OXFORD

Occupational Medicine, 2023, **73**, 300–303
https://doi.org/10.1093/occmed/kqad086

Commentary

Organic solvents and Multiple Sclerosis: the doubled risk dilemma

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Background Compensation for industrial disease in the UK may be obtained in two ways. A State scheme includes a list of accepted associations between occupations and diseases with evidence of a causative association. Epidemiological evidence of a doubled risk in the occupation concerned is usually required. This takes no account of variation of exposures within occupations, excluding many occupations where risk is less than doubled. In such cases, compensation for a perceived industrial illness may be obtained in Civil Courts, where excessive exposures can be considered.

Aims To show that in the Civil Courts evidence of excessive exposure may lead to compensation for diseases which are not yet compensable as Industrial Injuries in the UK and to draw attention to the association of multiple sclerosis (MS) with solvent exposure.

Methods We report the case of an industrial spray painter, who claimed his MS had been caused by high-level exposure to organic solvents, and our examination of the epidemiological evidence submitted.

Results The painter received compensation by an out-of-court settlement, despite the overall epidemiological risk in relation to solvent exposure having been shown to be less than doubled. The evidence hinged on individual risk in relation to high exposure, genetic susceptibility and demonstration of a plausible mechanism.

Conclusions High organic solvent exposure may lead to the development of MS. Those giving evidence in Court need to be able to discuss the epidemiological and toxicological issues in relation to exposure in the individual case.

Introduction

Doctors are expected to ask patients about their work for two reasons—health's influence on ability to work and work's influence on health, but the question 'What is your job?' is often insufficient. What matters is exposure to hazards and its intensity. In industry, dose of a toxic agent is estimated from exposure, the product of duration and concentration. This may be obtained from detailed occupational histories and knowledge of the materials used and individual work practices. Such estimates are essential to exposure–response relationships in epidemiology.

Many occupational epidemiological studies have relied simply on the duration of employment as an indication of exposure. However, the reality in industry is that exposure concentrations vary widely, and may be extreme, so duration is a weak indicator of dose. In large epidemiological studies, occasional excessive individual exposures may have little impact on the overall results; such individuals, although *epidemiological* outliers, are *clinically* those most likely to suffer harm. If there is a small, but statistically significant, say 15%, increase in risk of a disease in the population studied, that part of the population that generated the 15% risk increase is likely to include the most susceptible and highly exposed individuals. A 15% increase in risk in a population, which may be thought of as a small increase, will obviously understate the risk of highly exposed and/or susceptible individuals. This is important in the case of individuals seeking compensation for work-related illness as, in the UK, no-fault industrial injuries compensation (IIC) is not usually available unless employment in the industry in question has been shown epidemiologically to entail a doubled (100% increase) risk of the disease [1].

This exclusive doubled risk criterion is justified in order to recognize some diseases, such as chronic obstructive pulmonary disease in coal miners, where the condition is common in the non-exposed population, yet there is a statistically significant increase in risk in the industrially exposed population. A doubled risk in the overall exposed population makes it possible to argue that anyone exposed to the toxic agent in that population is more likely than not to have acquired the disease as a result of exposure and may therefore be eligible for compensation. To make this case, however, requires a considerable

Key learning points

What is already known about this subject:

- Multiple sclerosis is an auto-immune disease with both environmental and genetic risk factors.
- Epidemiological studies have shown exposure to organic solvents at work increases risks of multiple sclerosis by up to 50%.
- Toxicological studies have shown links between lung inflammation and effects on the brain that could trigger multiple sclerosis.

What this study adds:

- Within an epidemiological population, exposures to toxic factors may vary considerably.
- Even where the overall risk of disease is less than doubled, those with proven high exposures may be able to obtain compensation through civil Court action.
- Detailed exposure estimates and understanding of toxicology are more relevant than clinical knowledge in doctors venturing to give evidence in Court in such cases.

What impact this may have on practice or policy:

- Increase awareness among doctors of the association of chronic neurological diseases with toxic workplace exposures.
- Encourage research into multiple sclerosis to a different concept of understanding its causation.
- Remind regulatory bodies and employers to ensure compliance with workplace standards for organic solvents.

amount of epidemiological evidence in relevant industries, and for that evidence to contain convincing data on exposure–response relationships, criteria that are rarely satisfiable.

The consequence of this is that relatively few chronic conditions in which occupational exposure may be a risk factor get onto the official list of scheduled diseases in the UK and, thus, many workers exposed to dangerous levels of toxic agents in their work are excluded from obtaining no-fault Government-funded compensation. Claimants may then take civil legal action against the employer. We illustrate this by commenting on a legal case of MS in an industrial painter and the key epidemiological evidence given at the trial.

Methods

An industrial painter (the plaintiff) developed MS 10 years after starting work. He had been exposed frequently to concentrations of organic solvents, often in confined spaces with inadequate protection, and recalled having regularly suffered acute symptoms of solvent intoxication (dizziness, euphoria and headaches). After hearing the evidence in Court, his employer (the defendant) agreed to an out-of-court settlement resulting in compensation for the plaintiff.

Since it may surprise many doctors that workplace exposure may cause MS, we explain and re-examine the evidence that led to this outcome. The logic of the plaintiff's argument was that (1) organic solvents, notably trichloroethylene and dichloromethane, are of known neurotoxicity, associated with a wide range of responses [2,3]; (2) the plaintiff had regularly suffered symptoms characteristic of acute intoxication at work; (3) his exposures were estimated to have frequently exceeded regulated concentrations; (4) such exposures had been shown epidemiologically to be a risk factor for MS [4] and (5) a plausible mechanism can be demonstrated relating organic solvent exposure to the risk of MS. The defendant challenged the evidence in that meta-analyses had shown only a significant 50% increase in the population risk of developing MS as a result of workplace exposure to organic solvents [5,6], too low to suffice for compensation under the rules of the IIC scheme [1].

The plaintiff argued that recent Swedish research had revealed a highly significant exposure–response relationship in terms of average hours of work per week with solvents and the risk of MS [4]. This work also demonstrated that Human Leukocyte Antigen (HLA) genes modified the strength of the environmental risk factors; the plaintiff's genetic susceptibility became an issue in the case. Crucially, the plaintiff demonstrated that his personal exposure, estimated by an expert occupational hygienist, would have ranked among the highest in the population enrolled in this critical study. This paper reports a re-examination of the Swedish data by two authors of the original paper (A.H. and L.A.) as part of their continuing ethically approved study and those who gave expert evidence for the plaintiff in the case.

Results

The Swedish paper on which the case rested had reported an epidemiological study of 2042 incident cases of MS and 2947 controls and had shown a significant overall 50% increase of risk (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.2–1.8, $P = 0.0004$) associated with any exposure to organic solvents, with a significant exposure duration–response relationship [4]. The risks were also strongly related to HLA type and smoking. After the case concluded, the original authors re-examined these relationships among an expanded population (5980, of whom 2544 were cases with MS). The increase in risk remained (OR 1.48; 95% CI 1.21–1.81). Exposure was estimated in average hours working with solvents per week. Those below 20 hours had an OR of 1.35 (1.07–1.71) while exposure of 20+ hours had an OR of 2.03 (1.21–3.41).

In this re-analysis, the interactions between HLA status, smoking and solvent exposure remained strong. For those subjects with HLA DRB1*15:01 and exposure for 20+ hours per week, compared with non-exposed subjects, the OR was 7.01 (2.68–18.70). From the earlier paper [4], those with highest risk of MS were smokers positive for DRB1*15:01 and negative for A*02:01. Among the population with this combination of risk factors, 11 of the 2544 MS cases but none of the 3436 controls had exposures of 20+ hours per week.

The plaintiff's argument was strengthened by a plausible causative mechanism. Evidence suggests that aerosols of organic solvents can inflame lung and cause the release of inflammatory mediators that can access the brain [7–9]. The inhalation route is relevant since smoking, rather than moist snuff, has been shown to confer an excess risk of MS [10,11].

Discussion

The setting of preventive standards for occupational chemical exposure was originally based largely on case reports and animal toxicology but epidemiological evidence is now an important component. This is particularly so for chronic neurological diseases requiring long-term exposure where animal models may not be available. In the case we report, the toxicological evidence for interaction between organic solvents, smoking and HLA genes strongly suggests a plausible mechanism—that these environmental risk factors act on CD8+T lymphocytes [4], the cell type involved in immune-mediated/auto-immune diseases, such as MS, rheumatoid arthritis or Crohn's disease. The exact mechanisms remain unclear, but include induction of pro-inflammatory cytokines, increase in, and reduced regulation of, lymphocytes, and lung inflammation, increasing the likelihood of auto-immunity [4]. Experimental evidence on murine auto-immune encephalitis (EAE) suggests the lung contains potentially auto-aggressive lymphocytes, which can become activated to migrate into the central nervous system and induce auto-immunity [9, 12].

The place of epidemiology requires careful consideration and it is well to be familiar with the viewpoints of Sir Austin Bradford Hill on examining the evidence for a causative association more broadly [13]. Epidemiology demonstrates and quantifies risk in *populations* and is taken with other evidence to examine the likelihood of a causative association for setting preventive exposure standards. If such an association has been shown, the risk to *individuals* will depend on their personal exposure and susceptibility.

Many cases coming to the Courts will have suffered exposures far above the range recorded in most epidemiological studies, and it may be inappropriate to assume that published data include individuals with exposures comparable to that of the claimant. In the case we report, the defendant relied on the requirement for there to be a doubled risk of MS in populations exposed to solvents. When the relevance of individual high exposures was put forward, the employer decided to settle the case rather than wait for judgement. Epidemiology describes relationships between risks and exposure in groups, whereas individuals are subject to their own personal multiple risk factors. The crucial study, in this case, drew attention to three such—HLA type, smoking and high solvent exposures [4].

This case raised several important issues, which have been summarized below, including a warning to doctors who venture to give expert advice on causation of disease.

- Judges rely less on clinical medical status and experience of the condition under litigation, but expect expertise in the epidemiological and toxicological literature concerning its causation.
- Forensic examination may sometimes bring to light convincing evidence of a previously unrecognised cause of disease, can lead to improved regulation in workplaces, and may even provide a stimulus to research into aetiological mechanisms.
- Many diseases remain of unknown aetiology, and virtually, all will have both genetic and environmental contributions. In our experience, few doctors are aware of the evidence associating chronic neurological disease with environmental factors other than head injury [14]. But exposure to pesticides has been shown to increase the risk of Parkinson's disease [15], and evidence from two detailed meta-analyses suggests that exposure to organic solvents significantly increases the risk of MS [5, 6]. There is also some evidence that solvents increase the risk of motor neurone disease [16]. Research on these diseases is primarily focused on genetics, but researchers should also consider the environment and its interactions with genetics, remembering that genes not only influence susceptibility but also influence the metabolism and thus toxicity of many common organic chemicals.

Funding

None declared.

Competing interests

A.S. and K.S. gave expert evidence at the trial, for which they received fees. A.S. donated his, less taxation, to charity.

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