Industrial Injuries Advisory Council Information note

Bladder cancer and mineral oils

May 2015

1. During a horizon scanning exercise the Industrial Injuries Advisory Council (IIAC) identified bladder cancer and work involving exposure to mineral oils as a potential topic for review. This review stemmed from the Council's consideration of the Health and Safety Executive's (HSE) identified priorities for cancer, the results of the HSE's commissioned research project *Cancer Burden in the UK* by Rushton et al, 2010 (HSE Executive Board meeting paper HSE/12/36) and a report by the International Agency for Research on Cancer (IARC).

2. Mineral oils (also known as base oils, mineral base oils or lubricant base oils) are chemical substances prepared from naturally occurring crude petroleum oil[1]. Crude oil is distilled first at atmospheric pressure and then under high vacuum to yield vacuum distillates and residual fractions that can be further refined to mineral oils. Mineral oils are complex mixtures of aliphatic hydrocarbons, naphthenics, and aromatics, the relative distribution of which depends on the source of the oil and the method of refinement[2]. End-use products contain a variety of additives, and contamination by other agents generally occurs during use. Agents which are carcinogenic, or suspected to be carcinogenic, include polycyclic aromatic hydrocarbons (PAH) (particularly benz[a]pyrene), nitrosamines, chlorinated paraffins, long-chain aliphatics, sulfur, N-phenyl-2-naphthylamine and formaldehyde.

3. In 2012, IARC classified untreated or mildly treated mineral oils as a group 1 (established) human carcinogen[1]. This evaluation was not based specifically on studies of bladder cancer, and the report concluded that "there has been sporadic and inconsistent support for an association with bladder cancer". Rather, the evaluation was based on sufficient evidence of skin cancer in humans, and sufficient evidence of cancer in experimental animals. The animal evidence relates to untreated vacuum distillates, acid-treated oils, and aromatic oils, mildly hydro-treated oils, and used gasoline engine oil. There is also weak evidence on the mechanisms involved, based on genotoxic (mutagenic) activity of mineral oils in bacteria and a single cytogenetic study of glassworkers exposed to aerosols of mineral oils.

4. The Council's Research Working Group conducted a literature review, focussing on research reports on bladder cancer and mineral oils. Account was also taken of two key reviews (Calvert *et al.*[3] and Tolbert[2]) together with key reviews in the IARC monograph. All studies considered in the Council's search are summarized in the accompanying Table.

5. Overall, a number of published studies have shown excess risks of bladder cancer in turners, foundry workers, sheet-metal workers, drill press operatives and blacksmiths[4-6], in workers exposed to cutting and lubricating oils[4,7], and in machinists[8]. The associated agents are the cutting and lubricating oils[4] These sometimes contain aromatic amines as additives and N-nitrosamines can be found in the semi-synthetic and synthetic cutting fluids.

6. Calvert *et al.*[3] reviewed the literature on cancer risks in workers exposed to metal-working fluids, and concluded that there is substantial evidence for an increased risk of cancer at several sites including the bladder. Calvert *et al.* reported relative risks for length of exposure [3]. With increased duration of exposure the relative risk (RR) for bladder cancer was 2.9 for drill press operatives[5], 2.3 for turners[4] and 3.1 for machine tool operators[9].

7. Tolbert[2] also reviewed the evidence on oils and cancer. The review was restricted to occupations involving substantial dermal and inhalational exposure and for which an epidemiologic literature exists: metal machining, print press operating, and cotton and jute spinning. The heterogeneity of this exposure makes epidemiologic study difficult and meta-analysis inappropriate. Nonetheless, several associations emerge from the literature with varying degrees of support. There is clear evidence that early formulations of mineral oils used in cotton and jute spinning and in metal machining were carcinogenic to the skin. Associations of mineral oil exposure with laryngeal and rectal cancer have received some support in the literature, particularly with respect to straight oils (oils that do not contain water). Evidence is suggestive that grinding operations (which can entail either mineral oil-based or ethanolamine-based fluids) are associated with excess risk of cancer of the oesophagus, stomach, and pancreas. A number of bladder cancer case-control studies have noted an association with work as a machinist. Tolbert also noted that the PAH and nitrosamine content of current formulations is lower than in the past and the implications of these changes in composition to the carcinogenicity of the formulations are not yet known.

8. A number of more recent studies have been published since the reviews of Calvert and Tolbert.

9. Hours *et al.* [7] found an elevated odds ratio (OR) of 2.6 (95% CI (Confidence Interval) 1.2-1.4) for bladder cancer cases exposed to cutting fluids after adjusting for socio-professional status and tobacco smoking, compared with general population referents.

10. Friesen *et al.*[10-12] have conducted several studies of cancer risks in workers exposed to oils. They concluded that increased bladder cancer risk was associated with straight metalworking fluids (MWFs) but not other types of metal working fluids (soluble, synthetic), or with other exposures in the industry. Increased bladder cancer risk was

associated with straight MWFs but not with any other exposure. The hazard ratio increased with cumulative exposure to a maximum of 2-fold observed at 75 mg/m^3-year straight MWF exposure (lagged 20 years).

11. Dryson *et al*.[13], on the other hand, found no association between work as a sheet metal worker and bladder cancer (OR 0.39, 95% CI 0.15–1.00) in a case-control study from New Zealand.

12. Colt *et al*.[14] conducted a case-control study of occupation and bladder cancer in Northern New England. Male precision metalworkers and metalworking/plastic working machine operators had significantly elevated risks and significant trends in risk with duration of employment (precision metalworkers: OR 2.2, 95% CI 1.4 to 3.4, p(trend) = <0.01; metalworking/plastic working machine operators: OR 1.6, 95% CI 1.01 to 2.6, p(trend) = 0.05). Men reporting use of metalworking fluids (MWF) had a significantly elevated bladder cancer risk (OR 1.7, 95% CI 1.1 to 2.5).

13. Overall, these studies indicate clear evidence that there is an increased risk of bladder cancer arising from occupational exposure to mineral oils. However, as may be seen from the Table, the relative risks are not consistently greater than doubled (the threshold the Council normally applies in recommending prescription). Against the studies mentioned above are numerous risk estimates that have fallen short of a doubling (e.g. reports by Decoufle, 1978[15]; Jarvholm *et al.*, 1987[16]; Leon *et al.*, 1994[17]; Delzell *et al.* 1993[18]; Greene *et al*., 1979[19]; Zoloth *et al*., 1986[20]; Silverstein *et al.* 1988[21]; Park *et al.*, 1988[22]; Silverman *et al*. 1983[8]; Coggon *et al*. 1984[23]; Vineis *et al*. 1985[24]; and Siemiatycki *et al*., 1987[25]). Thus, when the evidence is considered in its entirety, there is not consistent evidence of a RR which is greater than two.

14. There remains the possibility that there may be consistently doubled risks in some subgroups of workers exposed to oils, but the available evidence does not provide enough information on specify types of exposures (e.g. straight oils, cutting oils, lubricating oils) to reach firm conclusions.

15. In summary, in considering whether to recommend to Minister that a condition and its exposure is eligible for prescription IIAC seeks consistent and robust evidence that the risk of a particular disease is greater than doubled in exposed workers compared with a suitable comparator population. This threshold has not been reached for occupational exposure to mineral oils and bladder cancer. IIAC has, therefore, concluded that this exposure-outcome circumstance does not warrant prescription. The Council will, however, keep the topic of cancer and occupational exposure to mineral oils under review.

This information note contains technical terms which are explained in the accompanying glossary.

References

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Table.Summary evidence about the risks of bladder cancer from exposure to mineral oils			
Research paper	**Study location and sample size**	**Description of sample**	**Relative Risks or comments**
Cohort studies			
Decoufle, 1978[15]	Michigan, USA, n=5,189	White male workers at metal machining plant with five or more years of exposure to oil mist	RR 1.2, CI not reported
Jarvholm and Lavenius, 1987[16]	Sweden, n=792	Grinders and turners at bearing ring plant	RR 1.0, 95% CI 0.4 to 2.2
Leon *et al.*, 1994[17]	England, UK, n=9,500	Unskilled rotary process operators	RR 1.2, 95% CI 0.5 to 2.7
Coggon *et al.*, 1984[23]	England, UK, n=291	Men with high exposure to printing inks	RR 5.0, 95% CI 1.0 to 25.8
Delzell *et al.*, 1993[18]	Michigan and Ohio, USA, n=123,232	Automotive manufacturing workers	SMR 1.0, 95% CI 0.7 to 1.2 (white) SMR 0.8, 95% CI 0 to 1.4 (black)
Friesen *et al.*, 2009[11]	Michigan, USA, n=21,999	Male automotive workers, followed from 1985 through 2004	"Increased bladder cancer risk was associated with straight MWFs but not with any other exposure. The hazard ratio increased with cumulative exposure to a maximum of 2-fold observed at 75 mg/m(3)-year straight MWF exposure (lagged 20 years)"
Zhao *et al.*, 2005[26]	California, USA, n=6,107	Workers employed at an aerospace company between 1950 and 1993	Looked at cancer (including bladder) and mineral oil exposure – no mention of association found between mineral oil and bladder cancer
Mortality studies			
Greene *et al.*, 1979[19]	USA, n=347	Men in general printing	PMR=1.4, 95% CI 0.9 to 2.2
Vena *et al.*, 1985[27]	New York, USA, n=769	Not specified	PMR=7.3, CI not reported
Zoloth *et al.*, 1986[20]	USA, n=1,401	Men in general printing	PMR=1.1, 95% CI 0.06 to 2.0
Silverstein *et al.*, 1988[21]	Connecticut, USA,	White male ball bearing plant workers	PMR=1.3, 95% CI 0.8 to 2.2

	n=1,766		
Park *et al.*, 1988[22]	Connecticut, USA, n=702	White male ball bearing plant workers	PMR=0.24, 95% CI 0.1-1.31
Dolin *et al.*, 1992[28]	Coastal and estuarine regions of England and Wales, n=2,457	Males aged 25-64 during 1965-1980	"Use of a job-exposure matrix revealed elevated risk for occupations in which most workers were exposed to paints and pigments, benzene and cutting oils."
Park and Mirer, 1996[29]	Detroit, USA, n=1,870	White male workers engine plant 1 White male workers engine plant 2 Grinding with straight oil Machining or heat treatment employment	PMR=2.16, 95% CI 0.79 to 4.70 PMR=1.13, 95% CI 0.37 to 2.64 PMR=2.99, 95% CI 1.15 to 7.77 PMR=2.86, 95% CI 1.14 to 7.18
Case-control studies			
Howe and Lindsay, 1980[30]	Canada, n= 415,309	Ever metal machinist	OR=2.7, 95% CI 1.1 to 7.7
Cartwright, 1982[31]	England, UK, n=991	Workers exposed to high speed presses	OR=3.1, 95% CI 1.4 to 6.8
Silverman *et al.*, 1983[8]	Detroit, MI, USA, n=2,100	All male machinists Tool and die workers	OR=1.1, 95% CI 0.8 to 1.5 OR=1.5, 95% CI 0.9 to 2.7
Coggon *et al.*, 1984[23]	United Kingdom, n=291	Exposure to cutting oils	OR=1.5; 95% CI 0.8-2.8
Vineis and Magnani, 1985[24]	Italy, n=512	Ever employed in machine tools 6 months or more	OR=1.5, 95% CI 0.7 to 3.3
Schifflers *et al.*, 1987[32]	Belgium, n=74	All metal workers Turners	OR=2.5, 95% CI 1.3 to 4.7 OR=2.6, 95% CI 0.9 to 7.2
Steenland, 1987[33]	Ohio, USA, n=1,250	Ever grinding machine operator Ever machinist	OR=2.0, CI not reported OR=0.7, CI not reported
Siemiatycki *et al.*, 1987[25]	Montreal, Canada, n=3,726	Ever exposed to cutting oils	OR=1.2, 95% CI 1.1 to 1.6
Malker *et al.*, 1987[34]	Sweden, n=11,702	Toolmaker or machinist in 1961-79	OR=1.2, CI not reported
Claude *et al*., 1988[4]	Germany	Ever turner Ever metal worker	OR=2.3, 95% CI 1.0 to 5.6 OR=0.8, 95% CI 0.5 to 1.1

Gonzalez *et al.*, 1989[35]	Spain, n=497	Ever toolmaker 6 months or more Ever machinery adjuster, assembler or mechanic 6 months or more	OR=0.8, 95% CI 0.5 to 1.1 OR=1.9, 95% CI 1.2 to 2.8
Silverman *et al.*, 1989a[5]	USA, n=2,100	Ever machinist 6 months or more Ever drill press operator 6 months or more Ever metal machinery workers Ever printers (all results are for white males)	OR=1.3, 95% CI 1.0 to 1.7 OR=1.4, 95% CI 0.9 to 2.1 OR=1.1, 95% CI 0.6 to 1.9 OR=0.8, 95% CI 0.5 to 1.2
Silverman *et al.*, 1989b[36]	USA, n=126	Non-white males, metal machinery worker	OR=1.1, 95% CI 0.6 to 1.9
Ugnat *et al.*, 2004[37]	Western Canada, n= 549 cases, 1099 controls	Exposure at work to mineral, cutting or lubricating oil	OR=1.6, 95% CI 1.1 to 2.6
Dryson *et al.*, 2008[13]	New Zealand n=213 cases, 471 controls	Sheet metal workers	OR 0.39 [95%CI 0.15–1.00]
Colt *et al.*, 2011[14]	Northern New England, USA, n=1158	Male metal precision workers Male metalworking/plastic working machine operators Men reporting use of metalworking fluids (MWF)	OR 2.2, 95% CI 1.4 to 3.4 OR 1.6, 95% CI 1.0 to 2.6 OR 1.7, 95% CI 1.1 to 2.5

Glossary

Types of study

Case-control study: A study which compares people who have a given disease (cases) with people who do not (controls) in terms of exposure to one or more risk factors of interest. Have cases been exposed more than non-cases? The outcome is expressed as an **Odds Ratio**, a form of **Relative Risk**.

Cohort study: A study which follows those with an exposure of interest (usually over a period of years), and compares their incidence of disease or mortality with a second group, who are unexposed or exposed at a lower level. Is the incidence rate higher in the exposed/more exposed workers than the unexposed/less exposed group? Sometimes the cohort is followed forwards in time ('prospective' cohort study), but sometimes the experience of the cohort is reconstructed from historic records ('retrospective' or 'historic' cohort study). The ratio of risk in the exposed relative to the unexposed can be expressed in various ways, such as a **Relative Risk**, or **Standardised Mortality Ratio.**

Measures of association

Statistical significance and P values: Statistical significance refers to the probability that a result as large or small as that observed, or more extreme still, could have arisen simply by chance. The smaller the probability, the less likely it is that the findings arise by chance and the more likely they are to be 'true'. A 'statistically significant' result is one for which the chance alone probability is suitably small, as judged by reference to a pre-defined cut-point. (Conventionally, this is often less than 5% ($P<0.05$)).

Relative Risk (RR): A measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. *A value greater than 1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or **confounding**.) Various measures or proxies of RR exist, some of which are mentioned in this report: the **Odds Ratio**, **Hazard Ratio**, **SMR** and **PMR** (see below).

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 ratios and relative risks are numerically very similar, so the OR can be thought of as a **Relative Risk**

Hazard Ratio: A form of **Relative Risk** used in survival analysis (a branch of statistics that deals with analysis of the elapsed time until events occur); the ratio of the *hazard rate* in the exposed to the unexposed (where a *hazard rate* represents the event rate at a given time, assuming survival until that time or beyond).

Standardised Mortality Ratio: 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).

Proportional Mortality Ratio: A measure of the strength of association between exposure and mortality; another form of **Relative Risk** in which the outcome is death. The PMR is the proportion of deaths in the study population attributed to a specific cause divided by the proportion of deaths in the general population attributed to that same specific cause.

By convention, SMRs and PMRs are usually multiplied by 100. Thus, an SMR (or PMR) of 200 corresponds to a RR of 2.0. For ease of understanding in this report, SMRs and PMRs 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.

Other epidemiological terms

Confidence Interval (CI): The **Relative Risk** reported in a study is only an *estimate* of the true value in the underlying population; a different sample may give a somewhat different estimate. The CI defines a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. The commonly chosen 95%CIs give a range in which there is a 95% chance that the true value will be found (in the absence of bias and confounding). *Small studies generate much uncertainty and a wide range, whereas very large studies provide a narrower band of compatible values*.

Confounding: Arises when the association between exposure and disease is explained in whole or part by a third factor (confounder), itself a cause of the disease, that occurs to a different extent in the groups being compared.

For example, smoking is a cause of lung cancer and tends to be more common in blue-collar jobs. An apparent association between work in the job and lung cancer could arise because of differences in smoking habit, rather than a noxious work agent.

Studies often try to mitigate the effects of ('control for') confounding in various ways such as: restriction (e.g. only studying smokers); matching (analyzing groups with similar smoking habits); stratification (considering the findings separately for smokers and non-smokers); and mathematical modelling (statistical adjustment).

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