I I A C

THE INDUSTRIAL INJURIES ADVISORY COUNCIL

POSITION PAPER 39

Renal cancer and occupational exposure to trichloroethylene

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Position Paper

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September 2017

Summary

1. This report concerns the possible prescription of renal cancer 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 (IIAC) as part of its rolling programme of work.
2. TCE has been classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen (definitely carcinogenic to humans) (IARC, 2014), the underlying human data appearing strongest for renal cancer, and, to a lesser extent, certain haematological malignancies and cervical cancer. IIAC has therefore considered the case for prescription of occupational exposure to TCE in relation to these tumour types: this report focuses on the evidence in relation to cancer of the kidney; other reports will cover TCE and cancers of the blood and cervix.
3. Research findings support the conclusion of IARC, that occupational exposures to TCE can cause kidney cancer. However, as detailed below, the Council has not identified circumstances that would meet the legal requirements for prescription under the IIDB Scheme.

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

Trichloroethylene (TCE): uses and concerns

4. TCE is best known for its use in cleaning and degreasing metal parts. However, the solvent has numerous other uses, including as an anaesthetic, a heat-transfer medium, an extraction agent for fats and oils, a chemical intermediate, and an ingredient of many products with industrial and consumer applications, such as plastics, jewellery, motor vehicles, textiles, paper and glass.
5. Historically, demand for TCE was driven mainly by the development of vapour

degreasing after the 1920s and by the growth of the dry-cleaning industry in the 1930s. Its use in dry-cleaning fell away in the mid-1950s. Metal cleaning is now the main source of exposure in the workplace. Degreasing is necessary in metalworking and maintenance operations to remove oils, greases, waxes, tars and moisture before surface treatments, such as galvanising, electroplating, painting, anodising and application of conversion coatings. TCE has also been used in the United States (US) to clean kerosene-fuelled rocket engines and a number of studies on its long-term effects stem from the aerospace industry (see below).

6. The chemical also has wide applications as a feedstock for products such as paints, adhesives and cleaners; as a reactant to produce pesticide intermediates; in the synthesis of flame-retardants; as a solvent in the pharmaceutical industry; and as a carrier solvent in consumer products such as insecticides, fungicides, and paint removers.
7. Occupational exposure to TCE is commonplace, given its multiple uses. The European CAREX (CARcinogen EXposure) project estimated that in the early 1990s some 276,000 workers were exposed to TCE across 15 countries of the European Union. Heavy industrial use has also led to the chemical's wide distribution (at low concentrations) in water supplies, groundwater and the general environment.
8. TCE has several well recognised toxic properties. High intensity exposure produces acute depression of the central nervous system (a property initially exploited in anaesthetics); other symptoms mimic those of alcohol intoxication and include headaches, dizziness, confusion and drowsiness. Occupational studies have also established toxic effects on the liver and kidney, and research by the US National Cancer Institute showed that the solvent can induce liver cancer in mice and kidney cancer in rats.
9. Subsequent research led IARC to classify TCE as a human carcinogen. Genotoxic metabolites of TCE form in the kidney, and the strongest evidence IARC found on carcinogenicity in humans related to studies of renal cancer.

Kidney cancer

10. Kidney cancer is the seventh most common type of cancer in the UK, accounting for 4% of all new cancer cases diagnosed in men and just over 2% of all new cancers in women. In 2013, some 11,900 new cases were recorded; in the previous year there were 4,252

deaths from kidney cancer (about 3% of all cancer deaths in the UK). The global incidence of the disease has been increasing since the 1970s; in Great Britain it tripled in women and more than doubled in men between 1975 and 2011.

11. The tumour is rare in young adults and children, but rates rise after the age of 40 and 75% of diagnoses are made in those aged over 60 years. The disease is twice as common in men as women and risks are higher when a first degree relative has been affected, implying a genetic component in some people. Other risk factors for kidney cancer (some of which may underlie the rise in disease occurrence over time) include obesity, smoking, high blood pressure, chronic kidney disease, thyroid cancer, radiotherapy and long-term regular use of certain painkillers. Evidence in relation to occupational exposure to TCE and kidney cancer is reviewed below, following some context-setting remarks.

The Industrial Injuries Disablement Benefit Scheme

12. The Industrial Injuries Disablement Benefit Scheme (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 Social Security (Industrial Injuries) (Prescribed Diseases) Regulations 1985). The benefit is no-fault, tax-free, non-contributory and administered by the Department for Work and Pensions.

The Industrial Injuries Advisory Council

13. The Industrial Injuries Advisory Council (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

14. 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.

15. 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.
16. 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.
17. 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. 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.

18. Since renal cancer is not specific to occupation, and clinically indistinguishable in occupational instances than in those which are unrelated to occupation, the principles in paragraphs 16 and 17 are relevant in the context of this report.

Methods of investigation

19. Specifically, the Council has sought evidence on circumstances of occupational exposure to TCE sufficient to more than double risks of renal cancer. 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

20. Tables 1 and 2 summarise findings from 29 relevant scientific reports 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 renal cancer or death from renal cancer were compared with expected numbers from a reference group (an unexposed group within the cohort or general population) (Table 1); (2) case-control studies, in which cases of renal cancer were compared with non-cases in terms of their previous occupational history of exposure to TCE (Table 2).
21. In all, 17 reports of the cohort type (based on 13 studies) and 12 of the case-control type (11 studies) were highlighted by the Council's review, together with two pooled analyses (Karami et al, 2012, Hansen et a, 2013) that pooled risk estimates across different investigations.
22. Studies came from the United States, Sweden, Finland, Germany, Denmark, Norway, France, Canada, Scandinavia, and Central and Eastern Europe. The cohort studies included 9 reports from the American aircraft, aerospace and rocket industries, as well as reports from a facility processing uranium, a cardboard factory, a train repair and maintenance workshop, and two studies of workers from multiple workplaces, monitored for exposure to TCE under national arrangements.
23. 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 169 men (Henschler et al, 1995); most cohorts included several thousand subjects. Sample sizes also varied considerably in the case-control studies: at one extreme over 76,000 cases of renal cancer known to the cancer registries of several Nordic countries were linked with census data on occupation (Vlaanderen et al, 2013), but at the other, several reports were based on fewer than 90 cases (Vamvakas et al, 1998; Charbotel et al, 2006; Charbotel et al, 2009); five involved more than 400 cases.

24. It should be noted that studies of the case-control and cohort design have complementary strengths and weaknesses. Since the development of renal cancer is a rare event, cohort studies (unless very big and prolonged) may lack the statistical power to rule out chance associations or quantify risks precisely: thus, many of the cohort studies did not have the numbers to rule out a possible doubling of risks from exposures. Case-control studies have the relative advantage that their starting point can be many instances of the disease; on the other hand, since the studied groups are patients from the general population, exposure levels tend to be lower and less well characterised than in cohorts from selected workplaces.
25. In both types of study design exposure assessment rested on an employment history. Cohort studies had the advantage that employment details had generally been recorded contemporaneously and independent of the affected person, whereas case-control studies typically depended on the memory of participants or their next of kin, with the potential for bias, should ill people or their close relatives recall exposures more completely than controls did or over-report them.
26. Detailed occupational histories were reconstructed in most studies, but direct measurements of exposure were scarce (and confined to cohort studies). Typically, experts called 'industrial hygienists' judged individuals' exposures from information on the jobs they had held, the tasks they had undertaken and the materials likely to have been used; they assigned each job or task a probability and a likely level of exposure to TCE. Occasionally, expert judgement was informed by measurements of TCE or industry-wide or company wisdom on exposure patterns in different eras. Thus, for example, in the report by Vlaanderen et al (2013), the experts assigned 300 job categories estimates of the likelihood and level of exposure over four calendar periods between 1945-1994, assigned cases and controls an occupational code for each calendar year of their working careers and (under certain assumptions) estimated each

individual's cumulative exposure to TCE in "unit-years".

27. Despite such attention to detail, the final definitions of exposure used in analyses were usually crude – for example: 'exposed to TCE or not' at a given level of certainty; likely to have been exposed at 'high', 'medium', or 'low' intensity; 'longest held job was in an industry with TCE exposure'; 'monitored for metabolites of TCE in urine'. Further details, which differ somewhat between reports, appear in the tables. In the context of the IIDB Scheme, it should be noted that exposure definitions based on expert judgement and framed in broad ill-specified terms do not offer a practical basis for defining the occupational section of the prescription schedule.
28. More usable are assessments of risk based on job title, focussing on occupations thought to be highly exposed to TCE, such as metal degreaser. A limited number of reports defined exposures precisely in such terms (Morgan et al, 1998; Lipworth et al, 2011; Pesch et al, 2000; Bruning et al, 2003); and several others gave an indication of the occupations and work activities being combined in analysis (Antilla et al, 1995; Henschler et al, 1995; Vamakas et al, 1998; Boice et al, 2006; Charbotel et al, 2006; Radican et al, 2008; Christensen et al, 2013; Buhagen et al, 2016).

Estimates of risk

Cohort studies

29. In the largest of the cohort studies, mortality from renal cancer was studied in almost 78,000 employees of Lockheed Martin manufacturing facilities in California over five decades (Boice et al, 1999; Lipworth et al, 2011). Some 13% of men and 6% of women from the cohort had intermittent or routine exposure to TCE, but mortality risks from renal cancer were not elevated in the cohort and no relationship was found with years of exposure. Nor were strong associations found with work in occupations where >70% of workers were TCE-exposed: only in metal bonders were risks doubled (standardised mortality ratio, SMR 2.40), based on 6 cases, a finding that was not statistically significant; in similarly classified occupations, such as process operators and development mechanics, risks were not elevated.
30. Several other reports concerned mortality or cancer incidence in relatively large cohorts of US aviation, aerospace, and rocket test workers. One study (Morgan et al, 1998) assessed mortality in 20,508 workers from an aircraft manufacturing site in Arizona. Jobs were classified by their proximity to work areas with degreasing machines

and individuals according to their time spent in such jobs. The SMR for 'high' exposure was 1.78, indicating a 78% increase in estimated relative risk (RR); but cancer cases were few in number and findings were not statistically significant at the 5% level. The definition of 'high' exposure was complex, seemingly including work of any duration on degreasing machines. In no analysis was the risk as much as doubled.

31. Three reports on mortality from renal cancer arose from a cohort of some 14,000 civilians employed at a military airbase in Utah. Exposures to TCE arose principally in the degreasing of metal parts. In preliminary reports (Spiritas et al, 1991; Blair et al, 1998), risks were notably elevated in unexposed and low-exposed workers and fell away at higher levels of estimated cumulative exposure. A more recent update, with longer follow-up time (Radican et al, 2008), generated several estimates of RR using different metrics of exposure, but with a broadly similar pattern: the RR was 1.18 overall, but 1.87 among men with 'low' exposure and 1.78 in men with regular daily exposures at a 'low' level; by contrast, RRs were lower in those with 'middle' or 'high' exposures or 'frequent peaks' of exposure (0.31 to 1.16). In no analysis were risks as much as doubled.
32. In a third cohort study, of aircraft builders from San Diego (Garabrant et al, 1988), mortality from renal cancer was below that expected from national and local statistics (SMR 0.93) and no pattern was found by duration of employment. Around a third of jobs were considered to involve exposure to TCE. Risks were not assessed by individuals' level of exposure.
33. In a fourth cohort, of workers engaged in rocket engine testing in California, mortality and incidence of renal cancer were assessed relative to expected rates. In one report on the cohort (Boice et al, 2006), mortality was close to expectations (SMR 1.06), but higher in test stand mechanics (a group believed to be more exposed to chemicals) (SMR 1.78, P>0.05) and in workers potentially exposed to TCE (SMR 2.22, P>0.05, based on 7 cases of cancer). No trend was found with duration of employment. In a second report, involving cohorts assembled with differing entry criteria (Zhao et al, 2005), there was a trend towards higher mortality and cancer incidence with greater estimated cumulative exposure: in the 'high' group, the RR for death from kidney cancer was 2.03 (based on only 3 cases) and that for cancer incidence was elevated almost five-fold (based on only 4 cases of cancer). The former finding was not statistically significant at the 5% level, but the latter was. Potential co-exposure to other chemical agents,

including some carcinogens, was noted.

34. Two studies from Sweden and Finland defined exposure on the basis of national monitoring programmes for metabolites of TCE in workers' urine (Axelson et al, 1994; Anttila et al, 1995). Cases of renal carcinoma were identified through national cancer registries and incidence rates compared with expected rates. Neither study estimated risks by level of urinary metabolite, but that by Anttila et al (1995) provided estimates of mortality risk by duration of employment in a monitored job. RRs were somewhat higher with long employment, but fell well short of the Council's doubling of risk criterion, ranging from 0.87 to 1.39 across the two reports; only 6 cancers occurred in each cohort. In a similarly designed study from Denmark, based on exposure monitoring in urine or air (Hansen et al, 2001), the standardised incidence ratio (SIR) in men was 0.9; that in women exceeded 2, but the estimate was based on only a single case and the findings could easily have been explained by chance alone.
35. In a cohort of uranium processors from Ohio (Ritz, 1999), the SMR from renal cancer was reduced (0.65) among those with 'light' or 'moderate' exposure vs. no exposure. However, in a cohort that had been assembled to study other hazards, exposure levels to TCE were comparatively low and no subject was classed as heavily exposed.
36. In contrast, a cohort of German cardboard-making factory workers (Henschler et al, 1995) was considered to be heavily and continuously exposed to TCE, principally in metal degreasing. The SIR was elevated 8-10 fold, based on 5 cases, and was statistically significant. Cohort members numbered only 169 individuals, and the reported high rate of disease represents an outlier relative to other cohort reports. This cohort may have been studied following the observation of a cluster of kidney cancer cases (e.g. Borak et al, 2000), and so the statistical significance associated with the excess should be disregarded.
37. In another cohort (Buhagen et al, 2016), drawn from a train repair workshop in Norway in which TCE was used "extensively" for degreasing, risks were moderately elevated (SIR 1.7, based on 13 cases). No exposure-response analysis was presented, but 10 of the 13 cases had 'light' daily exposure to TCE.
38. 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. SIRs were only moderately elevated - 1.2 overall and 1.7 in a sub-cohort employed for 5 years or more in blue-collar work before 1970, when

exposures are likely to have been higher. In no analysis were risks as much as doubled. Exposure levels were not known at the individual level.

Case-control studies

39. The largest of the case-control studies (Vlaanderen et al, 2013) identified 76,130 cases from the cancer registries of four Nordic countries and compared them with 380,650 controls chosen from census records. Linkage to national census data enabled individuals' occupations to be defined and an expert job-exposure matrix (JEM) was applied to estimate cumulative exposure to TCE. Estimates of RR were not elevated (odds ratio (OR) 1.00 to 1.02) and no relationship was found with extent of exposure.
40. Other case-control studies were considerably smaller, as judged by numbers with renal cancer. Nonetheless, some reports involved some 900 to 1,200 cases. Among reports of this size were a study that collected cases from five regions of Germany, a second that pooled cases across two US states and a third based on cases from four countries in Central and Eastern Europe.
41. In the German report (Pesch et al, 2000), risks were only slightly elevated among men, even for 'very long' employment as a metal degreaser (OR 1.3) or 'substantial' cumulative exposure, estimated in various ways (OR 1.3); and non-significantly among women, only for 'substantial' exposure estimated in one particular way (OR 1.8). Risks were not more than doubled in any analysis relating to TCE, although they were for several occupations without any suspected link to TCE.
42. In the American study (Purdue et al, 2016), risks were only elevated for 'high' intensity exposure (based on a complex judgement about proximity to the solvent, effectiveness of controls, process variables and temperature); and were only as much as doubled in those exposed at high intensity for >15 hours/week and those in the highest third of cumulative high intensity exposure (only the last of these estimates was statistically significant). The OR for the longest employment duration (10 or more years) at high intensity of exposure was 1.4, substantially below the normal threshold for prescription in the IIDB Scheme.
43. In the report from Central and Eastern Europe (Moore et al, 2010), risks were doubled only for analyses where there was 'high confidence' by the expert in the exposure assignment. Most findings were then significant statistically. ORs>2 were found for 'confident' assignment of exposure at any level, as well as for $\geq$1,080 hrs, $\geq$13.5 years in

these employments, a cumulative exposure ≥1.58 ppm-years, and an average daily intensity of ≥0.076 ppm. A feature of the study was that subjects were genotyped for certain alleles suspected of involvement in the development of renal cancer. Risks differed markedly by genotype, being elevated in some circumstances but not in others.

44. Smaller case-control studies differed in their findings. A population-based study from Montreal, involving 177 cases and 2,532 controls, similarly found no evidence of risk, even with 'substantial' exposure to TCE (Christensen et al, 2013, OR 0.6); a population-based study from the US (Dosemeci et al, 1999), involving 438 cases of renal cancer, reported no increase in risk in men (OR 1.04) but a near doubling in women (OR 1.96) (no data were available by level or duration of exposure); while a small French study (Charbotel et al, 2006, 2009) of 87 cases found a doubling of risk in those with high cumulative exposure (OR 2.16, P<0.05) and higher risks still for high exposures "with peaks", a "good level of confidence in the exposure assessment (ORs 2.73 to 3.80) and high average exposures per shift (no increase in risk was found for metal working involving cleaning operations). An analysis by Greenland et al (1994), nested in a cohort of workers in a transformer assembly facility, identified over 500 deaths from cancer of all causes, but only 12 of these with job histories had died of renal cancer. The OR was 0.99, but this risk estimate was subject to wide statistical uncertainty.
45. Two small German case-control studies were conducted in the same locality as the cardboard factory studied by Henschler et al (paragraph 36); they too produced markedly higher estimates of risk than studies of the same design from other settings. Vamvakas et al (1998) studied 58 cases undergoing surgery for renal cancer in one county hospital and compared them with patients from the accident wards of three neighbouring hospitals. The overall OR was 8.96, ranging from 6.61 in those with light (+) exposure up to 11.42 in those with heavy exposure (+++), all findings being significant statistically. In a follow-on study covering a later time period (Brüning et al, 2003), 134 cases were compared with controls from local departments of surgery and geriatrics. The OR for ever working as a degreaser was 5.57 (95% confidence interval (95%CI) 2.33-13.32), based on 15 exposed cases. Using an expert Job Exposure Matrix (JEM), risks were not raised in relation to 'high' lifetime exposures but were doubled for a 'low' lifetime exposure to degreasing agents (P>0.05). Self-estimates of exposure produced higher and generally more than doubled estimates of risk, but most findings were not significant statistically. The discrepancy between self-estimated and expert-

assessed findings raises the possibility that risk estimates for the former could have been inflated by so-called 'recall' bias (see paragraph 25).

46. The high and outlying risk estimates from the three studies from Arnsberg in Germany (paragraphs 36 and 46) have been much debated. The authors highlighted that exposures to the suspect carcinogen were atypically high in comparison with other settings but aspects of the methods have proved controversial and others have disputed the significance of the findings (e.g. Borak et al, 2000).

Pooled analyses

47. A report by Hansen et al (2013) pooled and compared findings from the Swedish, Finnish, and Danish studies by Axelson et al, Antilla et al, and Hansen et al mentioned in paragraph 34, providing over 100,000 person-years of observations in Scandinavian men and more than 150,000 person-years in Scandinavian women. The combined SIR in men was 1.03 (95%CI 0.66-1.53, based on 24 cases) and 0.63 in women (based on 17 cases).
48. An analysis by Karami et al (2012) pooled risk estimates across a range of other studies. The combined or 'meta'-RR for cohort studies was 1.26 (95%CI 1.02 to 1.56), for case-control studies was 1.35 (95%CI 1.17 to 1.57) and for all types of study was 1.32 (95%CI 1.17 to 1.57), suggesting sufficient evidence for an overall increased risk of kidney cancer following occupational exposure to TCE, but in general not a doubling of RRs.

Discussion and conclusions

49. Findings on TCE and renal cancer have been somewhat mixed. Some studies have reported no association or a relatively moderate one overall (e.g. Garabrant et al, 1988; Axelson et al, 1994; Greenland et al 1994; Anttila et al, 1995; Dosemeci et al, 1999; Ritz, 1999; Pesch et al, 2000; Raaschou-Nielsen et al, 2001; Hansen et al, 2001; Radican et al, 2008; Lipworth et al, 2011; Hansen et al 2013; Christensen et al, 2013; Vlaanderen et al, 2013), whereas others have found high risks (Henschler et al, 1995; Vamvakas et al, 1998; Brüning et al, 2003; Charbotel et al, 2006).
50. Similarly, some reports have found a tendency to higher risks with higher estimates of exposure dose (e.g. Morgan et al, 1998; Zhao et al, 2005; Vamvakas et al, 1998; Charbotel et al, 2006; Moore et al 2010; Purdue et al, 2016), whereas others have found

little relationship or an inconsistent pattern (e.g. Pesch et al, 2000; Radican et al, 2008; Lipworth et al, 2011; Christensen et al, 2013; Vlaanderen et al, 2013), and yet others have not been able to explore the issue.

51. Broadly speaking, however, the balance of evidence supports IARC's conclusion that TCE is a human carcinogen. It should be noted that the challenges inherent in estimating occupational exposures post-hoc could have led to underestimation of risks across studies; also, that there is experimental evidence in animals that TCE can induce kidney cancer, at least in some circumstances.
52. IARC's classification of TCE as a human carcinogen is important because it highlights a preventative need. Considering the scope for prescription within the IIDB Scheme, however, it is not sufficient to accept that the chemical can cause kidney cancer. There is a requirement to define the occupational circumstances, or dose, that will more than double risks of the disease, and to define these in a way that can be administered effectively by decision-makers who lack access to the complex expert judgements employed in epidemiological research.
53. Several reports have included risk estimates that exceed two, in at least some of their analyses (e.g. Henschler et al, 1995; Zhao et al 1995; Vamvakas et al, 1998; Brüning et al, 2003; Charbotel et al, 2006; Moore et al 2010; Purdue et al, 2016). Of these, however, reports based on expert JEM-assessed scores of high intensity exposure (Zhao et al 1995; Charbotel et al, 2006; Moore et al 2010; Purdue et al, 2016) cannot be translated into an exposure schedule for benefit purposes, even if inconsistencies with other evidence were overlooked.
54. A critical test the Council has considered is whether prescription is possible for work as a 'degreaser' (by consensus one of the most highly exposed of all occupations). Direct evidence in favour of this comes from two of the German case-control studies (Vamvakas et al, 1998; Brüning et al, 2003) in which risks far exceeded two; but in the much larger German case-control study by Pesch et al (2000) 'very long' employment as a degreaser carried only a RR of 1.3; and estimates from other studies where the predominant exposure was thought to arise in degreasing did not reach the doubling of risk threshold (e.g. Axelson et al, 1994; Anttila et al, 1995; Morgan et al, 1998; Radican et al, 2008; Buhagen et al, 2016).
55. In the circumstances, the Council has concluded that no circumstances have been identified in which prescription can be recommended within the Scheme. The topic will

be kept under review however.

Prevention

56. As highlighted in this report, a general body of evidence indicates that TCE is a human carcinogen and occupational exposures to the chemical can adversely affect workers' health and safety in various other 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.
57. 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.

Equality and diversity

58. The Industrial Injuries Advisory Council is aware of issues of equality and diversity and seeks to promote 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 this review of renal cancer and exposures to TCE no diversity and equality issues were apparent. (A separate report considers the risks of cervical cancer in women exposed occupationally to TCE.)

Table 1: Cohort studies of trichloroethylene and kidney cancer

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 death certificates or California Death Tapes	a) Employed vs not b) vs. US national rates	SMR 0.93 (0.48-1.64, 12)	Study undertaken to evaluate overall mortality and 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. Trend in risk with duration of employment was not presented for renal cancer.
Axelson et al, 1994 (updating Axelson et al, 1978)	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) monitored vs. not	SIR 1.16 (0.42-2.52, 6)	No risk estimates for renal cancer by level of urinary TCA or duration of employment. Risk of renal cancer not examined for women in the cohort.
Anttila et al, 1995	Cohort of 1,698 male and 1,391 female workers biologically monitored for urinary TCA under Finnish labour legislation from 1965-1982	1967-1992 100%	Finnish Cancer Registry	a) Record of at least one U-TCA b) Incidence in monitored cohort (vs. national incidence rate)	SIR (both sexes), 0.87 (0.32-1.89, 6) SMR (years since first measurement): 0-9y, 0.53 (0.01-2.95, 1); 10-19y, 1.39 (0.45-3.24, 5); ≥20y, no cases	Individual measurements of urinary TCA were obtained, but analysis was based on years since first measurement, not urinary levels. TCE was used mainly in degreasing or cleaning metal surfaces, but also in rubber work, gluing, dry cleaning and in cleaning fluids.
Henschler et al, 1995	Cohort of 169 men exposed to TCE for ≥ 1	1956-1992	Cancer Registry of the	a) Employment records	SIR using Danish Cancer Register for	Origins of study were probably a cluster of kidney cancer (Borak et

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
	year between 1956 and 1975 in a German cardboard manufacturing factory); 190 unexposed workers who worked at the factory at the same time, matched for age and physical job activity	Not stated	former German Democratic Republic	b) Incidence in exposed (vs. rates in the Danish and German Cancer Registries)	reference, 7.97 (2.59-18.59, 5) SIR using German Cancer Register for reference, 9.66 (3.14-22.55, 5) No cases in the control group	al, 2000). Exposed men worked were in 3 areas: the cardboard machine area, where they degreased felts and sieves with 'large amounts' of TCE (2 cases); and in the locksmiths' area (1 case) and the electrical workshop (2 cases), where they had 'continuous exposure' to TCE at lower levels in metal degreasing. TCE was also used regularly to clean floors, work clothes and hands.
Morgan et al, 1998	Cohort of 20,508 workers from an aircraft manufacturing site in Arizona, employed for $\geq$6 months between 1950 and 1985 (4,733 TCE-exposed)	1950-1993 Cause of death could not be found for ~ 3% of deaths	Vital status from National Death Index and Social Security Administration data files	a) Long-term workers rated exposure for each job, then a hygienist compiled a JEM; b) any, low, or high cumulative exposure vs none, with expected numbers based on national rates	SMR Any: 1.32 (0.57-2.60, 8) Low: 0.47 (0.01-2.62,1) High: 1.78 (0.72-3.66, 7) Peak medium & high vs. low/none: 1.89 (0.85-4.23, 8)	Jobs were classified as 'high' in exposure if they involved work *on* degreasing machines; as 'medium' if they were *near* the degreasing area with "more than occasional" contact with TCE; and as 'low' if *away* from the degreasing area. Final classification was based on employment spells in these settings: 'low' = $\leq$ 5 years in low exposure jobs or $\leq$ 1.4 years in medium exposure jobs; 'high' was any other pattern of exposure – viz >1.4 years in a medium exposure job or (seemingly) any time in a high

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
						exposure job.
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	Social Security Administration and National Death Index	a) Exposure assessed by experts from job titles and work areas: for TCE classed into 3 bands, 'none' 'light', 'moderate'; b) any (light or moderate) vs. national rates (also vs. none in an internal analysis)	SMR overall, 0.65 (0.21-1.51, 5)	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. In an internal analysis, by level and duration of exposure, cases of renal cancer (5) and bladder cancer (8) were combined. No risk estimates were available by employment duration or level of exposure.
Raaschou-Nielsen et al, 2001	Cohort study of 40,049 workers employed for ≥3 months in one of 347 Danish companies that were documented users of TCE	1964-1997 >99% (~80% for >10 years)	Danish cancer registry record of renal cell carcinoma	a) Use of TCE in companies was determined by archive records; b) blue-collar employment (i) overall, (ii) by duration, (iii) by year first employed (vs. national rates)	SIR (i): Men, 1.2 (0.9-1.5, 68); women: 1.2 (0.5-2.4, 8) (ii) (≥5 years employment): men, 1.6 (1.1-2.3, 29); women, 1.5 (0.3-4.3, 3) Year first employed: (a) pre-1970, men, 1.7 (1.2-2.3, 44); women, 1.9 (0.7-4.1)	While use of TCE was documented in these companies, it was unknown at the individual level (but see Hansen et al, 2001). The probability of exposure was raised by focussing on blue-collar occupations and particular periods (exposures were expected to be 4-5 times higher in the 1960s than in the 1980s) and higher in small companies, but few cases were observed and no consistent

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
					(b) 1970-9, men, 0.7 (0.4-1.2); women, no cases (c) post 1980, men, 0.9 (0.4-1.7, 8); women, 2.4 (0.3-8.5, 2)	pattern. In a sub-cohort of workers believed to be more exposed by virtue of ≥1 year of employment pre-1980, the overall SIR in men was 1.4 and that in women was 1.7; if employed for ≥5 years, 1.7 and 1.9 respectively.
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 but likely to be close to 100%	Danish cancer registry	a) Exposure was indicated by a record of urinary TCA or TCE-in-air; b) exposed vs. not	SIR Men: 0.9 (0.2-2.6, 3) Women: 2.4 (0.03-14, 1)	Mean urinary TCA 40 mg/L, median 15 mg/L, based on 1,519 samples over 1947-1989. Mean air-TCE 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 the study by Raaschou-Nielsen et al.)
Zhao et al, 2005	Cohort of male workers employed between 1950 and 1993 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	1950-2001 (mortality) 1988-2000 (incidence) Not stated	Vital status from California death tapes and death index, National Death Index, pension benefit, social security and other files; cancer	a) Personnel records & interviews with long-term workers b) JEM to give time-dependent intensity scores, then scores of cumulative	Mortality: Low: 1.0 (n = 7) Medium: 1.43 (0.49-4.16, 7) High: 2.03 (0.50-8.32, 3) P-value for trend 0.307 Incidence (zero lag): Medium: 1.87 (0.56-6.20, 6) High: 4.90 (1.23-19.6,	Adjusted for time since first employment, socioeconomic status, age at event. Further adjustment for other carcinogens strengthened relations with incidence (with wide confidence intervals, e.g. RR for 'high' score, 7.71 (0.65-91.4, 4)), but weakened relations with mortality (e.g. RR for 'high' score, 0.96 (0.09-9.91, 3)). There was potential co-exposure

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
	analysis based on 5,049 workers alive and cancer-free in 1988)		incidence from 9 state cancer registries	exposure (low, medium, high vs none)	4) P-value for trend 0.023	to other carcinogens, e.g. benzene. Findings were not much changed when the exposure lag was 20 years. 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	1948-1999 >99%	Vital status as for Zhao et al, 2005	a) As for Zhao et al, 2005 b) job title & duration, work location, likely exposure to TCE (vs. Californian population rates)	SMR All facilities: 1.06 (0.83-1.33, 74) Field laboratory: 1.15 (0.71-1.76, 21) Test stand mechanics: Overall, 1.78 (0.77-3.51, 8) Potentially exposed, 2.22 (0.89 -4.57, 7)	Overlap with Zhao et al, 2005. No significant trends by duration of employment. Test stand mechanics were singled out as a group with greater potential exposure to chemicals. There was potential co-exposure to various other chemicals, e.g. hydrazines and benzene.
Lipworth et al, 2011 (updating Boice et al, 1999)	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 benefit, social security and other files	a) JEM based on personnel files, linked with industrial hygiene files, walk-through surveys and interviews of long-term workers b) Routine, intermittent or no exposure to	SMR (to 1996) Overall: 0.99 (0.40-2.04, 7) Years of TCE exposure: 0 yrs (n = 22) <1 yr, 0.97 (0.37-2.50, 6) 1-4 yrs, 0.19 (0.02-1.42, 1) ≥5 yrs, 0.69 (0.22-2.12, 4)	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 primers, perchloroethylene and other solvents. No increase in risk in painters, process operators, electroplaters, fabrication and structure

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
				TCE (vs. Californian or US population rates)	SMR (to 2008) Overall: 0.66 (0.38 - 1.07, 16) Years of TCE exposure: 0 yrs (n = 33) <1 yr, 0.52 (0.21-1.30, 6) 1-4 yrs, 0.42 (0.13-1.42, 3) ≥5 yrs, 0.85 (0.33-2.19, 6)	development mechanics and final assemblers. SMR in plastics part fabricators, 1.73 (0.86-3.09, 11); in welders, 1.17 (0.32-2.99, 4); and in metal bonders, 2.40 (0.88-5.23, 6).
Radican et al, 2008 (updating Spiritas et al, 1991; Blair et al, 1998)	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) (i) overall; (ii) by tertile of TCE 'score'; (iii) by intensity and frequency	(i) RR 1.18 (0.47-2.94, 18) (ii) (Men) Low: 1.87 (0.59-5.97, 10); middle: 0.31 (0.03-2.75, 1); high: 1.16 (0.31-4.32, 5) (iii) (Men) Low intermittent: 1.58 (0.52-4.76, 15); low continuous: 1.79 (0.57-5.62, 11); peak infrequent: 1.04 (0.19-5.70, 2); peak frequent 1.11 (0.31-3.96, 6)	Insufficient measurements of exposure existed, so a 'score' was constructed. 'Low' was defined as bench top work in cleaning small parts, 'peak' as work with vapour degreasers; 'intermittent' was defined as infrequently through the working day and "continuous" as regularly through the day. There were only 2 cases in women and no clear exposure-response pattern. (In earlier analyses, risks of renal cancer were elevated in unexposed and lowly workers

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
						and fell off as estimated cumulative exposure rose.)
Buhagen et al, 2016	Norwegian cohort of 997 male workers employed for at least one year at some time from 1954a train repair and maintenance workshop in Trondheim.	1960-2010 Not stated	Norwegian Cancer Registry	a) No exposure assessment; b) Union and company data on employment for >1 year in the workshop since 1954 (vs. national cancer incidence rates)	SIR 1.7 (1.0 to 3.0, 13)	No measurements of exposure existed, but TCE was used "extensively" in the workshop (mainly for degreasing) between the 1950s and 1990s. 3 cases were considered to have moderate daily exposure and 10 to have light but daily exposure.

Table 2: Case-control studies of trichloroethylene and kidney cancer

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 who worked at some time between 1937 and 1968 at 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	0.99 (0.30-3.32)	TCE was used as a degreasing agent at the facility approximately between 1930 and 1977. Only 12 of 16 deaths from renal cancer had available job histories.
Vamvakas et al, 1998	Hospital-based case-control study in Germany (58 of 72 cases, 84 controls). Cases were patients having a nephrectomy in one country hospital; controls, who were unmatched, were patients from the accident wards of 3 nearby hospitals	1987-1992 79%, ~75%	Interview: history of solvent-exposed jobs; scored by an index of exposure duration plus frequency and severity of 'pre-narcotic' symptoms	(i) Overall; (ii) by exposure category: +, ++, +++	(i) 8.96 (2.90-27.75, 19) (ii) '+', 6.61 (0.50-87.76, 2); '++', 11.92 (2.55-55.60, 9); '+++', 11.42 (1.96-66.79, 8)	Most cases were said to have been engaged in metal-degreasing processes, with poor ventilation, no gloves and the breathing zone directly above the degreasing tubs. Analysis was adjusted for age ((i) and (ii)) and blood pressure (ii). An analysis which included exposures to perchlorethylene as well as TCE, produced an OR of 10.80 (3.36-34.75) adjusted additionally for other factors.
Dosemeci et al, 1999	US population-based case-control study. Cases (273 men and 165	1988-1990 87%, 86%	Interview: most recent and usual	Exposed to TCE vs. not	Overall: 1.30 (0.9-1.9, 55) Men: 1.04 (0.6-1.7,	5-6% of subjects were classified as TCE-exposed. No information was provided, however, on the level or

	women) were identified via a state cancer registry. Controls were recruited by random digit dialling and systematic sampling of patient lists of a healthcare financing administration		occupation, classified by JEM		33) Women: 1.96 (1.0-4.0, 22)	duration of exposure or the nature of exposed jobs. Analysis allowed for age, sex, smoking, BMI, hypertension and/or use of diuretics or anti-hypertensive drugs.
Pesch et al, 2000	Population-based case-control study in five German regions (935 cases; 4,298 controls). Controls were age, sex and region-matched and were selected from local residency registries	1991-1995 88%, 71%	Interview: occupations held for ≥1 year and task-specific questions. 2 job-task exposure matrices applied (expert ratings on probability and intensity of exposure)	(i) metal degreaser – medium, long, very long duration; (ii) JEM – medium, high, substantial; (iii) JTEM – medium, high, substantial Separate data given for each sex	Men (i) medium, 1.0 (0.9-1.9, 47); long, 1.1 (0.8-1.6, 38); very long, 1.3 (0.7-2.3, 15) (ii) medium, 1.1 (0.9-1.4, 135); high, 1.1 (0.9-1.4, 138); substantial, 1.3 (0.9-1.8, 55) (iii) medium, 1.3 (1.0-1.8, 68); high 1.1 (0.8-1.5, 59); substantial 1.3 (0.8-2.1, 22) Women (i) 9 exposed cases, ORs: 1.0, 1.3, and 1.5 (ii) medium, 1.2 (0.8-1.8, 28); high, 1.3 (0.8-2.0, 29); substantial, 0.8 (0.3-1.9, 6) (iii) medium 1.3 (0.7-2.6, 11); high 0.8 (0.4-1.9, 7); substantial 1.8	Analyses adjusted for smoking, age and region. Analyses of risk by job title identified several other occupations where risks were substantially elevated. These included male managers (OR 3.3), male and female electrical assemblers (3.2, 2.7), female rubber and plastic makers (6.0) and male railway workers (6.2). No explicit link was proposed to TCE, but the report suggested that "substantial exposure to metals and solvents may be nephrocarcinogenic".

					(0.6-5.0, 5)	
Brüning et al, 2003	German case-control study (134 cases who had undergone a nephrectomy vs. 401 controls from local departments of surgery and geriatrics with no diagnosis of cancer or dementia, frequency-matched by age and sex)	1992-2000 83%, not stated	Interview with patient or next-of-kin (21 deceased cases). Job history, JEM, respondent-assessed exposure history	a) Longest held job in industry with TCE/PER exposure; b) ever worked as degreaser; c) lifetime JEM exposure to degreasing agents; d) self-assessed TCE exposure	a) 1.80 (1.01-3.20, 117) b) 5.57 (2.33-13.32, 15) c) low: 2.11 (0.86-5.18, 9); high: 1.01 (0.40-2.54, 7) d) Any: 2.47 (1.36-4.49, 25) <10 yrs: 3.78 (1.54-9.28, 11) 10-20 yrs: 1.80 (0.67 - 4.79, 7) ≥20 yrs: 2.69 (0.84-8.66, 6)	Adjusted also for smoking. Large difference between results for self-reported exposures and those assessed by JEM.
Charbotel et al, 2006; Charbotel et al, 2009	French case-control study (87 cases (19 (22%) deceased), identified from local urologists in the Arve valley and specialists (urologists and oncologists) from teaching hospitals which might receive referrals from this valley; 316 age- sex- and area-matched controls, from the same local urologists or, the GPs of hospital-recruited cases, excluding	1993-2003 74%, 78%	Interview with patient or next of kin: work questionnaire and task exposure matrix	a) Any exposure; b) cumulative exposure; c) cumulative exposure + peaks; d) c but with a "good level of confidence"; e) average TCE exposure, ≥35 ppm, ≥50 ppm, ≥75 ppm	a) 1.64 (0.95-2.84, 37) b) Low: 1.62 (0.75-3.47, 12) Medium: 1.15 (0.47-2.77, 9) High: 2.16 (1.02-4.60, 16) c) Low/medium, no peaks: 1.35 (0.69-2.63, 18) Low/medium + peaks: 1.61 (0.36-7.30, 3) High, no peaks: 1.76 (0.65-4.73, 8) High + peaks: 2.73 (1.06-7.07, 8) d) High, no peaks: 2.74	Study conducted in a region where exposed jobs were common in the population. Analysis adjusted for tobacco smoking, BMI and co-exposure to cutting fluids and petroleum oils (which was common). No increased risk was found for metal working involving possible cleaning, when classified by industry or job title. Analysis for which there was a "good level of confidence" in the exposure assessment was based on 60 of 87 (69%) cases and 225 of 315 (71%) controls; 16 cases were considered to be exposed at some level.

	subjects with chronic kidney disease or urogenital cancer)				(0.66-11.42, 4) High + peaks: 3.80 (1.27-11.40, 7) e) >35 ppm, 1.62 (0.77-3.42); >50 ppm, 2.80 (1.12-7.03); >75 ppm, 2.92 (0.85-10.09)	
Moore et al 2010	Hospital-based case-control study, with cases drawn from 7 centres in 4 countries in Central and Eastern Europe (1,097 cases, 1,476 controls). Controls were matched on age, sex and hospital from among inpatients and outpatients free of cancer or genitourinary disorders (except for benign prostatic hyperplasia)	1999-2003 Not stated	Interview about jobs held for >1 year (tasks, machines, work location, duration) – task exposure matrix applied; a subgroup was defined where there was high confidence in assessments	a) Any exposure; b) cumulative (years, hours, ppm-years); c) average intensity	'High confidence' assessments: a) 2.05 (1.13-3.73, 29) b) ≥1080 hrs, 2.86 (1.31-6.23, 20); ≥13.5 years, 2.25 (0.95-5.29, 14); ≥1.58 ppm-years, 2.23 (1.07-4.64, 20) c) ≥0.076 ppm, 2.41 (1.05-5.56, 16) All assessments: Values were lower: a) 1.63; b) 1.82 to 2.02; c) 2.34	Subjects were genotyped for certain alleles suspected of involvement in disease causation. Risks were elevated for the *GSTT1* 'active' genotype but not the 'nul' genotype; and markedly (OR 6.6-12.8) for certain homozygous variants (SNPs) of *CCBL1*.
Christensen et al, 2013	Population-based case-control study in Montreal, Canada (177 male cases of kidney cancer were identified from the 18 largest hospitals in the metropolitan area; 533 male controls were recruited from random samples of electoral	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,	a) Any exposure vs. none; b) 'substantial' exposure vs. none	a) 0.9 (0.4-2.4, 5) b) 0.6 (0.1-2.8, 2)	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, repairing occupations (13% exposed) and metal shaping and forming (11% exposed).

	lists)		high)			
Vlaanderen et al, 2013	Case-control study nested within a cohort comprising the populations of Finland, Iceland, Norway and Sweden. 76,130 cases were identified from Nordic cancer registries, with 380,650 controls randomly selected from census records.	Varied (maximum 1953 -2005) 100%?	Linkage with national census data enabled employment histories to be approximated. Cumulative exposure was estimated using a JEM	a) Lowest, b) middle, and c) highest third of cumulative exposure vs none	a) 1.01 (0.95-1.07, 1,217) b) 1.02 (0.97-1.08, 1,556) c) 1.00 (0.95-1.07, 1,372)	Further stratification by sex did not alter risk estimates much; nor did alternative approaches to estimating cumulative exposure with focus on high exposure groups.
Purdue et al, 2017	Population based case-control study carried out in two US states (1,217 cases, 1,235 controls). Incident cases were identified through a cancer surveillance system and review of hospital pathology reports; controls were identified from driver licensing and Medicare eligibility files, and were matched on age, sex and race	2002-2007 77%, 54%	Interview about jobs held for ≥1 year (hours, tasks, patterns and 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 hours/week; (iv) cumulative hours exposed For (ii)-(iv), 'any intensity' and 'high intensity only'.	(i) ≥90%, 0.8 (0.4-1.5, 32) High intensity (50%+ exposure probability): (ii) top third, 1.1 (0.5-2.4, 11); (iii) >6 hrs/week, 2.0 (0.5-7.4, 11); (iv) top third, 1.7 (0.8-3.8, 9)	'Highest third' of duration was defined as >4,680 hours for any exposure and >1,820 hours for high intensity exposure. Occupations with high intensity exposure were not defined. Rather, intensity of exposure was assessed on the basis of a combination of factors (location, proximity to solvent, effectiveness of local exhaust ventilation, mechanism of release (evaporation vs. active) and process temperature (room vs. elevated)).

Abbreviations: TCE = trichloroethylene; TCA = trichloroacetic acid (a metabolite of TCE); JTEM = job-task specific exposure matrix; TEM = task specific matrix; SMR = Standardised Mortality Ratio; OR = Odds Ratio; SIR = Standardised Incidence Ratio

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, Andersson K, Hogstedt C, et al .A cohort study on trichloroethylene exposure and cancer mortality. J Occup Med 1978; 20: 194-6.

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

Blair A, Hartge P, Stewart PA, et al. Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up. Occup Environ Med 1998;55: 161–171.

Boice JD, Marano DE, Fryzek JP, et al. Mortality among aircraft manufacturing workers. Occup Environ Med 1999;56:581–597

Borak J, Russi M, Puglist KP. Meta-analyses of TCE carcinogenicity. Environ Health Perspect 2000; 108: A542-A543.

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.

Brüning T, Pesch B, Wiesenhutter B et al. Renal cell cancer risk and occupational exposure to trichloroethylene: results of a consecutive case-control study in Arnsberg, Germany. Am J Ind Med 2003; 43: 274-285.

Buhagen M1, Grønskag A, Ragde SF, et al. Association Between Kidney Cancer and Occupational Exposure to Trichloroethylene. J Occup Environ Med 2016;58:957-9.

Charbotel B, Fevotte J, Hours M, et al. Case–Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part II: Epidemiological Aspects. Ann Occup Hyg 2006; 50: 777-787.

Charbotel B, Fevotte J, Martin JL, et al. Renal cell carcinoma and exposure to trichloroethylene: are the French limits of occupational exposure relevant? Rev Epidemiol Sante Publique 2009;57:41-7.

Christensen KY, Vizcaya D, Richardson H, Lavoué J, Aronson K, Siemiatycki J. 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.

Dosemeci M, Cocco P, Chow WH. Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. Am J Ind Med 1999; 36: 54-59.

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. International Archives of Occupational and Environmental 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.

Hansen J, Sallmen M, Selden AI, et al. Risk of cancer among workers exposed to trichloroethylene: Analysis of three Nordic cohort studies. J Natl Cancer Inst 2013; 105: 869-877.

Henschler D, Vamvakas S, Lammert M, et al. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. Archives of Toxicology 1995; 69: 291-299.

International Agency for Research on Cancer (IARC). Trichloroethylene, Tetrachloroethylene, and some other chlorinated agents. WHO, Geneva, 2014.

Karami S, Lan Q, Rothman N, et al. Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. Occup Environ Med 2012;69:858–867.

Lipworth L, Sonderman S, Mumma MT, et al. Cancer mortality among aircraft manufacturing workers: an extended follow-up. JOEM 2011; 53: 992-1007.

Morgan RW, Kelsh MA, Zhao K, et al. Mortality of aerospace workers exposed to trichloroethylene. Epidemiol 1998;9:424–431.

Moore LE, Boffetta P, Karami S, et al. Occupational trichloroethylene exposure and renal carcinoma risk: evidence of genetic susceptibility by reductive metabolism gene variants. Cancer Res 2010; 70(16): 6527–6536.

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 Epidemiology 2000; 29: 1014-1024.

Purdue MP, Stewart PA, Friesen MC, et al. Occupational exposure to chlorinated solvents and kidney cancer: a case-control study. Occup Environ Med 2017; 74: 268-274.

Raaschou-Nielsen O, Hansen J, McLaughlin JK, et al. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. Am J Epidemiol 2003;158:1182-92.

Radican L, Blair A, Stewart P, et al. 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.

Spirtas R, Stewart PA, Lee JS, et al. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br J Ind Med 1991;48:515–530.

Vamvakas S, Bruning T, Thomasson B et al. Renal cell cancer correlated with occupational exposure to trichloroethene. J Cancer Res Clin Oncol 1998; 124: 374-382.

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.

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. American Journal of Industrial Medicine 2005; 48: 249-258.

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 ratios** (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 or incidence: 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.

Published: September 2017