Industrial Injuries Advisory Council Information Note:

Trichloroethylene and Cervical Cancer

April 2017

Background and method of inquiry

1. As part of its horizon scanning activity, the Industrial Injuries Advisory Council (IIAC) has been considering the case within the Industrial Injuries Disablement Benefit Scheme (IIDB) for prescribing cervical cancer following occupational exposure to trichloroethylene (TCE). This Information Note sets out the recent evidence and the Council's position on it.

2. Cervical cancer is the thirteenth most common cancer in women in the UK, with around 3,200 cases diagnosed per year. Incidence rates in the UK are projected to rise by 43% by the year 2034.

3. Cervical cancer is more common in younger women, with more than half the cases diagnosed in women aged 45 years or under. Infection from the human papilloma virus (HPV) is a major cause of the main types of cervical cancer. Other risk factors include the Human Immunodeficiency Virus (HIV), other sexually transmitted infections, smoking tobacco, taking the contraceptive pill, the number and timing of having children, a family history of the disease, having a previous cancer, and having lower socioeconomic status.

4. TCE is a widely used industrial solvent. A principal use of it is in degreasing metal parts to remove oils, greases, waxes, tars, and moisture before surface treatments such as galvanising, electroplating, painting, anodising and application of conversion coatings.

5. A report by the International Agency for Research on Cancer (Guha *et al*, 2012) has provided the foundation for this review. The Council's Research Working Group supplemented this with a literature search for more recent research. Reports were evaluated for evidence of a more than doubling of risks of cervical cancer in women with occupational exposure to TCE. (The rationale for the doubling of risk threshold is set out in previous reports of the Council.) Eight studies on the topic are summarised in a table and several others (mainly in relation to work in the dry cleaning industry) are reviewed additionally in the text that follows.

Findings

6. Three studies involved aircraft manufacturing workers. In Boice *et al* (2006) and Lipworth *et al* (2011) mortality from cervical cancer was close to or below that in the local population (Standardised Mortality Ratios (SMR) 0.50 to 1.07); while in Lipworth's study no evidence was found of a trend in risk by duration of employment.

7. Mortality was higher in the Hill Air Force Base NCI cohort (Radican *et al*, 2008), however, with a relative risk (RR) of 1.67; and higher still in subgroups assessed as having 'high' exposure (2.83) or 'peak frequent' exposures (2.30). Cancer numbers were very small however, and no finding was significant statistically.

8. In the cohort study by Raaschou-Nielsen *et al* (2003), the overall RR was 1.9, and 2.4 in those first employed in the 1970s (but not after 1980). There was some evidence of a doubling of the risk in workers employed for less than 1 year (RR 2.5), but not in those employed for longer.

9. The study by Hansen *et al* (2013) pooled data from workers under statutory national surveillance for TCE in three Nordic countries. It followed earlier reports from Finland (Antilla *et al*, 1995) and Denmark (Hansen *et al*, 2001) which had reported significantly raised RRs of 2.4 and 3.8 respectively, there being indications in the former study that RRs were higher again in those with higher levels of urinary trichloroacetic acid (a metabolite of TCE) (U-TCA), and in the latter that risks particularly predated 1965, albeit based on small numbers. The pooled analysis also incorporated data from Sweden, although the Finnish findings contributed most to risk estimates since most exposures and cases arose in Finland. Overall, a more than doubling of RR was found in monitored workers compared with the general populations of the Nordic countries (Standardised Incidence Ratio 2.31, based on 16 cases), a finding that was statistically significant. RRs rose with the level of urinary metabolite in a dose-response pattern, up to 3.38 in those a U-TCA of >50 (vs. <5) mg/L; but the p-value for trend was not statistically significant and nor were individual estimates of risk by level of U-TCA.

10. A small French case-control study (Charbotel *et al*, 2013) found more than doubled RRs of cervical cancer with exposure to TCE, but in those with <5 years of exposure, rather than in those with 10 or more years; and in those with 'low' levels of cumulative exposure (1-90 ppm-years) rather than in those with 'medium' or 'high' cumulative exposures (>90 ppm-years). No increase in RR was statistically significant.

11. In addition to the papers summarised above and in the table, a review of TCE and cancer by Wartenberg *et al* (2000) highlighted four studies of mortality cancer and one of cancer incidence in female dry cleaners (Ruder *et al*, 1994; Katz & Jowett, 1981; Duh &

Asal, 1984; Blair *et al*, 1990; Lynge & Thygesen, 1990), as well as further mortality studies in lamp makers (Shannon *et al*, 1988) and jewellery workers (Dubrow *et al*, 1987), all of whom were potentially exposed to TCE. In the mortality studies RRs were elevated, but not doubled; in the two incidence studies, SIRs ranged from 0.8 to 1.1 (Lynge *et al*, 1990; Shannon *et al*, 1988).

Summary and conclusions

12. Only a relatively few studies have examined the relationship between occupational exposure to TCE and the subsequent development of cervical cancer.

13. Among them, the pooled analysis by Hansen *et al* (2013) and linked reports (Antilla *et al*, 1995; Hansen *et al*, 2001) provide the strongest indication that risks of cervical cancer could be as much as doubled in women occupationally exposed to TCE; that by Radican *et al*, also indicates that possibility among women in the highest exposure bands.

14. The reports of Boice *et al* (2006) and Lipworth *et al* (2011) did not indicate an increase in risk, although exposures in the cohorts studied may have been relatively light. Studies in laundry workers mostly pointed to an elevation, but not a doubling of risks of cervical cancer, and in two studies of jewellery workers and lamp makers, RRs were only slightly elevated.

15. The case-control study by Charbotel *et al* found a more than doubling of risk, but only with briefer lighter exposures, the opposite pattern to that expected in a causal relationship. One concern in studying the outcome of cervical cancer is its strong link to sexually transmitted disease (STD). STDs may confound associations, as they are liable to be correlated with exposures to TCE and are known to cause cervical cancer in their own right. The analysis by Charbotel *et al* attempted to allow for potential confounding by STDs but it is uncertain if this offset all of the confounding effect. No control for this confounder was possible in the analyses by Antilla *et al*, Hansen *et al* (2001), Hansen *et al* (2013), Radican *et al*, Boice *et al*, Lipworth *et al*, or in the studies described in paragraph 11.

16. At present, the Council considers that the balance of evidence does not define exposure circumstances to TCE that would double risks of cervical cancer and which can be recommended for prescription. However, it has identified a need to monitor the research literature on this topic for new evidence which might prompt a reconsideration of its position.

Prevention

17. A general body of evidence indicates that TCE is a human carcinogen (IARC, 2014) and that occupational exposures to TCE 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.

18. 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

19. 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 cervical cancer and exposures to TCE the only diversity and equality issue identified was that the tumour in question occurs only in women.

This Information Note contains some technical terms, the meanings of which are explained in the glossaries to the companion reports on trichloroethylene and cancers of the kidney and blood.

Table: Trichloroethylene & Cervical Cancer

Reference	Study Population and Sampling	Follow-up interval; completeness	Case Ascertainment	a) Exposure Assessment b) Comparison	Relative Risks (95% confidence intervals, number of events)	Additional Information
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) (i) overall, (ii) by years since first measurement, by (iii) U-TCA	(i) All, 2.42 (1.05-4.77, 8) (ii) 0-9 yrs, 3.39 (1.24-7.38, 6); 10-19 yrs, 0.84 (0.02-4.67, 1); 20+ yrs, 2.89 (0.07-16.1, 1) (iii) <100, 1.86 (0.38-5.45, 3); 100+, 4.35 (1.41-10.1, 5)	TCE was used mainly in degreasing or cleaning metal surfaces, but also in rubber work, gluing, dry cleaning and in cleaning fluids.
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) (i) exposed vs. not; (ii) period first employed; (iii) mean exposure	(i) 3.8 (1.0-9.8, 4) (ii) Pre-1965, 5.2 (1.1-16, 3) (iii) <19 mg/m^3, 3.4 (0.4-12, 2); $\geq$19 mg/m^3, 4.3 (0.5-16, 2)	Analyses were also presented by duration of employment and estimated cumulative exposure, but missing information reduced numbers to single cases per exposure band.
Raaschou-Nielsen *et al*, 2003	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	a) Use of TCE in companies was determined by archive records; b) blue-collar employment (i) overall, (ii) by duration, (iii) by year first	(i) 1.9 (1.42-3.27, 62) (ii) 1-4.9 y 1.6 (1.0-2.4, 22); $\geq$5 y 1.3 (0.6-2.4, 10) (iii) Before 1970, 2.4 (1.6-3.4, 31); 1970-1979, 1.9 (1.2-2.7, 26); 1990 or later 0.7 (0.2-1.7, 5)	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 time frames (exposures were expected to be 4-5 times higher in the 1960s

Reference	Study Population and Sampling	Follow-up interval; completeness	Case Ascertainment	a) Exposure Assessment b) Comparison	Relative Risks (95% confidence intervals, number of events)	Additional Information
				employed (vs. national rates)	(SIR)	than in the 1980s). Higher exposures were also expected in small companies and the SIR for companies with <50 employees was 2.4 (1.3-3.9, 15).
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 facilities in California	1948-1999 >99%	Vital status from California death tapes and death index, National Death Index, pension benefit, social security and other files; cancer incidence from 9 state registries	a) Personnel records & interviews with long-term workers – JEM; b) Cohort vs. Californian population rates	SMR All, 0.50 (0.20-1.04, 7); field laboratory, 1.07 (0.13-3.85, 2)	There was potential co-exposure to other carcinogens e.g. benzene. Both cases occurred in workers employed < 5 years.
Radican *et al*, 2008 (updating 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) Exposed vs unexposed; (ii) low, medium, high cumulative exposure score;	HR (i) 1.67 (0.54-5.22, 6) (ii) 'Low', 0.76 (1 case); 'medium' 0 cases; 'high', 2.83 (0.86-9.33, 5) (iii) Peak infrequent, 4.41 (0.89-21.86, 2); peak frequent, 2.30 (0.70-7.58, 5)	

Reference	Study Population and Sampling	Follow-up interval; completeness	Case Ascertainment	a) Exposure Assessment b) Comparison	Relative Risks (95% confidence intervals, number of events)	Additional Information
				(iii) pattern of exposure		
Lipworth et al, 2011 (updating Boice et al, 1999)	Retrospective cohort study 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 and interviews of long-term workers b) (i)Total, Factory, Non-Factory; (ii) duration of employment	SMR (i) 0.65 (0.40-0.99, 21); 0.76 (0.50-1.11, 27); 0.83 (0.57-1.18, 31) (ii) 1-9 yrs, 0.41 (0.05-1.49, 2); 10-19 yrs, 1.02 (0.33-2.37, 5); 20-29 yrs 0.73 (0.15-2.12, 3); ≥30 years 1.24 (0.15-4.49, 2)	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.
Hansen et al, 2013	Pooled cohort of 5553 workers with individual documented exposure to TCE in Finland, Sweden and Denmark monitored for U-TCA because of national legislation on worker protection.	1958-2008 Not stated, but likely to be near 100%.	National Cancer Registers of countries involved.	(a) Monitored & U-TCA level (b) (i) All countries; (ii) all, with 20-year lag; (iii) U-TCA (mg/L) (vs. <5)	SIR (i) 2.31 (1.32-3.75, 16); (ii) 2.22 (0.72-5.19, 5); HR (iii) 5-25 mg/L, 1.54 (0.38-6.26, 6); 25-50 mg/L, 2.41 (0.49-11.98, 3); > 50 mg/L, 3.28 (0.73-14.91, 4)	No analyses by duration of exposure or cumulative exposure. Findings were influenced substantially by the Finnish data which contributed 80% of the person-time at risk. An earlier related Finnish report (Antilla et al, 1995) found an overall SIR of 2.35 (1.06-4.46, 9)
Charbotel et al, 2013	Age-matched population-based case-control study in France (67 cases, 67 controls)	Not stated 92% for cases, 97% for controls	Cases recruited by volunteer gynaecologists working in the Arve Valley	(a) Interviews on job histories; task-exposure matrix then applied.	(i) OR 1.51 (0.42-5.41, 17); (ii) <5 yrs, 4.32 (0.51-36.24, 11); 5-10 yrs, 1.36 (0.18-10.65, 4);	Analysis adjusted for nulliparity, history or genital or anal wart, interval between first period and first sexual relation, number of sexual partners, and body mass

Reference	Study Population and Sampling	Follow-up interval; completeness	Case Ascertainment	a) Exposure Assessment b) Comparison	Relative Risks (95% confidence intervals, number of events)	Additional Information
				(b) (i) Ever exposed; (ii) years exposed ; (iii) Cumulative exposure (ppm-years) ('Low' 1-90, 'medium', 91-250, 'high' $\geq$ 251)	$\geq$10 yrs, 0.08 (0.003-1.78, 2) (iii) Low, 2.21 (0.37-13.34, 10); medium, 1.62 (0.16-16.82, 4); high, 0.80 (0.10-6.63, 3)	index

Notes:

Abbreviations: U-TCA = Urinary trichloroacetic acid a metabolite of TCE; TCE = trichloroethylene; JEM = job exposure matrix; SMR -= Standardised mortality ratio; SIR = Standardised incidence ratio

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