in

studies of employees engaged in the manufacture of acids, industrial alcohols, lead batteries, soap or fertilizers.

5. Various strands of evidence suggest that acid mists in high concentrations may cause cancer of the larynx. However, the amount of evidence in relation to any given exposure circumstance is limited, especially evidence which allows for the important potential confounding effects of smoking. These considerations have led the Council to decide against recommending prescription in each and all of the occupations reviewed.

6. *This report contains some technical terms, such as case control study and confidence interval, which are explained in the glossary included in the Appendix.*

Introduction

7. A report of the Industrial Injuries Advisory Council (IIAC) on cancer of the larynx in relation to occupational exposures to asbestos was released in August 1989 (Cm.779). In considering other potential workplace causes, the report noted supporting evidence related to sulphuric acid mists, but the Council felt that this was insufficiently strong to justify prescription. In an update to Cm.779, the Council has reviewed the further evidence available.

The Industrial Injuries Disablement Benefit Scheme

8. 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.
9. 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

10. 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.
11. 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.
12. 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.

13. 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

14. 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 their occupation may lie in its improvement when they are on holiday, and regression when they return to work, or 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

15. 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.
16. 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.

17. 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.

Laryngeal cancer

18. There are around 1800 new diagnoses of laryngeal cancer in the UK each year. The disease is about five times more common in men than in women and, rare below the age of 40, most commonly presenting in the seventh decade of life. Since the mid 1990's the age-standardised incidence of laryngeal cancer has been falling in men (from 6 to about 5 cases per 100,000), but not in women (1 case per 100,000). Laryngeal cancer not infrequently presents at an early stage, and most cases are treated surgically and with some success; there are about 800 deaths from the disease each year.
19. In 90% of cases the cancer is of squamous cell origin. There are strong and clear associations with smoking, with risks increased 9 to 44-fold in some reports (1;2¹) and some 6-fold with heavy alcohol intake (2); the two may be confounded (3). Other, non-occupational risks may include dietary deficiencies and chronic reflux of acid from the stomach.

Strong inorganic acid mists containing sulphuric acid

20. Sulphuric acid is among the commonest chemicals used in industry. It is a 'strong' acid, which in its pure form is a clear, odourless liquid with a boiling point of 290⁰C. The chemical forms a mist under appropriate conditions of temperature, evaporation, pressure and exothermic reaction with water. The combination of sulphuric acid and sulphur trioxide produces 'fuming sulphuric acid' (oleum) which is used as a sulphonating or dehydrating agent in the refining of petroleum and as a laboratory agent. Sulphuric acid is commonly transported as oleum.

¹ Italicised numbers refer to the reference list included at the end of the report.

21. Sulphuric acid is a high tonnage industrial chemical, with over 150 million tons produced globally and over 1.2 million tons produced in the UK each year. Mists containing sulphuric acid – and sometimes other strong inorganic acids – are encountered during the manufacture of sulphuric acid, nitric acid, ethanol, isopropanol and vinyl chloride; in the manufacture of phosphate fertilisers and lead-acid batteries; in the pickling and other acid treatments of metals, particularly steel; in the petrochemical and coal-product industries; and in printing, paper production, tanning and as an agricultural desiccant in crop treatment. According to a review (4) of published exposure data from various surveys prior to 1970, ‘high’ exposures to sulphuric acid mist (average $>1 \text{ mg/m}^3$ time-weighted average, (TWA)) have been linked with metal pickling and production of sulphuric acid and isopropanol; ‘moderate’ exposures (0.1 to 1 mg/m^3 TWA) with production of ethanol, nitric acid and soaps and detergents; and ‘low’ exposures (below 0.1 mg/m^3 TWA) with production of lead batteries and phosphate fertilizer, and the refining of copper and zinc.

Exposures in the UK

22. A Chemical Hazard Alert Notice issued by the Health and Safety Executive (HSE) in 2001 recommended that exposures to sulphuric acid mist be kept no higher than 0.3 mg/m^3 to protect against laryngeal inflammation.
23. Measurements in the HSE’s National Exposure Database suggest that current exposures in the metal finishing industry and in crop spraying rarely exceed 0.3 mg/m^3 .
24. Lead acid battery manufacture, another application, is in decline in the UK, with, in 2006, just five sites, each with exposed populations of between 75 and 150 (HSE, written communication 2009). A small series of recent measurements made by the HSE included eight (23%) that were 0.3 mg/m^3 or higher and two that exceeded 1 mg/m^3 .
25. Past exposures in most industries may have been higher but the Council was unable to obtain definitive information to confirm this.

Health risks

26. Strong inorganic acid mists are corrosive and irritant to the mucous membranes, particularly those of the eyes, nose and lower respiratory tract. Exposure to high intensities of acid mist will provoke watering of the eyes and nose and, in those who are

susceptible, symptoms of asthma. If sufficiently high, exposure produces 'chemical' burns in these sites – or of the skin.

27. Prolonged high level exposure to acid mists in the workplace may cause damage to dental enamel.
28. In 1992, on the basis of human evidence alone, the International Agency for Research on Cancer (IARC) concluded that chronic occupational exposure to strong inorganic acid mists containing sulphuric acid was carcinogenic with respect to laryngeal cancer (Group 1). Sulphuric acid itself (although a member of the class of chemicals labeled strong acids) has not been classified by IARC; but in 1996 the American Congress of Governmental Industrial Hygienists adopted an 'A2' classification (suspected human carcinogen) for the pure chemical.
29. The mechanism of probable carcinogenicity is debated. Two suggestions have been mooted, the first relating to the direct irritant effects of high acidity on cellular DNA, the second proposing an interaction with components of cigarette smoke.
30. Since the IARC report there have been six further publications relevant to this issue. The deliberations in this report are based on the totality of available evidence.

Consideration of the evidence

31. A literature search carried out by the Council identified 20 fully published reports of laryngeal cancer and exposure to strong acid mists. Fifteen described the experience of 12 separate cohorts of employees with workplace exposure to acid mists; the remainder were case-control studies of patients with cancer of the larynx.
32. In this respect, 'cohort' studies examine the risk of disease (laryngeal cancer) in a carefully defined group of employees with known exposure to acid mists and compare this with the risk in similar employees without such exposure or, after adjustment for age and sex, in the general population. Cohort studies have the potential advantages of being relatively free from bias and of having access to measured levels of exposure. Where the condition under study is rare, however – as is the case for cancer of the larynx – cohort studies may include few informative cases of disease. The risk measured by cohort studies is expressed as a 'relative risk' or 'standardized mortality ratio' (SMR) or 'standardized incidence ratio' (SIR). Risks of more than 1.0 indicate an increased risk.

33. In case-control studies, patients with cancer of the larynx are identified and their experience - in this case of exposure to acid mists - is compared with that of suitable controls who are free of laryngeal cancer. These types of study tend to include far more cases of disease but are generally disadvantaged by incomplete and sometimes biased information about preceding events. Risks measured by case-control studies are expressed as odds ratios in which, as above, measures above 1.0 indicate an increase in risk.
34. Laryngeal cancer, as with almost all cancers, has a long latency - that is, the exposure that is responsible for inducing disease generally precedes its identification by many years. For this reason, studies often consider specifically any 'lagged' exposure(s) which have occurred a decade or more before diagnosis, disregarding the most recent exposure history.
35. In both cohort and case-control studies it is important to take account of potentially confounding exposures to other causes of the disease in question; in this case, in particular to smoking and to heavy alcohol consumption. Information on these is often absent or incomplete. There may also be confounding by exposure to other workplace potential carcinogens such as, in this case, alkyl sulphates (5).
36. Since many patients with laryngeal cancer do not die from their disease, studies that focus only on mortality will underestimate the true rate of disease; this does not necessarily bias their findings in relation to exposure.

Cohort studies of laryngeal cancer and acid mist exposure (Table 1)

37. The Council identified 15 relevant cohort studies describing 12 separate workforce-based populations. These are summarized in Table 1 and described more fully below, ordered by the type of industry in which acid mist exposures were encountered.

Workers in steel plants

38. Five reports included employees in steel pickling, but in only one instance were they from the UK. Ahlborg and colleagues (6) studied 110 men employed in a Swedish steel pipe-making plant where sulphuric, nitric and oxalic acids were used. Over the period of mortality follow-up, three deaths from laryngeal cancer were observed where 0.6 would have been expected on the basis of standardized, national rates. Information on smoking

and on acid mist exposures was unavailable.

39. In 1987, Beaumont and colleagues (7) published the findings of their mortality study of 1165 men working in three US steel mills between around 1945 and 1965. The acid mists to which they were exposed comprised mostly sulphuric acid; the mean exposure (all acids) in the late 1970s was $0.29\text{mg}/\text{m}^3$, with few measurements above $1\text{mg}/\text{m}^3$ (estimated average daily exposure to sulphuric acid mists, $0.2\text{ mg}/\text{m}^3$). Two deaths from laryngeal cancer – against an expected number of 1.03 from national rates - were observed, giving a SMR of 1.93 (95% confidence interval (CI) 0.23-6.99). This estimate did not allow for potential effects of smoking and alcohol intake.
40. Two subsequent studies of the same workforce have been published using cancer incidence rather than mortality. In the first (8) nine cases were observed when, after an adjustment for smoking and alcohol consumption, 3.92 would have been expected; the SIR was thus 2.30 (95% CI 1.05-4.36). Deaths from laryngeal cancer arose at an average age of 53 years, some 26 years after first exposure and with an average exposure duration of 12.2 years. The risk was higher and more than doubled, in men who had been employed for more than five years (2.76) than in those who worked for a shorter duration (1.70). The authors had only limited information on workers' smoking habits and alcohol consumption; risk estimates were adjusted under the assumption that patterns mirrored those in a US population survey conducted in 1965. The findings were shown to be robust to other assumptions based on substantially heavier smoking in the workers studied.
41. A further follow up of the same cohort was published nine years later (9). By this point, 14 cases of laryngeal cancer had been identified of whom eight had died (but only two had a record of this on their death certificates). Seven cases had been exposed to sulphuric acid mists only, the remainder to a mixture of sulphuric and/or other acids; all the cases (but only 76% of the total cohort) were or had been cigarette smokers. An estimated 6.4 cases would have been expected from national rates, after an adjustment for smoking and drinking under the assumptions in the paragraph above. The relative risk was thus 2.2 (95% CI 1.2-3.7). No trend with either duration of exposure or by lagged exposures was found. The risk was a little higher for those employees who had had daily exposure to sulphuric acid mists (2.5, 95% CI 1.7-4.7).

Workers in steel plants or battery factories

42. In a study of UK employees, Coggon and colleagues (10) observed 4401 men of

whom 3158 (72%) were employed in two steel works, 2041 of them with definite or probable exposure to acid mists. The other 1243 men in the cohort worked in two battery factories, 1004 of them with acid mist exposures. The men were employed between about 1950 and about 1990 but the durations of their employment are not described. There were no acid mist measurements available from either steel mill; but exposures made in the 1970s in the battery factories ranged between 0.1 and 2.0 mg/m³. In the entire cohort, three deaths from cancer of the larynx were recorded, but only one among men with 'definite' exposure to acid mists (SMR 0.86 overall, and 0.48 for 'definite' exposure). Findings by industry were not reported. In a nested case-control study in the same cohort, the odds of upper aerodigestive cancer were doubled in men with at least five years of high exposure, but only three of the 15 cases analysed related to the larynx.

43. With the aim of examining the health risk of working with lead, Wong and colleagues (11;12) published two reports on a cohort study of mortality in 4518 men who had worked in ten US battery factories. No information on acid mist exposures or on smoking or alcohol intake was available. Over the period 1947 to 1995, seven deaths from cancer of the larynx were recorded, with a SMR of 0.90 (95% CI 0.36-1.85). No clear pattern with duration or era of employment was evident.

44. In a British report, no deaths from laryngeal cancer were reported in a cohort of 754 workers from four lead acid battery factories, studied between 1925 and 1976 (13).

Workers in primary chemical manufacture

45. Lynch and colleagues (5) published a small cohort study ($n^2 = 335$) of ethanol process workers in Louisiana, US. Four cases of laryngeal cancer were noted producing a standardized incidence ratio – in comparison with the US population - of 5.04 (approximate 95% CI 1.4 to 12.9). In a larger cohort of chemical and refinery workers from the same workforce seven cases of the disease were recorded (SIR 3.2 (approximate 95% CI 1.3 to 6.6)). Most cases had worked with strong acids; no adjustment for smoking or other potential confounders was made. The authors proposed that the excess risk was related to diethyl sulphate rather than acid mists.

46. The mortality experience of a cohort of 1031 US workers in ethanol/isopropanol production were reported by Teta and her colleagues (14). On the basis of two deaths from cancer of the larynx a SMR of 2.0 was estimated; one death occurred among those

² n = number in the cohort

who had been exposed for 10 years or more (0.2 expected). No measurements of acid exposure were reported.

47. In a small British study, by Alderson and Rattan in 1980 (15), no cases of laryngeal cancer were reported among 262 men employed in an isopropyl alcohol plant.
48. In a study reported only in Italian, Pesatori and colleagues (16) examined the mortality of 1096 men employed as 'labourers' in a Tuscan factory manufacturing sulphuric acid. Median acid exposures in or around the 1970s were of the order of $1\text{mg}/\text{m}^3$. Four deaths from laryngeal cancer were recorded where 3.1 would have been expected, a SMR of 1.30 (95% CI 0.35-3.33). No analyses using either acid exposures or potentially confounding exposures were reported.

Workers in phosphate fertilizer factories

49. Three cohorts of US workers in phosphate fertilizer manufacture have been studied. In two (17;18), each examining only deaths from cancer of the larynx, fewer deaths than expected were observed.
50. In the third (19), Block and colleagues examined the incidence (deaths and diagnoses) of laryngeal cancer in a cohort of 2607 white men who had been employed for six months or more. Two cases were found, corresponding to a SIR of 1.91. No further analyses were reported; and nor was there any information on acid mist exposures.

Workers in soap manufacture

51. The final cohort study concerns a relatively small ($n=361$) number of men who had worked for at least a year in a soap factory in Italy (20). Measurements of airborne sulphuric acid since 1974 ranged from $0.64\text{--}1.12\text{mg}/\text{m}^3$. One death from laryngeal cancer was recorded, equating to a SMR of 2.30 (95% CI 0.09-11.43); a further four cases were uncovered from hospital records available for some of the cohort. Depending on which population was used as a basis for comparison, the total five cases corresponded to SIR of 3.47 or 6.94, each statistically significantly raised above 1.0. No adjustment for smoking or other confounding was made; and no analyses by duration of exposure were reported.

Case-control studies (Table 2)

52. Two case-control studies designed specifically to examine the issue of acid mist

exposures have been identified by the Council; in addition, three population-based studies with relevant information have been examined. These are summarized in Table 2.

53. In 1984, Soskolne and colleagues (21) published the findings of a case-control study of laryngeal cancer among men working in ethanol production in the same US factory studied by Lynch (above) in 1979 (5). Retrospective estimates of occupational exposure to sulphuric acid were compared for 34 cases and a group of controls selected from the same workforce cohort. After adjustment for smoking and alcohol consumption, a very high estimate of risk was found for those with the highest 20% of exposures: odds ratio 13.4 (95% CI 2.08-85.99). No significantly increased risk was observed for those with lower exposures.
54. A more detailed assessment was achieved by a case-control analysis of 183 men with cancer of the larynx from general population of Southern Ontario (22). In comparison to community controls, and after adjustment for smoking and alcohol intake (both strong risk factors), cases had a 6.91-fold increase (95% CI 2.20-21.74) of ten years or more 'substantial' exposure to sulphuric acid mists, as judged by expert assessment of their job title; the risk associated with fewer than 10 years of similar exposure was 3.34 (95% CI 0.60-18.53). The equivalent estimates for those with 'probable' exposure were 3.85 (95% CI 1.60 – 9.24) and 2.66 (95% CI 1.09 – 6.49) respectively. In this context 'substantial' exposure was defined as the probable or certain assignment of an exposure above about 0.1 mg/m³ for at least 5% of the workday, at least five years of which preceded diagnosis by five years or more. The occupations in which cases arose were not listed; but the relatively high estimated prevalence of exposure to sulphuric acid mists was explained as arising from a high historic density of relevant industries (iron and steel pickling, fertilizer production, soap production, storage-battery production, sulphuric acid manufacture, metal drawing, metal extrusion and electroplating) in Southern Ontario.
55. Two population-based case control studies, one large one in Europe (23) and a smaller one in the US (24), failed to find increased risks of occupational acid exposure in patients with laryngeal cancer.
56. A third population-based study (25) reported an increased odds ratio of exposure to workplace acids in 352 men with cancer of the larynx. No further information was provided.

Summary of the evidence and conclusions

Steel pickling

57. A more than doubling of risks of laryngeal cancer was found among the cohort of US steel workers described in paragraphs 39 to 41. This investigation is notable for its attempt to adjust for the important confounding effect of smoking, although control may only have been partial. Adjustments for smoking and alcohol made little difference to the measured relative risk. There is some evidence that any doubling in risk was limited to those with more than five years exposure.
58. The very much smaller Swedish study in paragraph 38, although not allowing for the confounding effects of smoking, also points to a more than doubling of risk in the industry.
59. Set against these two inquiries are the findings of Coggon *et al.* (10) in the UK (paragraph 42), who did not find increased risks in a study population among whom 72% were steel workers, many with 'probable' exposure to sulphuric acid mists.
60. The evidence on steel pickling is suggestive, but the Council has decided that it is insufficient in depth, and relative to UK-based patterns of exposure, to support prescription.

Lead battery manufacture

61. The study in paragraph 42, and more specifically those in paragraphs 43 and 44 (including investigations from the UK), do not support prescription in relation to lead acid battery manufacture.

Primary chemical manufacture

62. Two US cohort studies of ethanol/isopropanol workers found risks raised some two to five-fold (paragraphs 45 and 46), although neither adjusted for smoking or alcohol consumption. A case-control study in one of these workforces found higher risks after allowing for patterns of smoking and drinking (paragraph 53).
63. The sole UK study of isopropyl alcohol production, however, found no increase in risk of laryngeal cancer (paragraph 47).

64. The Council found few data on risks from manufacturing sulphuric acid, none that suggested a doubling of risk, and none that came from the UK (paragraph 48).

65. This evidence base is considered insufficient in depth, and relative to UK-based patterns of exposure, to recommend prescription in relation to primary chemical manufacture.

Manufacture of phosphate fertilizers

66. The Council found no consistent evidence of a more than doubled risk of laryngeal cancer among manufacturers of phosphate fertilizers (paragraphs 49 and 50), and cannot therefore recommend prescription in relation to this exposure and this outcome.

Soap manufacture

67. Data on soap manufacture were limited to one small Italian study, which suggested a more than doubling of risk but did not control for the potential effects of smoking (paragraph 51). This evidence base is insufficient to recommend prescription.

Conclusions

68. A number of strands of evidence, individually and collectively, suggest that acid mists in high concentrations, may cause cancer of the larynx, as concluded by the IARC. However, the amount of evidence in relation to any given exposure circumstance is limited, especially evidence which allows for the important potential confounding effects of smoking (a strong non-occupational risk factor for this tumour). These considerations have led the Council to decide against recommending prescription in each and all of the occupations reviewed. It should be noted that evidence of carcinogenicity *per se* is not enough; attribution must be possible in the individual case, which is interpreted by the Council as reasonable evidence of a doubling of risk in well-defined circumstances of exposure (paragraphs 10 to 12). This standard is not yet met.

69. However, the Council welcomes further studies on sulphuric acid mists and cancer of the larynx, as these may influence the future balance of evidence. The Council will continue to monitor emerging research findings.

Prevention

70. The Control of Substances Hazardous to Health Regulations 2002 (as amended) (COSHH) apply to work with sulphuric acid. 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 sulphuric acid 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

71. 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 laryngeal cancer and strong acid mists containing sulphuric acid, no diversity and equality issues became apparent.

Table 1: Cohort studies concerning exposure to sulphuric acid mists and risk of laryngeal cancer

Reference	industry	Setting	Study	measure	Measurements of acid	Adjustment for smoking or alcohol	Main findings
Ahlborg <i>et al.</i> (1981) (6)	Steel pickling	Swedish steel pipe factory	110 men employed for >1 yr at a plant manufacturing steel pipes	mortality	none	none	3 deaths vs. 0.6 expected
Beaumont <i>et al.</i> (1987) (7)	Steel pickling	Three eastern US steel mills	Mortality study of 1165 men exposed to acid mists (mostly sulphuric acid)	mortality	1970s: mean=0.29 mg/m ³ (few exposures >1 mg/m ³)	none	For any acid exposure: 2 deaths vs. 1.03 expected; SMR 1.93 (95% CI 0.23 – 6.99) Data not available for sulphuric acid alone
Steenland <i>et al.</i> (1988) (8)	Steel pickling		879 men who had worked at least six months before 1965 and for an average of 9.5 years	incidence	1970s: averaged c. 0.2mg/m ³	smoking, alcohol	9 cases vs. 3.44 expected, or 3.92 adjusted for smoking – SIR 2.30 (95% CI 1.05 – 4.36). By duration: ≤ 5yrs = 1.70; >5 yrs 2.76 By time since first exposure: ≤ 20 yrs 3.27; > 20 yrs 2.03

Steenland (1997) (9)	Steel pickling		1031 men exposed on average for 9.2 years since 1949	incidence	Mean personal exposures in 1970s 0.19 mg/m ³ ; mean exposure in areas studied, 0.29 mg/m ³	smoking, alcohol	14 cases vs 5.6 expected - SIR 2.5, (95% CI 1.37-4.19) After adjusting for smoking and alcohol the estimated relative risk fell to 2.2 (95% CI 1.2 – 3.7). Relative risk for those with daily exposure 2.5. No associations with duration of employment; lagged analysis unchanged
Coggon <i>et al.</i> (1996) (10)	Steel pickling, battery manufacture	Two steel mills and two battery factories in the UK	Men employed since c.1950. 2,678 men with definite exposure to acid mists (mainly sulphuric acid) and 1723 others. Follow-up until 1993 (97% traced, 1277 deaths, including 3 cases of laryngeal cancer)	mortality and incidence	none	none	1 death in a worker definitely exposed to acid mists. Odds ratio 0.48 (0.01 – 2.7) Upper aero-digestive cancers + exposure for at least 5 yrs at >1 mg/m ³ : OR 2.0 (0.4 – 10) “Any risk (of ‘cancer’) from exposures below 1 mg/m ³ probably small”
Cooper <i>et al.</i> (1985) (11)	Battery manufacture	10 US lead battery plants	4519 men employed for ≥1 year between 1946 and 1970	mortality	none	none	6 deaths vs. 4.7 expected: SMR=128 (95% CI 47-280). No exposure-response or lagged analysis
Wong <i>et al.</i> (2000) (12)	Battery manufacture		4518 men employed 1946-1970	mortality	none	none	7 deaths vs. 7.81 expected: SMR=89.7 (95% CI 36.1-184.8). No exposure-response or lagged analysis
Lynch <i>et al.</i> (1979) (5)	Ethanol and isopropanol production	A single, southern US plant	335 (of total cohort of 743) workers employed at least 6 months between 1950 and 1976. 48 (123) deaths	incidence	none	none	4 cases among alcohol process workers: SIR 5.04. Cases had spent 70% of their time on the ethanol (strong acid) unit (vs. 20%

			and 32 (77) losses to follow-up				for the total cohort) 7 cases among chemical & refinery workers who had worked on the alcohol process units (SIR 3.2) No further exposure-response analysis; no lagged analyses; no smoking information
Teta <i>et al.</i> (1992) (14)	Ethanol and isopropanol production	Two US factories	1031 men employed between 1940 and 1978	mortality	none	none	1 death vs. 0.3 expected; SMR 3.3 (95% CI 0.1 – 18.6) In both plants combined, observed =2. expected =1, SMR 2.0 1 death employed >10 years. No further exposure-response analysis
Alderson <i>et al.</i> (1980) (15)	Isopropyl alcohol manufacture	A single UK factory	262 men employed between 1949 and 1975	mortality	none	none	0 reported cases of laryngeal cancer
Pesatori <i>et al.</i> (2006) (in Italian) (16)	Sulphuric acid manufacture	A single factory in Italy	1096 workers employed for at least a year between 1962 and 1997	mortality	1970s c.1 mg/m ³ (median 1.4 in 1977, 0.9 in 1979, 1.2 in 1981)	none	4 deaths vs. 3.1 expected. SMR 1.30 (95% CI 0.35 – 3.33)
Stayner <i>et al.</i> (1985) (18)	Phosphate fertiliser manufacture	A single US factory	3,199 men employed between 1953 and 1976, followed to 1977	mortality	1976: mean 0.11 mg/m ³ (range 0.013-0.22)	none	0 deaths vs. 0.43 expected
Checkoway <i>et al.</i> (1996) (17)	Phosphate fertiliser manufacture	A single US factory	22,992 men employed between 1949 and 1978 for an average of	mortality	none	none	12 deaths vs 16 expected. In the highest exposure category (all exposures) the SMR was 0.82,

			about 5 years				based on a single death
Block <i>et al.</i> (1988) (19)	Phosphate fertiliser manufacture	A single US factory	2607 white men employed for 6 months or more between 1950 and 1979, followed to 1981	incidence	none	none	2 deaths: SMR 1.91. No further analysis by exposure/lag. No deaths in 840 black men
Forastiere <i>et al.</i> (1987) (20)	Soap production	A single factory in central Italy	361 men employed for at least one year between <1964 and 1972	incidence	in hydrolysis and saponification areas in 1970s averaged 0.64 to 1.12 mg/m ³	none	SMR 2.30 (0.09 – 11.43) 5 incident cases vs. 0.72 expected (local hospital rates), relative risk = 6.94 (95% CI 2.25 – 16.21); vs. 1.44 expected (cancer registries in S. Europe), relative risk = 3.47 (1.12 – 8.10) All cases had latency >10 years. No exposure-response analysis

Table 2: Case-control studies concerning exposure to sulphuric acid mists and risk of laryngeal cancer

Reference	Setting	Country	n, cases	Exposure assessment	Main findings
Solskolne <i>et al.</i> (1984) (21)	Workplace-based ('nested'): ethanol production	US	30	Workplace records 'High exposure' = upper 20% of cumulative estimated dose	Cancer of the larynx, adjusted for smoking + alcohol: - high vs. not, relative risk 13.4 (2.08-85.99) - moderate vs. not, relative risk 4.6 (0.83-25.35)
Solskolne <i>et al.</i> (1992) (22)	Population-based	Canada	183	Lifetime jobs blinded to disease status, and job exposure matrix constructed for sulphuric acid exposure – based upon level of exposure (0, 1, 2, 3), frequency ($\leq 5\%$, 5-30%, $>30\%$ of workday), and certainty surrounding these estimates	≤ 10 yrs + probable exp: odds ratio 2.66 (95% CI 1.09 – 6.49) ≤ 10 yrs + substantial exp: odds ratio 3.34 (95% CI 0.60 – 18.53) >10 yrs + probable exp: odds ratio 3.85 (95% CI 1.60 – 9.24) >10 yrs + substantial exp: odd ratio 6.91 95% CI (2.20 – 21.74) Substantial = probable/certain assignment of a medium/high exposure ($\approx >0.1$ mg/m ³) for at least 5% of workday, at least 5 yrs of which preceded diagnosis by ≥ 5 yrs. Data adjusted for lifetime smoking and alcohol
Shangina <i>et al.</i> (2006) (23)	Population-based	316	Central and eastern Europe	73 occupational carcinogens examined – exposures determined by occupational hygienists etc from job histories	Odds ratio for exposure to inorganic mists 0.94 (95% CI 0.60-1.49)
Brown <i>et al.</i> (1988) (24)	Population-based	183	US	Lifetime work histories classified by a hygienist	22 cases and 42 controls counted as exposed to sulphuric acid – odds ratio 0.76 (95% CI 0.42 – 1.35), adjusted for smoking and alcohol. Numbers with high exposure not known
Zemla <i>et al.</i> (1987) (25)	Population-based	328	Poland		Odd ratio cancer of the larynx 4.27 (11 cases)

Appendix 1: 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 (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

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 ease 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, which 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

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).

Squamous cell: a flat, scale-like cell which forms a layer/s to line cavities and surfaces of the body.

'Strong' acid: an acid which is completely dissociated in an aqueous solution.

Exothermic reaction: a reaction which takes place giving out heat.

Oleum: fuming sulphuric acid

Sulphonating agent: a chemical agent which adds a sulphonic acid group to an organic compound.

Pickling: the treatment of metals to remove impurities, stains or rust with a 'pickle liquor' of strong mineral acids before extrusion, rolling, painting, galvanizing or plating. Sulphuric acid used for this purpose is increasingly being replaced by hydrochloric acid.

Dessicant: a substance which induces dryness.

Upper aerodigestive cancer: cancer occurring in the upper aerodigestive tract, which includes the lips, tongue, major salivary glands, gums and adjacent oral cavity tissues, floor of the mouth, tonsils, oropharynx, nasopharynx, hypopharynx and other oral regions, nasal cavity, accessory sinuses, middle ear, and larynx.

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