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Lymphatic and haematopoietic cancers and work involving exposure to trichloroethylene

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Position Paper
Lymphatic and haematopoietic cancers and work involving exposure to trichloroethylene
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Summary

1. This report concerns the possible prescription of certain blood-cell related malignancies under the Industrial Injuries Disablement Benefit (IIDB) Scheme in workers exposed to the industrial solvent trichloroethylene (TCE). The review was initiated by the Industrial Injuries Advisory Council as part of its rolling programme of work.
2. TCE is classified by the International Agency for Research on Cancer (IARC) as a group 1 (definite) human carcinogen, partly on the strength of occupational studies of kidney and blood cell cancers (IARC, 2014).
3. This is the second of two linked reports on TCE, a previous position paper having reported on cancer of the kidney.
4. Research findings support the conclusion of IARC, that occupational exposures to TCE can cause cancer. However, as detailed below, the Council has not identified circumstances that would meet the legal requirements for prescription of TCE and blood cell cancers under the IIDB Scheme.

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

Trichloroethylene (TCE)

5. TCE is a widely used industrial solvent with many applications. Its principal use these days is in cleaning and degreasing metal parts, to remove oils, greases, waxes, tars, and moisture before surface treatments such as galvanizing, electroplating, painting, anodizing and application of conversion coatings. Additionally, it has been used as an anaesthetic, a heat-transfer medium, an extraction agent for fats and oils (and so as a dry cleaning agent), and as a feedstock, chemical intermediate, or carrier solvent in processes that produce paints, adhesives, cleaners, pesticides, flame-retardants, paint strippers, plastics and many other materials. The many uses imply that many workers in the European Union have exposure to TCE and in low concentrations it can be found in water supplies, groundwater and the general environment.

6. High exposure to TCE produces acute depression of the central nervous system and symptoms that mimic those of alcohol intoxication (e.g. headaches, dizziness, confusion, drowsiness). It can also induce liver cancer in mice and kidney cancer in rats and genotoxic metabolites of TCE have been shown to form in the kidney. Subsequent research led IARC to classify TCE as a human carcinogen (IARC, 2014).

Lymphatic and haematopoietic malignancies

7. The human body operates two closely connected circulatory systems, the familiar one which carries red and white blood cells and oxygen, and the less familiar lymphatic system – a second network of vessels and associated tissue (e.g. bone marrow, tonsils, thymus, spleen, lymph nodes) which carry a fluid called 'lymph' that supports the immune function. Lymphatic vessels contain white blood cells (lymphocytes), waste products, cellular debris, bacteria and proteins. Associated lymphoid organs are sites of lymphocyte production (especially bone marrow and thymus) and concentration. Both red and white blood cells circulate in the blood stream, but only the white cells and plasma filter out from the blood to bathe and protect ordinary tissues; the lymphatic vessels act as a kind of overflow system or accessory return route to the blood for filtered plasma, while at the same time carrying foreign proteins to the lymph nodes, where the immune response is stimulated.
8. Cancers of the blood and lymphatic systems are numerous, heterogeneous and overlapping. The account that follows simplifies an extremely complex picture.
9. **Lymphoma** is the commonest lympho-haematopoietic cancer (15-20 new cases/100,000 population per year in Western countries). It is a tumour of the lymphatic system which develops from lymphocytes. Dozens of subtypes of lymphoma exist, and several classification systems use histology and other features to subdivide into categories relevant to treatment and prognosis. The two principal categories, however, are **Hodgkin's disease** (lymphoma) and **Non-Hodgkin's lymphoma** (NHL).
10. Hodgkin's disease has an incidence of about 3 cases/100,000 population/year in Europe and the USA (1% of cancer registrations), peaking at ages 20-29 years with a second smaller peak around age 60 years. In the UK, more than 12,000 people are diagnosed with non-Hodgkin lymphoma each year. The tumour has a special distinguishing pathology. It is far more common in identical twins, and risks are elevated about 4-fold in those previously infected by Epstein Barr virus and 8-fold in those with HIV. Survival following diagnosis has improved with modern chemotherapy.

11. Some 90% of all lymphomas fall into the catch-all group of NHL, an umbrella term covering 80 or more histologically and biologically heterogeneous subtypes, which can be divided according to the type of lymphocyte affected ('B-cell' or 'T-cell'), the sites where they arise (e.g. the lymph nodes or follicles, the spleen), and other features. Seventy per cent of cases are B-cell in origin. An added complexity is that the World Health Organisation's classification of lymphoid cancers includes within its list the most common type of leukaemia, **chronic lymphoid leukaemia** (CLL), which may be a stage of B-cell NHL, and **multiple myeloma**, a cancer of so-called 'plasma' B cells, which in many traditional textbook accounts is described separately from lymphoma.
12. About 60% of cases of NHL are "high grade" (more aggressive), including T-cell lymphoma and diffuse B-cell lymphoma, and these carry a poor prognosis relative to the indolent, relapsing course of "low grade" NHL (so-called follicular and marginal zone types).
13. NHL has an incidence of about 12/100,000 population/year but this rate rises with age, such that it is five times higher than this at age 75 years; the median age at diagnosis is 65-70 years. The disease can arise as a late manifestation of HIV and it has been linked with certain viral infections, chromosomal abnormalities, and immunosuppression (congenital or medically caused).
14. Multiple myeloma is a cancer of plasma cells (derived from B lymphocytes) and is notable because the cancerous cells produce large amounts of a single antibody (monoclonal IgG). The disease has an incidence of 4/100,000/year and it represents 1% of all malignancies and 10% of all haematological ones. It is most often diagnosed in the seventh decade of life. The causes of the disease are unknown. It has a significant 5-year mortality.
15. During the 1970s and 1980s in the US, the incidence rate of NHL almost doubled; some of the rise was attributable to HIV infection and some to improved diagnosis, but interest was sparked in whether exposures to solvents and pesticides in the workplace and environment had contributed to the rise. Subsequently, much research was undertaken on the risk of lymphatic and haematopoietic cancers in occupational settings.
16. This account focuses on findings in relation to exposures to TCE. Experimentally, TCE has been shown to impair immune function and stimulate unscheduled DNA synthesis in human lymphocytes (Karami et al, 2013), marking it out as a candidate chemical for lymphoid neoplasia. Risks are reviewed for lymphomas (NHL and Hodgkin's disease)

and where analysed, NHL subtypes and putative subtypes including CLL and myeloma. Studies in the area sometimes report also on leukaemia more generally and IARC has assessed these risks in TCE-exposed workers; for completeness, these data are also summarised.

The Industrial Injuries Disablement Benefit Scheme

17. The IIDB Scheme provides a benefit that can be paid to employed earners because of an occupational accident or 'prescribed' disease (listed in Schedule 1 of the 1985 Regulations). The benefit is no-fault, tax-free, non-contributory and administered by the Department for Work and Pensions.

The Industrial Injuries Advisory Council

18. IIAC is an independent statutory body established in 1946 to advise the Secretary of State for Social Security on matters relating to the IIDB Scheme. IIAC advises on the prescription of occupational diseases; matters referred by the Secretary of State; draft regulations or proposals concerning the Scheme; and any other matter relating to the Scheme or its administration. IIAC is a non-departmental public body and has no power or authority to become involved in individual cases or in their decision making processes.

Prescribed Disease provisions of the IIDB Scheme

19. The Social Security Contributions and Benefits Act 1992 states that the Secretary of State may prescribe a disease where he or she is satisfied that the disease: (a) "Ought to be treated, having regard to its causes and incidence and any other considerations, as a risk of the occupation and not as a risk common to all persons; and (b) Is such that, in the absence of special circumstances, the attribution of particular cases to the nature of employment can be established or presumed with reasonable certainty." 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 can be reasonably presumed in individual cases.
20. Some occupational diseases are relatively simple to verify, as the link with occupation is clear-cut. Some only occur due to particular work (e.g. pneumoconiosis in coal miners); or are almost always associated with work (e.g. mesothelioma in the UK); or have

specific medical tests that prove their link with work (e.g. occupational asthma); or have a rapid link to exposure or other clinical features that make it easy to confirm the work connection (e.g. certain infections and chemical poisonings). Thus, 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, and in the demonstration that they are allergic to a specific substance with which they come into contact only at work.

21. However, many 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 depends on epidemiological evidence that work in the prescribed job or with the prescribed occupational exposures causes the disease on the balance of probabilities (previous reports of the Council give further detail). In turn the Council looks for evidence that a particular occupational exposure or circumstance increases the risk of developing the disease by a factor of two or more.
22. The requirement for, at least, a doubling of risk follows from the fact that if a hazardous material 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 only do so 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 an individual case occurring in the exposed population, there would be 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. 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.
23. Since lymphatic and haematopoietic cancers are not specific to occupation, and since they are clinically indistinguishable in occupational instances from those which are unrelated to occupation, the Council sought evidence on the circumstances of exposure to TCE that might be sufficient to more than double risks of NHL, Hodgkin's disease and allied cancers.

Methods of investigation

24. The research reports identified by IARC were examined with this criterion in mind and a separate search was conducted by the Councils' Research Working Group for further peer-reviewed research evidence on hazard and risk.

Available research

25. Tables 1 and 2 summarise findings from 23 relevant scientific reports (22 studies) identified by the Research Working Group. Broadly, investigations fell into two types: (1) cohort studies, in which occupational groups with known exposure to TCE were monitored over time and instances of lymphatic and haematopoietic cancer were compared with expected numbers from a reference group (an unexposed or general population) (Table 1); (2) case-control studies, in which cases of cancer were compared with non-cases in terms of their previous occupational history of exposure to TCE (Table 2).
26. In all, 12 studies of the cohort type and 10 of the case-control type (11 reports) were highlighted by the Council's review, together with two analyses (Hansen et al, 2013; Karami et al, 2013) that pooled data across different investigations.
27. Studies came from the United States, Canada, Sweden, Finland, Norway, Iceland, Germany, Denmark, France, Italy, Spain and Ireland. The cohort studies included multiple reports from the American aircraft, aerospace and rocket industries, as well as reports from uranium processing facilities, and studies of workers from multiple workplaces, monitored for exposure to TCE under national arrangements.
28. One cohort study involved a mortality analysis of almost 78,000 workers (Boice et al, 1999; Lipworth et al, 2011), but at the other extreme another involved just 803 people (Hansen et al, 2001); most cohorts included several thousand subjects. Sample sizes also varied in the case-control studies: at one extreme over 69,000 cases of NHL known to the cancer registries of several Nordic countries were linked with census data on occupation, resulting in over 3,600 cases with exposure (Vlaanderen et al, 2013); but in some case-control studies the exposed cases numbered fewer than 20 (Greenland et al, 1994; Hardell et al, 1994; Persson et al, 1999; Christensen et al, 2013).
29. It should be noted that rarity of blood cell-related cancers meant that cohort studies typically did not have the numbers to rule out a possible doubling of risks from exposures. Case-control studies had the advantage that their starting point was a collection of instances of rare disease; but the studied groups (patients from the general

population) may have had relatively low and poorly characterised exposure levels, more so than in cohorts from selected workplaces.

30. Challenges also arose in exposure assessment. In most studies, detailed occupational histories were reconstructed but direct measurements of exposure were scarce. In lieu of more precise information, experts (industrial hygienists) formed a judgement as to the probability of exposures to TCE and their likely intensity and frequency. The metrics featuring in analyses (e.g. 'high', 'medium', or 'low' intensity; 'longest held job in an industry with TCE exposure'; 'monitored for metabolites of TCE in urine') would be difficult to translate into a prescription schedule and apply in the context of the IIDB Scheme, and risks were seldom assessed by job title.

Estimates of risk

Non-Hodgkin's lymphoma and its sub-entities

31. A total of 9 cohort studies and 9 case control studies provided risk estimates for **NHL**, together with data from the pooled analyses of Hansen et al (2013) and Karami et al (2013).
32. In the largest of the cohorts, mortality from NHL was studied in almost 78,000 employees of Lockheed Martin manufacturing facilities in California over five decades (Lipworth et al, 2011). Among those with ≥30 years of employment, mortality risks were little elevated (Standardised Mortality Ratio (SMR) 1.29), although only a minority of the cohort had intermittent or routine exposure to TCE.
33. Other reports on NHL in relatively large cohorts of US aviation, aerospace and rocket workers have produced similar estimates of risk. In workers engaged in rocket engine testing in California, mortality from NHL was assessed relative to expected rates (Boice et al, 2006). In field laboratory workers the SMR was 1.02; rates were not elevated in test stand mechanics (a group believed to be more exposed to chemicals); and no trends were found with duration of employment in the laboratory. In an overlapping analysis (Zhao et al, 2005), which combined NHL with leukaemia, the SMR from 'high' cumulative exposure to TCE was 1.30, while an incidence analysis based on the same exposure category and outcomes reported no elevation in risks. In a cohort of some 14,400 civilians employed at a military airbase in Utah (Radican et al, 2008), the SMR for NHL was 1.56 in men and 1.18 in women. None of the findings in these 3 reports were significant statistically.

34. A large study from Denmark (Raaschou-Nielsen et al, 2001) linked data on cancer incidence and employment across 40,000 workers from 347 different companies with recorded use of TCE use. Standardised Incidence Ratios (SIR) for NHL were only slightly elevated (1.2 in men, 1.4 in women,), although higher in men and women with ≥5 years of employment (1.4 and 1.8 respectively). Elevated risks were confined to first employment before 1970 (1.4 and 1.6). No finding was statistically significant.
35. In a cohort mortality study based in an American uranium enrichment facility (Bahr et al, 2011), the overall SMR for NHL was 1.49 ($p<0.05$), but barely increased above expected (1.05) in the subgroup believed most likely to have been exposed to TCE.
36. A report from Sweden (Axelson et al, 1994) defined exposure on the basis of a national monitoring programme for tricholoroacetic acid (a metabolite of TCE) in workers' urine (U-TCA). The overall SIR in men was 1.56, but much higher SIR (8.33) in a subgroup with ≥2 years of exposure and ≥100 mg/L of U-TCA; the last finding was based on a single case however, and findings could well have been explained by chance alone.
37. A second study of similar design from Finland (Anttila et al, 1995) reported an overall SIR of 1.81, but higher in the subgroup with ≥20 years since first exposure (SIR 3.24). Risks were more than doubled in those with U-TCA <100 μmol/L (based on 2 cases), but close to expected (SIR 1.08) in those with U-TCA >100 μmol/L (based on 5 cases). No finding was statistically significant.
38. By contrast, a study of workers similarly monitored by the Labor Inspection Services in Denmark (Hansen et al, 2001) reported a significantly elevated SIR in men (3.5, 95%CI 1.5-6.9, based on 8 cases) and even higher (SIR 4.2) in men with ≥75 months of employment.
39. A subsequent report by Hansen et al (2013) pooled data across the study groups in Sweden and Finland and Denmark (paragraphs 36-38) in an analysis providing over 100,000 person-years of observations in men, over 50,000 person-years in women and 38 deaths from NHL. The overall SMR was 1.26 (1.55 in men and 0.63 in women, $p>0.05$). Relative to workers with U-TCA levels of <5 mg/L, risks were raised in groups with higher urinary levels of the metabolite, but not as much as doubled.
40. Among the case-control studies of NHL, several reported Odds Ratios (OR) of ≤1.2 (Persson et al, 1999; Miligi et al, 2006; Christensen et al, 2013; Vlaanderen et al, 2013). Among these were the very large Nordic cancer registry study by Vlaanderen et al mentioned in paragraph 28 and a case-control study of lymphoma in 11 Italian regions, involving over 1,400 incident cases of NHL (Miligi et al, 2006), neither of which found a

relationship with cumulative exposure.

41. The large multi-centre Epilymph Study (Cocco et al, 2010) also found no increase in risk in an analysis that was restricted to **B-cell NHL**, a finding echoed by a six-region German study (Seidler et al, 2007).
42. Siedler et al also explored risks by sub-entity of B-cell NHL and in subjects with T-cell NHL, and a more nuanced picture emerged. More than doubled risks were found for **diffuse large B-cell lymphoma**, **follicular lymphoma**, **marginal cell lymphoma** and **T-cell NHL** among those with the highest estimated levels of exposure to TCE (>35 ppm-years), although findings were not significant statistically.
43. In partial support of this report, Purdue et al (2011) found a more than doubling of risks of diffuse large B-cell lymphoma and follicular lymphoma in those in the top third of weekly intensity and cumulative hours of exposure, and for follicular lymphoma these findings were significant statistically (based on 6 exposed cases). Deng et al (2013) also found a doubling of risk of diffuse large B-cell lymphoma, but no important increase in risk of follicular lymphoma; while findings on these cancer types in the Epilymph Study (Cocco et al, 2010) were essentially negative. Further analysis by Deng et al raises the possibility that risks for the sub-entities are genotype-specific, but information on this is limited at present.
44. Findings on **CLL** have also been mixed, but more negative than for other B-cell sub-entities. In the study by Purdue et al (2011), ORs were raised 2.7-3.0 fold ($p>0.05$) for the highest bands of exposure; but no elevation in risk was found in the case-control studies by Miligi et al (2006), Seidler et al (2007), Cocco et al (2010) and Deng et al (2013). Two cohort studies also failed to find elevations in risk; in that by Boice et al (paragraph 33), mortality from CLL was lower than expected in rocket engine workers, including field laboratory workers and test stand mechanics with assumed exposure to TCE, while in that by Lipworth et al (paragraph 32), mortality from CLL was raised only in the band with shortest duration of exposure (1-9 years, SMR 1.78) and not in those with long durations of exposure (e.g. 30 years, SMR 0.9 (95%CI 0.45-1.61)).

Multiple myeloma

45. A total of 6 cohort studies and 2 case control studies provide risk estimates for **multiple myeloma**, together with data from the pooled analyses (Hansen et al, 2013; Karmai et al, 2013).
46. In the cohort studies by Axelson et al (1994), Raaschou-Nielsen et al (2001) and Boice et

al (2006), RRs were below or close to those expected in the general population (0.57-1.1), while in that by Lipworth et al (2011) they were only moderately elevated (SMR 0.96 to 1.42). In the Hill Air Force base NCI cohort (Radican et al, 2008), RR was more than doubled (although not significantly so) in the women (2.37) but not in the men (1.08).

47. In the Finnish study by Antilla et al (paragraph 37), the overall SIR for myeloma was 1.62, but greater in subgroups with higher levels of U-TCA (2.41) or long elapsed time since first measurement of U-TCA (3.78). No finding was statistically significant. Subsequently, Hansen et al (2013) pooled these Finnish data with those from Sweden (Axelson et al) and further data from Denmark, providing a larger sample size. In this pooled analysis, incidence rates of myeloma were lower than expected from national rates (0.47 in men, 0.65 in women).
48. In the case-control study by Seidler et al (2007) odds of the disease were slightly lower among exposed subjects; and similarly in the large case-control by Vlaanderen et al (2013), which was based on over 35,500 cases of myeloma. This last investigation explored but found no evidence for an exposure-response relationship.

Hodgkin's lymphoma

49. A total of 7 cohort reports provided risk estimates for **Hodgkin's disease** (Antilla et al, 1995; Morgan et al, 1998; Ritz et al, 1999; Raaschou-Nielsen et al, 2001; Boice et al 2006; Radican et al, 2008; Lipworth et al, 2011). In only one of these reports was the estimate of RR as much as doubled (Ritz, SMR 2.09) and in the remainder it ranged from 0.6 to 1.57. No finding was statistically significant; in that by Lipworth et al, the only study with exposure-response information, the SMR for those with $\geq$30 years of exposure was 0.61. By contrast, two small case-control studies by the same research group, in contiguous areas of Sweden, found a doubling of risks in crude analyses (unadjusted for other factors), the larger of these being statistically significant (7 cases with exposure).

Leukaemia

50. A total of 10 cohort studies and one nested case-control study provided risk estimates for leukaemia, together with data from the pooled analyses of Hansen et al (2013) and Karami et al (2013).

51. In most reports, estimates of RR were below or close to expected rates (Garabrant et al, 1988; Greenland et al, 1994; Morgan et al 1998; Ritz 1999; Boice et al 2006; Radican et al, 2008; Lipworth et al 2011) or only moderately elevated (Bahr et al, 2011, SMR 1.47).
52. In a few analyses, higher RRs were found, notably in the Finnish study by Antilla et al (paragraph 37), in subgroups with higher levels of U-TCA (2.65) or long elapsed time since first measurement of U-TCA (2.72), but also among women (but not men) in the study by Raaschou-Nielsen et al (SIR 1.7) and in men (but not women) in that by Hansen et al (1.9). Such analyses were based on few cases though, and could have arisen by chance alone ($p>0.05$). In the statistically more powerful pooled analysis by Hansen et al (referred to in paragraph 39), the SIR for leukaemia was 1.19 in men and 1.06 in women.

Meta-analysis of lymphatic and haematopoietic cancers

53. A review by Karami et al (2013) combined risk estimates from 24 different studies on NHL, 13 studies on Hodgkin's lymphoma, 11 on multiple myeloma, 7 on CLL and 12 on leukaemia. A significantly raised RR was found for NHL and occupational exposure to TCE, but estimates fell well short of the doubling of risk threshold employed in prescription in the IIDB Scheme (1.32, 95%CI 1.14-1.54). For Hodgkin's disease, the meta-estimate of RR was 1.14, for multiple myeloma it was 1.05, for CLL 0.98, and for leukaemia it was 1.03.

Summary and conclusions

54. Findings on TCE and lymphatic and haematopoietic malignancy present a complex picture. The balance of evidence at present, however, appears not to support a doubling or more of risks for Hodgkin's lymphoma (paragraphs 49 and 53), leukaemia (paragraphs 50-53), or the lymphoma subtypes of CLL (paragraphs 44 and 53), or multiple myeloma (paragraphs 45-48 and 53).
55. Regarding the more commonly studied outcome of NHL, among the 13 studies summarised in paragraphs 31-40, only those by Antilla et al (1995) and Hansen et al (2001) identified subgroups with risks potentially reaching the threshold for prescription under the IIDB scheme. However, the findings could have arisen by chance being based on small numbers, and risk estimates no longer reached the prescription threshold when these data were combined with other observations in a later more powerful pooled analysis (Hansen et al, 2013). The balance of evidence, therefore, does

not support prescription for NHL overall in workers exposed to TCE; the meta-analysis by Karami et al adds weight to that conclusion.

56. The findings summarised in paragraphs 41and 42 raise the possibility that risks from TCE could vary by sub-entity of NHL and by genotype, and might perhaps be as much as doubled in certain circumstances (e.g. for diffuse large-B cell lymphoma at the very highest levels of exposure). However, research studies with this focus are few in number so far, and findings are not entirely consistent and perhaps explained by chance. More evidence is needed before drawing any conclusions.
57. The Council will continue to monitor the research literature. At present, however, it has not been able to identify any circumstances that would meet the legal requirements for prescription of TCE in relation to lymphatic and haematopoietic cancers under the IIDB Scheme.

Prevention

58. A more general body of evidence indicates that TCE is a human carcinogen (IARC, 2014), and as highlighted in this report, occupational exposures to TCE can adversely affect workers' health and safety in various ways. The Control of Substances Hazardous to Health Regulations 2002 (COSHH) aim to protect workers from being exposed to hazardous substances in the workplace and apply to a wide range of substances including TCE that have the potential to cause harm if inhaled, ingested or absorbed through the skin. COSHH requires the employer to carry out a risk assessment to establish the hazards associated with the substances being used, and for the employer to put processes in place to control those risks.
59. COSHH requires TCE exposure to be controlled to as low a level as reasonably practicable. Where it is not possible to prevent exposure by substitution with a safer substance or by totally enclosing the process, exposure must be adequately controlled by the use of appropriate work processes, systems and engineering controls and measures including local exhaust ventilation systems to control exposure at source. Suitable respiratory protective equipment may be used where adequate control cannot otherwise be achieved.

Table 1: Cohort studies of trichloroethylene and haematological malignancy

Reference	Study population and sampling	Follow-up interval & completeness	Case ascertainment	a) Exposure assessment b) Comparison	Relative Risks (95% confidence intervals, n of events)	Additional Information
Garabrant et al, 1988	Cohort of 14,067 workers (11,898 men, 2,169 women) employed for ≥4 years in an aircraft manufacturing facility in San Diego, USA	1958-1982 95.3%	Vital status from California Death Tapes	a) Employed vs not b) vs. US national and county mortality rates	All haematological: 0.78 (0.56-1.08, 38) Leukaemia: 0.82 (0.47-1.34, 36) *(SMR)*	Study undertaken to investigate risks of brain and scrotal cancer and melanoma. No information on individual exposure to TCE but 37% of jobs said to involve exposure.
Axelson et al, 1994	Cohort of 1,421 Swedish men from 115 companies who underwent biological surveillance for TCE during 1955-1975	1958-1987 96.7%	Swedish Cancer Registry	a) urinary measurements of TCA; b) by mean U-TCA and years of exposure	NHL with≥2 years' exposure, 10 year latency & U-TCA: - Any, 1.85 (0.38-5.41, 3) - 0-49 mg/L, 1.64 (0.20-5.92, 2) - 100+ mg/L, 8.33 (0.22-46.43, 1) Myeloma: 0.57 (0.01-3.17, 1) *(SIR (men)*	Overall SMR for NHL in men, without latency or exposure details, 1.56 (95%CI 0.51-3.64, 5 cases)
Anttila et al, 1995	Cohort of 1,698 male and 1,391 female workers biologically monitored for urinary TCA under Finnish labour legislation	1967-1992 100%	Finnish Cancer Registry	a) Record of at least one U-TCA b) Incidence in monitored cohort (vs. national incidence rate) by years since first measurement & U-TCA	All haematological: 1.51 (0.92-2.33, 20) NHL, by years since first measurement): Any, 1.81 (0.78-3.56, 8) -9y, 0.83 (0.02-4.64, 1) 10-19y, 1.74 (0.48-4.47, 4) ≥20y, 3.24 (0.67-9.45, 3) NHL, by U-TCA: <100 µmol/L, 2.01 (0.65-4.69, 2) ≥100 µmol/L, 1.08 (0.35-	TCE was used mainly in degreasing or cleaning metal surfaces, but also in rubber work, gluing, dry cleaning and in cleaning fluids.

Reference	Study population and sampling	Follow-up interval & completeness	Case ascertainment	a) Exposure assessment b) Comparison	Relative Risks (95% confidence intervals, n of events)	Additional Information
					2.53, 5) Hodgkin's disease, by years since first measurement: Any, 1.45 (0.30-4.23, 3) Myeloma, by years since first measurement: Any, 1.62 (0.44-4.16, 4) -9y, 1.52 (0.04-8.44, 1) 10-19y, 0.79 (0.02-4.38, 1) ≥20y, 3.78 (0.46-13.7, 2) Myeloma by U-TCA: <100 µmol/L, 1.48 (0.18-5.35, 2) ≥100 µmol/L, 2.41≥100 µmol/L, 2.41 (0.29-8.71, 2) Leukaemia, by years since first measurement: Any, 1.08 (0.35-2.53, 5) 0-9y, 1.76 (0.36-5.16, 3) 10-19y, 0 cases ≥20y, 2.72 (0.33-9.83, 2) Leukaemia, by U-TCA: <100 µmol/L, 0.39 (0.01-2.19, 1) ≥100 µmol/L, 2.65 (0.72-6.78, 4) *(SIR*)	
Morgan et al, 1998	Cohort of 20,508 workers from an aircraft manufacturing site in	1950-1993 Not stated	Vital status from National Death Index	a) Long-term workers rated exposure for	All haematological: Any, 0.99 (0.64-1.47, 25); high, 0.95 (0.53-1.57, 15)	Jobs were classified as 'high' in exposure if they involved work *on* degreasing

Reference	Study population and sampling	Follow-up interval & completeness	Case ascertainment	a) Exposure assessment b) Comparison	Relative Risks (95% confidence intervals, n of events)	Additional Information
	Arizona, employed for ≥6 months between 1950 and 1985 (4,733 TCE-exposed)		and Social Security Administration data files	each job, then a hygienist compiled a JEM; b) any, high exposure vs none, with expected numbers based on national rates	All lymphopoietic: Any, 1.01 (0.51-1.81, 11); high, 1.03 (0.41-2.12, 7) Hodgkin's disease: Any, 0.60 (0.02-2.81, 1); high, 0 cases Leukaemia & aleukaemia: Any, 1.05 (0.50-1.93, 10); high: 1.17 (0.47-2.41, 7) *(SMR)*	machines; as 'medium' if they were *near* the degreasing area with "more than occasional" contact with TCE; and as 'low' if *away* from degreasing. Final designation was based on spells in these settings: 'low' = ≤ 5 years in low exposure jobs or ≤ 1.4 years in medium exposure jobs; 'high' was any other pattern of exposure.
Ritz, 1999	Cohort study of 3,814 white men employed for ≥3 months during 1951-1972 at a uranium processing facility in Ohio, USA	1951-1989 Not stated		a) Exposure assessed by experts from job titles and work areas: 3 bands, none light, moderate; b) any; light or moderate; duration (vs. national rates)	All haematological (15 year lag): Light exposed, >2 yrs, 1.45 (0.68-3.06, 15); >5 yrs, 1.79 (0.78-4.08, 12) Moderately exposed, >2 yrs, 1.17 (0.15-9.00, 1); >5 yrs, 0 cases Lymphopoetic cancer: 1.28 (0.90-1.77, 37) Hodgkin's lymphoma: 2.09 (0.76-4.54, 6) Leukaemia/aleukaemia: 1.09 (0.56-1.91, 12 *(SMR)*	The cohort was originally established to examine effects of radiation. Only 179 workers had 'moderate' exposure to TCE (as set-up workers, riggers, degreasers and electricians) while none had 'heavy' exposure; 2,792 had 'light' exposure and 843 had no exposure.
Raaschou-Nielsen et al, 2001	Cohort study of 40,049 workers employed for ≥3 months in one of 347	1964-1997 ~80% for >10	Danish cancer registry record of renal cell	a) Use of TCE in companies was determined by	NHL: (i) Men, 1.2 (0.98-1.52, 83); women, 1.4 (0.73-2.34, 13)	While use of TCE was documented in these companies, it was unknown

Reference	Study population and sampling	Follow-up interval & completeness	Case ascertainment	a) Exposure assessment b) Comparison	Relative Risks (95% confidence intervals, n of events)	Additional Information
	Danish companies that were documented users of TCE	years	carcinoma	archive records; b) blue-collar employment (i) overall, (ii) by duration, (iii) by year first employed (vs. national rates)	(ii) (≥5 years employment): men, 1.4 (0.9-2.0, 27); women, 1.8 (0.6-4.3, 5) Year first employed: (a) pre-1970, men, 1.4 (1.0-2.0, 38); women, 1.6 (0.6-3.5, 6); (b) post 1980, men, 0.7 (0.3-1.3, 10); women, 0.5 (0.0-3.0, 1) Hodgkin's lymphoma: (i) Men, 0.9 (0.51-1.37, 18); women, 0.8 (0.09-3.00, 2) Myeloma: Men 1.1 (0.70-1.52, 28); women, 0.9 (0.18-2.56, 3) Leukaemia: Men, 1.1 (0.84-1.37, 69); women, 1.7 (0.89-2.86, 13) *(SIR)*	at the individual level (but see Hansen et al, 2001). The probability of exposure was raised by focussing on blue-collar occupations and particular time frames (exposures were expected to be 4-5 times higher in the 1960s than in the 1980s). Higher exposures were also expected in small companies, but few cases were observed and no consistent pattern.
Hansen et al, 2001	Cohort of 803 workers with known exposure to TCE, as determined by the Labor Inspection Services in Denmark. Subjects came from many different companies	1968-1996 Not stated	Danish cancer registry	a) Exposure was indicated by a record of urinary TCA or TCA-in-air or TCE-in-air; b) (i) exposed vs. not; (ii) duration of employment; (iii) exposure	NHL: (i) Men, 3.5 (1.5-6.9, 8); women, 0 cases (ii) Men, <75 months, 2.5 (0.3-9.2, 2); ≥75 months, 4.2 (1.1-11.1, 4) (iii) Men, <19 mg/m^3, 3.9 (1.1-10, 4); ≥ 19 mg/m^3, 3.2 (1.1-10, 4) Leukaemia: (i) Men, 1.9 (0.6-4.4, 5); women, only 1 case	Mean urinary TCA 40 mg/L, median 15 mg/L, based on 1,519 samples over 1947-1989. Mean air-TCA 101 mg/m^3, median 28 mg/m^3, during 1974-1989. (For 36% of urinary and 48% of air measurements, the individual worker could not be identified.) (Possible overlap with Raaschou-Nielsen et al.)

Reference	Study population and sampling	Follow-up interval & completeness	Case ascertainment	a) Exposure assessment b) Comparison	Relative Risks (95% confidence intervals, n of events)	Additional Information
					(SIR)	
Zhao et al, 2005	Cohort of male workers employed for >2 years in the aerospace division of rocket engine testing field laboratory in California. (Mortality analysis based on 6,044 of 6,107 workers employed before 1980; incidence analysis based on 5,049 workers alive and cancer-free in 1981)	1950-2001 (mortality) 1988-2000 (incidence) Not stated	Vital status from California death tapes and index, National Death Index, pension benefit, social security and other files; cancer incidence from 9 state cancer registries	a) Personnel records & interviews with long-term workers b) JEM to give time-dependent intensity scores, then scores of cumulative exposure (none, low, medium, high)	NHL and leukaemia: *Mortality analysis* Low: 1.0 (n = 27) Medium: 1.49 (0.86-2.57, 27) High: 1.30 (0.52-3.23, 6) P-value for trend 0.37 *Incidence analysis (no lag):* Low: 1.0 (n = 28) Medium: 0.88 (0.47-1.65, 16) High: 0.20 (0.03-1.46, 1) P-value for trend 0.097	Adjusted for time since first employment, socioeconomic status, age at event. Overlap with Boice et al, 2006.
Boice et al, 2006	Retrospective cohort of 8,372 US workers employed for ≥6 months in rocket engine testing during 1948-1999 at a field laboratory or nearby facility in California	1940-1999 >99%	Vital status as for Zhao et al, 2005	a) As for Zhao et al, 2005 b) work location, job title & duration, likely exposure to TCE (vs. Californian population rates)	All haematological: All facilities, 0.92 (0.81-1.04, 264); field laboratory, 0.94 (0.73-1.19, 68) NHL: All, 0.93 (0.76-1.12, 104); lab, 1.02 (0.69-1.47, 29) Hodgkin's disease: All, 1.12 (0.66-1.77, 18); lab, 1.26 (0.41-2.94, 5) Myeloma: All, 0.84 (0.60-1.14, 40); lab, 0.91 (0.46-1.63, 11) CLL: All, 0.96 (0.57-1.52, 18); lab,	Overlap with Zhao et al, 2005. Field laboratory workers were presumed more likely to be exposed, and test stand mechanics were singled out as the group with greater potential exposure to chemicals. No significant trends with duration of employment in the lab were found for any haematological cancer, or between length of employment as a test stand mechanic and the two

Reference	Study population and sampling	Follow-up interval & completeness	Case ascertainment	a) Exposure assessment b) Comparison	Relative Risks (95% confidence intervals, n of events)	Additional Information
					0.61 (0.13-1.79, 3) Leukaemia & aleukaemia: All, 0.91 (0.74-1.11,99); lab, 0.84 (0.53-1.26, 23); *(SMR)*	commonest cancers, NHL and leukaemia.
Radican et al, 2008	Cohort of 14,455 civilians employed at an airbase in Utah for ≥ 1 year during 1952-1956 (the Hill Air Force base NCI cohort)	1952-2000 Not stated	Vital status from National Death Index	a) Interviews with long-serving employees plus historical records, worker compensation files and walk-through surveys – JEM; b) overall, by tertile of TCE 'score' and by intensity and frequency	*Overall* All haematological: Men, 1.12 (0.72-1.73, 88); women, 1.00 (0.55-1.83, 18) NHL: Men, 1.56 (0.72-3.35, 37); women, 1.18 (0.49-2.85, 9) Hodgkin's disease: Men, 1.47 (0.17-12.58, 5); women, 0 cases Myeloma: Men, 1.08 (0.43-2.71, 19); women, 2.37 (0.67-8.44, 6) Leukaemia: Men, 0.77 (0.37-1.62, 24); women, 0.36 (0.10-1.32, 3) *(HRs)*	No measurements of exposure existed but a 'score' was constructed. In 30 comparisons by sex and level of TCE for the 5 cancer groups, risks tended not to increase with exposure. They were more than doubled only for (i) women with myeloma (at any level, 6 cases) and (ii) men with Hodgkin's disease, at the highest levels (5 cases). No finding was significant statistically.
Lipworth et al, 2011	Retrospective cohort of 77,943 workers employed ≥ 1 year during 1960-1996 at Lockheed Martin manufacturing facilities in California	1960-2008 (initially 1960-1996) 98.3%	Vital status from California death tapes and death index, National Death Index, pension	a) JEM based on personnel files, linked with industrial hygiene files and interviews of long-term workers	(Years of exposure) NHL: 1-9 y, 0.88 (0.67-1.14, 59); 10-19 y, 0.94 (0.68-1.28, 41); 20-29 y, 1.10 (0.82-1.44, 52); ≥30 y, 1.29 (1.00-1.63, 69) Hodgkin's disease: 1-9 y, 0.76 (0.31-1.57, 7); 10-	5.3% of men and 3.2% of women judged to have 'routine' exposure to TCE, and another 7.7% and 2.7% respectively to have 'intermittent' exposure. There was potential co-exposure to chromate-based

Reference	Study population and sampling	Follow-up interval & completeness	Case ascertainment	a) Exposure assessment b) Comparison	Relative Risks (95% confidence intervals, n of events)	Additional Information
			benefit, social security and other files	b) years of exposure to TCE (vs. Californian or US population rates)	19 y, 1.14 (0.42-2.48, 6); 20-29 y, 1.57 (0.68-3.08, 8); 0.61 (0.07-2.18, 2) Myeloma: 1-9 y, 1.31 (0.93-1.79, 39); 10-19 y, 1.37 (0.92-1.96, 29); 20-29 y, 0.96 (0.61-1.44, 23); ≥30 y, 1.42 (1.01-1.94, 39) All leukaemia & aleukaemia: 1-9 y, 1.18 (0.93-1.48, 77); 10-19 y, 0.62 (0.41-0.90, 27); 20-29 y, 0.98 (0.72-1.30, 48); ≥30 y, 1.11 (0.85-1.43, 60) CLL: 1-9 y, 1.78 (1.08-2.74, 20); 10-19 y, 0.58 (0.19-1.34, 5); 20-29 y, 1.70 (1.01-2.69, 18); ≥30 y, 0.90 (0.45-1.61, 11) *(SMR)*	primers, perchloroethylene and other solvents. In an analysis of the 3 commonest cancers in 7 occupations (21 comparisons), only one SMR was more than doubled (in welders, for multiple myeloma: 2.27, 95%CI 0.83-4.94, based on 6 cases). The trades with the highest likelihood of TCE exposure had little elevation in risk for any of the blood malignancies analysed.
Bahr et al, 2011	Cohort mortality study of 6,820 workers at a uranium enrichment facility in Kentucky USA	1953-2003	Kentucky Cancer Registry	a) JEM based on discussions with employers; b) (i) overall, (ii) in groups most likely to be exposed (4 & 5) vs. expected in the Registry	NHL: (i) 1.49 (1.02-2.10, 32); (ii) 1.05 (0.52-1.88, 11) Leukaemia & aleukaemia: (i) 1.15 (0.74 -1.72, 24); (ii) 1.47 (0.82-2.43, 15) *(SMR)*	Exposure occurred in the degreasing of fabricated metal parts, the most exposed jobs being laboratory workers, maintenance-electricians, waste and chemical operators.
Hansen et al, 2013	Pooled analysis based on Axelson et al, Antilla	See above	See above	a) on monitoring	NHL: (i) Men, 1.55 (1.06-2.20, 32);	>100,000 person-years of exposure in men and >50,000

Reference	Study population and sampling	Follow-up interval & completeness	Case ascertainment	a) Exposure assessment b) Comparison	Relative Risks (95% confidence intervals, n of events)	Additional Information
	et al and Hansen et al above: biologically monitored workers from Sweden, Finland and Denmark			registers – see above; b) (i) incidence in monitored cohort vs. national rates; (ii) by U-TCA (vs. <5 mg/L)	women, 1.26 (0.89-1.73, 38) (ii) 5-25 mg/L, 1.16 (0.53-3.09, 14); 25-50 mg/L, 1.56 (0.63-3.81, 8); >50 mg/L, 0.66 (0.21-2.03, 4) Myeloma: Men, 0.47 (0.13-1.20, 4); women, 0.65 (0.28-1.27, 8) Leukaemia: Men, 1.19 (0.72-1.86, 19); women, 1.06 (0.67-1.60, 23) *(SIR)*	person-years in women; separate risk estimates for Denmark (1968-2008), Sweden (1958-2003) and Finland (1967-2004).

Table 2: Case-control studies of trichloroethylene and haematological malignancy

Reference	Study population & sampling	Study period, response rates (cases, controls)	Exposure assessment	Exposure comparison(s)	Odds ratios (95% confidence intervals, n exposed cases)	Additional Information
Greenland et al, 1994	Case-control study, nested in a cohort of male employees of a transformer assembly facility in the US. Cases were workers who had died of cancers of all types (n=512); controls died of other causes (n=1,202)	1969-1984 Not stated	Company employment and hygiene records were used to apply a JEM to job histories	Any exposure vs. none	Lymphoma: 0.76 (0.24-2.42) Leukaemia: 1.10 (0.46-2.66)	TCE was used as a degreasing agent at the facility between 1930 and 1977. Only 22 deaths with leukaemia and 15 with lymphoma had available job histories.
Hardell et al, 1994	Case-control study from Umea, Sweden (105 cases of NHL admitted to a department of oncology; 335 matched controls drawn from a population registry)	1974-1978 Not stated	Lifetime working history (jobs, location, exposures	(i) Exposed to TCE vs. not; (ii) Exposed to degreasing agents vs. not	NHL: (i) 7.2 (1.3-42, 4) (ii) 11 (2.9-72)	Exposure assessment not described in detail. Risk estimates unadjusted. Timing of exposures unclear.
Persson et al, 1989; 1993; 1999	Two population-based case-control studies in geographically adjacent areas of Sweden (maximum of 199 cases identified from a cancer registry and an oncology register; 479 controls chosen at random from	1964-1986 96%, 90% for case series, not stated for controls.	Postal questionnaire: occupational exposures >1 year (5-45 years before diagnosis/time of selection)	Any exposure to TCE vs. none	NHL: Persson, 1999: 1.2 (0.5-2.4, 16) Hodgkin's disease: Persson, 1989: 2.8, 1.1-7.2*, 7) (Persson, 1993: 2.0 (0.7-5.8*, 5)	In Persson (1999), data from the two earlier studies were merged. ORs for NHL were then presented by job title but not for the occupation of metal degreaser. In metal workers the OR for NHL was 1.0, based on 42 exposed cases (and risks were only significantly elevated in lumberjacks).

	population registers)					
Miligi et al, 2006	Case-control study of lymphoma in 11 regions of Italy (1,428 incident cases of NHL & 304 of Hodgkin's disease from hospitals, pathology departments and haematology centres; 1530 local community controls, identified through demographic and health service files)	1991-1993 83%, 73%	Interviews for job- and industry-specific work history; expert ratings, likely intensity/ probability of exposure taking into account work controls	(i) Very low/low (just above population); (ii) medium/high (moderate, poor, or no workplace controls); (iii) >15 years of medium/high exposure (vs. none)	NHL: (i) 0.6 (0.-1.3, 35); (ii) 1.2 (0.7-2.0, 35); (iii) 1.0 (0.5-2.6, 12)	OR for diffuse NHL was 1.9 (0.9 to 3.7, 13) but ORs were not elevated for other histological subtypes. Small numbers precluded analysis for Hodgkin's disease and TCE.
Seidler et al, 2007	Case-control study from 6 regions of Germany (710 incident cases of lymphoma diagnosed by local hospitals and physicians; 710 matched controls	1993-2003 87%, 44%	Interview for occupational history; expert exposure assignment, blind to case-control status (intensity, frequency, duration)	Cumulative exposure: (i) 'low' (<4.4 ppm-y), (ii) 'medium' (>4.4-35 ppm-y), (iii) 'high' (>35 ppm-y) vs. none	All lymphoma: (i) 0.7 (0.4-1.1, 40) (ii) 0.7 (0.5-1.2, 32) (iii) 2.1 (1.0-4.8, 21) B-cell NHL: (i) 0.7 (0.5-1.2, 32) (ii) 0.8 (0.5-1.3, 27) (iii) 0.8 (0.5-1.3, 17) T-cell NHL: (i) 0.7 (0.2-3.3, 2) (ii) 1.1 (0.2-5.1, 2) (iii) 4.7 (0.8-26.1, 2)	Within B-NHL, for the sub-entities diffuse large B-cell lymphoma, follicular lymphoma and marginal zone lymphoma, ORs were elevated 2.6 to 4.2-fold with 'high' exposure but no findings were statistically significant. More generally, the authors described the association between TCE and malignant lymphoma as "of borderline statistical significance".
Wang et al, 2009; Deng et al, 2013	Case-control study of NHL in women from Connecticut, USA (601 cases; 717 matched controls obtained by random digit dialling and personnel files of healthcare	1996-2000 72%, 69% (community controls)/47% (administrator controls)	Interviews for job history; expert JEM applied	(i) Ever, (ii) low, (iii) medium-high average intensity and probability vs. none	NHL: (i) 1.2 (0.9-1.8, 77) (ii) 1.1 (0.8-1.6, 64) (iii) 2.2 (0.9-5.4, 13)	The later study considered risks by genotype and sub-entities. For the AT/AA genotype, odds of NHL and diffuse large B-cell lymphoma were more than doubled (2.09 and 2.66 respectively, $p<0.05$), and raised 1.71-fold for follicular lymphoma; ORs for the TT genotype were lower

	administrators)					(0.59 to 0.82, p>0.05).
Cocco et al, 2010	Multicentre case-control study of lymphoma (Epilymph) (2,348 cases from treatment centres in the Czech Republic, France, Germany, Ireland, Italy and Spain; 2,462 controls, recruited by random population sampling (2 centres) and hospital controls (4 centres)	1998-2004 88%, 81% (hospital controls)/52% (community controls)	Interview for occupational history (full-time jobs held for ≥1 year); expert JEM applied (based on assessed probability, frequency and intensity of exposure)	(i) Any; (ii) low; (iii) medium; (iv) high cumulative exposure vs. none	B-cell NHL: (i) 0.8 (0.6-1.1, 71); (ii) 0.9; (iii) 0.5; (iv) 1.0	Within B-NHL, risks for the sub-entities diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphatic leukaemia and multiple myeloma were assessed overall and by exposure level. Among 16 risk estimates, only 1 was >1.2 (OR 2.4 for follicular lymphoma in the lowest exposure group); there were no trends by exposure level for any of the cancer types.
Christensen et al, 2013	Population-based case-control study in Montreal, Canada (215 male cases of NHL were identified from the 18 largest hospitals in the metropolitan area; 533 male controls were recruited from random samples of electoral lists)	1979-1985 Not clear, 72%	Occupational questionnaire; experts coded jobs blind to case-control status, rating the likely frequency of exposure, relative level (low, medium, high)	a) Any exposure vs. none; b) 'substantial' exposure vs. none	NHL: a) 1.2 (0.5-2.9, 7); b) 1.0 (0.3-3.5, 3)	Occupations deemed to have a high prevalence of exposure to TCE included mechanics and repairmen (26% exposed), metal machining occupations (18% exposed) and electrical/electronic fabricating, assembling and repairing occupations (13% exposed).
Vlaanderen et al, 2013	Case-control study nested within a cohort comprising the populations of Finland, Iceland, Norway and Sweden. 69,254 cases of NHL and 35,534 of	1953 -2005 100%?	Linkage with national census data enabled employment histories to be approximated.	a) Lowest, b) middle, and c) highest third of cumulative exposure vs none	NHL: a) 1.01 (0.95 to 1.07, 1213); b) 0.93 (0.88 to 1.00, 1183); c) 0.97 (0.91 to 1.03, 1211) Myeloma: a) 0.93 (0.84-1.03,	Further stratification by sex did not alter risk estimates much; nor did alternative approaches to estimating cumulative exposure with focus on high exposure groups.

	multiple myeloma were identified from Nordic cancer registries, with 380,650 controls randomly selected from census records.		Cumulative exposure was estimated using a JEM		468); b) 0.92 (0.84-1.01, 574); c) 0.96 (0.88-1.06, 541)	
Purdue et al, 2017	Case-control study of NHL from the US (State of Iowa, Los Angeles County, Seattle, Detroit and Michigan (1,189 incident cases were identified through cancer surveillance registries; 982 community controls were recruited by random digit dialling and from residents listed in Medicare files)	1998-2000 59%, 44%	Interview about jobs held for ≥1 year (hours, tasks, patterns extent of solvent use, etc.); JEM and task-specific matrices applied, based on an expert review of the literature	(i) Probability of exposure; (ii) years exposed; (iii) average ppm-hours per week; (iv) cumulative hours exposed; (v) average intensity (ii)-(v) at any intensity and ≥50% exposure probability	NHL: (i) ≥50%, 1.4 (0.8-2.4, 45); (ii) ≥24 years, 1.7 (0.5-5.8, 7), p for trend 0.40; (iii) >150 ppm-hrs/week (top third, 2.5 (1.1-6.1, 7), p for trend 0.02; (iv) >112,321 ppm-hrs (top third), 2.3 (1.0-5.0), p for trend 0.08; (v) >99 ppm (top third), 1.3 (0.7-2.7, 22)	Intensity of exposure was assessed using a combination of factors (e.g. location, proximity to solvent, process temperature (room vs. elevated)). Analyses (iii) and (iv) were repeated by sub-entity of NHL. For chronic lymphatic leukaemia, ORs were raised 2.6 to 3.0-fold in the top two-thirds of exposure bands; and for follicular lymphoma, raised 3.3 to 3.7-fold in the top third. For diffuse large-B cell lymphoma, were raised 1.9-2.5 fold in the top third of exposure.

Abbreviations: TCE = trichloroethylene; TCA = trichloroacetic acid; JEM = job exposure matrix; SMR = Standardised Mortality Ratio; OR = Odds Ratio; SIR = Standardised Incidence Ratio; NHL = non-Hodgkin's lymphoma; ppm = parts per million; * Crude 95%CI (calculated and not author-supplied)

References

Anttila A, Pukkala E, Sallmén M, et al. Cancer Incidence among Finnish Workers Exposed to Halogenated Hydrocarbons. J Occup Environ Med 1995; 37: 797-806.

Axelson O, Selden A, Andersson K, Hogstedt C. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. J Occup Med 1994; 36: 556-562.

Bahr DE, Aldrich TE, Seidu D, et al. Occupational exposure to trichloroethylene and cancer risk for workers at the Paducah Gaseous Diffusion Plant. Int J Occup Med Environ Health 2011; 24: 67-77.

Boice JD Jr, Marano DE, Cohen SS, et al. Mortality among Rocketdyne workers who tested rocket engines, 1948-1999. J Occup Environ Med 2006; 48: 1070-1092.

Christensen KY, Vizcaya D, Richardson H, et al. Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal. J Occup Environ Med 2013; 55: 198-208.

Cocco P, t'Mannetje A, Fadda D, et al. Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case–control study. Occup Environ Med 2010; 67: 341-347.

Deng Q, Zheng T, Lan Q, et al. Occupational solvent exposure, genetic variation in immune genes, and the risk for non-Hodgkin lymphoma. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 2013; 22: 77-82.

Garabrant DH, Held J, Langholz B, Bernstein L. Mortality of aircraft manufacturing workers in southern California. Am J Ind Med 1988; 13: 683-693.

Greenland S, Salvan A, Wegman DH, et al. A case-control study of cancer mortality at a transformer-assembly facility. Int Arch Occup Environ Health 1994; 66: 49-54.

Hansen J, Raaschou-Nielsen O, Christensen JM, et al. Cancer incidence among Danish workers exposed to trichloroethylene. J Occup Environ Med 2001; 43: 133-139.

Hardell L, Eriksson M, Degerman A. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of Non-Hodgkin's lymphoma. Cancer research 1994; 54: 2386-2389.

Karami S, Bassig B, Stewart PA, et al. Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers: a meta-analysis. Occup Environ Med 2013; 70: 591-599.

Lipworth L, Sonderman JS, Mumma MT, et al. Cancer mortality among aircraft

manufacturing workers: an extended follow-up. J Occup Environ Med 2011; 53: 992-1007.
Miligi L, Costantini AS, Benvenuti A, et al. Occupational exposure to solvents and the risk of lymphomas. Epidemiol 2006; 17: 552-561.
Persson B, Dahlander A-M, Fredriksson M, Noorlind Brage H, Ohlson C-G, Alexson O. Br J Ind Med 1989;46:516-20.
Persson B, Fredrikson M. Some risk factors for non-Hodgkin's lymphoma. Int J Occup Med Environ Health 1999; 12: 135-142.
Persson B, Fredriksson M, Olsen K, et al. Some occupational exposures as risk factors for malignant lymphomas. Cancer 1993;72:1773-8.
Pesch B, Haerting J, Ranft U, et al. Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. International Journal of Epidemiol 2000; 29: 1014-1024.
Purdue MP, Bakke B, Stewart P, et al. A case–control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma. Environ Health Perspect 2011; 119: 232-238.
Raaschou-Nielsen O, Hansen J, Christensen JM, et al. Urinary concentrations of trichloroacetic acid in Danish workers exposed to trichloroethylene, 1947-1985. Am J Ind Med 2001; 39: 320-327.
Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow up. J Occup Environ Med 2008; 50: 1306-1319.
Ritz B. Cancer mortality among workers exposed to chemicals during uranium processing. J Occup Environ Med 1999; 41: 556-566.
Seidler A, Möhner M, Berger J, et al. Solvent exposure and malignant lymphoma: a population-based case-control study in Germany. Journal of Occupational Medicine and Toxicology 2007; 2: 2.
Vlaanderen J, Straif K, Pukkala E, et al. Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries. Occup Environ Med 2013; 70: 393-401.
Wang R, Zhang Y, Lan Q, et al. Occupational Exposure to Solvents and Risk of Non-Hodgkin Lymphoma in Connecticut Women. Am J Epidemiol 2009; 169: 176-185.
Zhao Y, Krishnadasan A, Kennedy N, et al. Estimated effects of solvents and mineral oils

on cancer incidence and mortality in a cohort of aerospace workers. Am J Ind Med 2005; 48: 249-258.

Experts consulted

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Glossary

Types of study

Cohort study: A study which follows up a population of individuals (usually defined by a workplace) over time and compared the rate of disease or mortality among those within the cohort or with an external comparison population. The outcome is expressed as a Rate Ratio or **Relative Risk**, **Standardised Incidence Ratio**, or **Standardised Mortality Ratio**, depending on the type of analysis and the disease outcome being studied.

Case-control study: A study which compares people who have a given disease (cases) with people who do not (non-cases, also known as 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**. In a **nested-case control study**, cases and controls are sampled from the members in a **cohort study** – often, all the cases occurring in the cohort and a sample of non-cases.

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 alone and the more likely they are to be 'true'. A 'statistically significant' result is one for which the chance alone probability is suitably small, as judged by reference to a pre-defined cut-point. (Conventionally, this is often less than 5% ($P<0.05$)).

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

Odds Ratio (OR): A measure of the strength of association between exposure and disease. It is the odds of exposure in those with disease relative to the odds of exposure

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

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

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

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

Other epidemiological terms

Job-exposure matrix (JEM): a tool used to assess exposure to potential health hazards in occupational epidemiological studies. A JEM comprises a list of levels of exposure to a variety of harmful (or potentially harmful) agents for selected occupational titles. In large population-based epidemiological studies, JEMs may be used as a quick and systematic means of converting coded occupational data (job titles) into a matrix of possible exposures, obviating the need to assess each individual's exposure in detail. A **job-task- specific exposure matrix** (JTEM) is a variation on this theme.

Meta-analysis: The statistical procedure for combining data from multiple studies. When the treatment effect (or effect size) is consistent from one study to the next, meta-analysis can be used to identify this common effect.

Risk: The probability that an event will occur (e.g., that an individual will develop disease within a stated period of time or by a certain age).

Prevalence: The proportion of a defined group or population who share a characteristic (e.g. disease/cancer) in common at a specific point in time.

Incidence rate: The rate of occurrence of a new event of interest (e.g. cancer) in a given population over a given time period. (The rate is often expressed in terms of cases per year of 'person-time', and so incorporates the numbers at risk of the event, the time for which they are at risk and the numbers that go on to develop that event.)

Confidence Interval (CI): The **Relative Risk** reported in a study is only an estimate of the true value of relative risk 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.

Bias: A systematic tendency to over- or under-estimate the size of a measure of interest in a study.

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.

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