

**The neurobehavioural effects of chronic exposure
to organic solvents**

Industrial Injuries Advisory Council

Position Paper

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Summary

1. The Industrial Injuries Advisory Council commissioned a report from Dr Anne Spurgeon on the neurobehavioural effects of organic solvents as a separate part of its review of the chemical prescribed diseases completed in February 2002 (Cm. 5395). Dr Spurgeon conducted a structured, systematic literature search according to the principles of the evidence-based review process. The report was delivered to the Council in September 2002. The study investigated the development of chronic adverse effects on cognitive functioning, and psychiatric disorders, following long-term occupational exposure to organic solvents.
2. The Council concluded that although chronic long-term exposure to solvents might result in some neurobehavioral changes there was a lack of epidemiological evidence of sufficient strength or consistency to establish the nature or duration of such effects, or to specify an association with one or more definite clinical outcomes of importance. It cannot, therefore, recommend, based on present knowledge, that such exposure should be included in the list of prescribed diseases.

Background and Objectives

3. During its review of the schedule of the prescribed chemical diseases, announced in 1997, the Industrial Injuries Advisory Council (IIAC) felt that the subject of the effects of chronic, long-term occupational exposure to organic solvents warranted individual attention due to the complexity and wealth of scientific literature available.

4. The crux of the debate was whether organic solvents absorbed into the body could cause detrimental changes to the brain and central nervous system sufficient to alter a person's personality and behaviour sufficiently for a psychiatric illness to be diagnosed. If so, which solvents were responsible, at what dose, and which psychiatric conditions might arise and were these reversible or not? The Council commissioned a systematic literature review and analysis of the evidence of neurobehavioural effects of organic solvents from Dr Anne Spurgeon from the Institute of Occupational Health at the University of Birmingham. She completed this in September 2002 and attended a subsequent meeting of the Council to answer questions from the Council members. The Council accepted Dr Spurgeon's report in full. Dr Spurgeon's report was placed on the IIAC website for 3 months for public consultation. This report constitutes a new style of IIAC paper – the “Commissioned paper” – which consists of the results and conclusions from Dr Spurgeon's report, which summarise her key findings, together with the Council's own conclusions and recommendations.

5. The objectives of the commissioned report were to determine from the current literature whether:

- (i) there was evidence for the development of chronic adverse effects on cognitive functioning or psychiatric disorders following long-term occupational exposure to organic solvents
- (ii) the size and nature of any identified chronic adverse effects, together with valid and reliable methods of assessment could be defined
- (iii) the duration and level of exposure associated with any identified chronic adverse effects could be determined
- (iv) it was possible to determine the size of the risk of developing adverse effects on cognitive functioning or psychiatric disorders, associated with long-term occupational exposure to organic solvents.

The legal requirements for prescription

6. The Social Security Contributions and Benefits Act 1992 states that the Secretary of State may prescribe a disease where he is satisfied that the disease:
 - a) ought to be treated, having regard to its causes and incidence and any other relevant 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 the employment can be established or presumed with reasonable certainty.

7. In other words, a disease may only be prescribed if the risk of contracting it in a given occupation is greater than that in the general population, and the link

between the occurrence of the disease, and the person's occupation can be established or presumed with reasonable certainty in each individual case.

8. In practice, the Council first establishes a workable definition of the disease and then seeks scientific evidence to demonstrate that the disease can be attributed to occupational exposure with reasonable confidence in the individual case. The Council can ascribe a disease to a particular occupational exposure in two ways – from the clinical features of the disease or by establishing from epidemiological studies that the occupation carries with it a risk of the condition that is more than double the risk in the general population.

9. The requirement for, at least, a doubling of risk is not arbitrary. It follows from the fact that if a hazardous exposure 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 did so only as a consequence of their exposure while the other 50 would have been expected to develop the disease, even in the absence of the exposure. Therefore, for any individual case occurring in the exposed population, there would be a 50% chance that the disease resulted from exposure to the hazard, and a 50% chance that it would have occurred even without the exposure. By establishing that the risk is more than doubled the probability of causation lies in favour of the occupational exposure and can be attributed to the occupation with reasonable certainty.

Method of investigation

10. A structured, systematic literature search of the neurobehavioural effects of chronic, long-term occupational solvent exposure was completed according to the principles of the evidence-based review process by Dr Anne Spurgeon of the Institute of Occupational Health at the University of Birmingham. In all, 7 databases were searched using pre-defined search terms and criteria. The literature search focussed on solvent mixtures – which are the most usual type of occupational exposure encountered and on which the majority of literature is based.

11. The initial search identified 206 papers of which 123 were retained following application of inclusion and exclusion criteria. 58 papers reported studies involving neurobehavioural testing of solvent-exposed workers. Of these, 39 also covered reported symptoms. A further 16 papers were based exclusively on reports of symptoms. 18 papers were identified which described case series and a further 9 papers reported on follow-up studies of diagnosed patients. 19 papers reported cohort or case-referent studies. Finally, 3 papers discussed diagnostic criteria and case identification in the context of the wider European experience.

12. Details of each type of study were presented in a series of Tables and the data were evaluated in the light of the objectives of the review. Results were discussed in 3 sections (i) studies involving neurobehavioural testing (ii) studies involving questionnaire data on symptomatology (iii) cohort and case-referent studies of neuropsychiatric illness. Section (iii) also contained a discussion on case

definition and diagnostic criteria and included reference to case series and follow-up studies.

Results

(i) Neurobehavioural studies

13. A total of 58 studies were identified which involved neurobehavioural testing of active workers and one of retired (non-patient) workers. The majority of these studies were cross-sectional in design, either involving a comparison of the performance of exposed workers and a control group or investigating the relationship between test performance and a measure of exposure in a single group of exposed workers. On the basis of criteria Dr Spurgeon developed from EU recommendations on the evaluation of neurobehavioural studies, 33 studies were judged to be of good methodological quality. Taking these studies alone, the weight of the evidence was felt to support the view that long-term exposure to organic solvents can result in impairment of cognitive functioning. However, the wide variation in the tests used and in the approaches to assessment of exposure did not allow any conclusions to be reached on the size or specific nature of the effect, or on the duration of exposure required to produce that effect. It was also noted that the studies included a number of different occupational groups exposed to a variety of solvent mixtures. In situations of mixed exposure it proved difficult to determine the relative contributions of the different components of the mixture to any identified neurobehavioural effects.

14. Only 4 longitudinal studies were identified and only one of these was considered useful for the purposes of the current review. This study, (Nordling Nilson, 2002)

consisted of an 18 year follow-up of a group of 50 floor-layers and 50 referents originally studied in a cross-sectional investigation in 1986. The follow-up study identified a significant effect on cognitive functioning which appeared to interact with age in that it occurred only in the sub-group over the age of 55 years. Although only small numbers of subjects were involved, the superiority of longitudinal over cross-sectional data makes this the most persuasive evidence of solvent-related effects which can be derived from the neurobehavioural data.

(ii) Symptomatology studies

15. A total of 55 studies were identified which reported results describing symptomatology, mainly in relation to mood or mental health. The majority used at least one questionnaire which was standardised in the sense that its original publication was accompanied by data on validity and/or reliability. The studies were exclusively cross-sectional in design. Those which used a questionnaire which was purpose-developed to assess general neurotoxicity (mainly the Q16) reported a high percentage of positive findings. Those which used measures developed in other contexts, to assess specific psychiatric disorders such as anxiety and depression, reported fewer effects. Several authors reported exposure-effect relationships. The most useful study in this respect in Dr Spurgeon's view was that carried out by Chen *et al* (1999) in UK dockyard painters which identified a significant increased risk of a high level of symptom reporting with increasing duration of exposure (RR 2.27 for <5 years exposure, rising to 3.41 for >15 years exposure).

(iii) Case-definition

16. Studies involving neurobehavioural testing or symptom reporting appear to have achieved only limited success in terms of defining the specific nature of the adverse effects of solvent exposure. Reports of patient investigations were considered as an alternative source of information in this respect. 18 such investigations were identified but none provided evidence of a consistent pattern of effects which would, for example, be identifiable from the type of information sources typically employed in cohort and case-referent studies. Follow-up studies of diagnosed cases were similarly uninformative in this respect. The results of follow-up studies were fairly consistent in demonstrating that the test results of patients remain stable following original diagnosis. This was interpreted by most authors included in the review as evidence that effects were unlikely to be progressive if patients were removed from solvent exposure. However, one author, on comparing the follow-up results of patients with those of non-patient referents, found no differences after adjustment for potential confounders, leading him to question the original diagnosis (Gade *et al*, 1988).

17. Two international workshops have been convened (both in 1985) in an attempt to reach a consensus on disease classification and diagnostic criteria for conditions associated with long-term solvent exposure. These meetings reached broadly similar conclusions although there were some classificatory differences. At this point most countries appeared to adopt the term Chronic Toxic Encephalopathy (CTE) to describe the condition. However recent surveys (van der Hoek *et al*, 2001; Triebig and Hallermann, 2001) carried out across EU member states have revealed a lack of application of either of the classification systems or of the diagnostic criteria, together with wide variation in assessment methods and

interpretation of results. Partly as a consequence of this there continue to be large differences between countries in terms of the number of diagnosed cases.

(iv) Cohort and case-referent studies

18. Cohort and case-referent studies have tended to focus on 2 types of case-definition, those relating to psychiatric disorders of various types and those relating to cognitive impairment, notably forms of dementia. The early influential study by Mikkelsen published in 1980 identified a significant increased risk of “dementia” in painters. However, questions about the nature and severity of this condition as defined in the Danish context compared to that in some other countries have arisen over the definitions used in this study. 4 subsequent case-referent studies failed to find any association between solvent exposure and Alzheimer’s disease, though one study in the USA did find that males diagnosed with Alzheimer’s were significantly more likely to have had previous solvent exposure.

19. 8 case-referent studies were identified which focussed on patients in receipt of disability pensions following diagnosis of a psychiatric disorder. 6 of these studies demonstrated a significantly increased risk associated with previous solvent exposure although the evidence tended to be stronger for psychiatric disorders in general than for any specific conditions. 2 studies which compared younger psychiatric and non-psychiatric hospital admissions did not identify any increased exposure to solvents in psychiatric cases. However, a study of geriatric admissions found that those with a neuropsychiatric diagnosis did, on the basis of questionnaire and interview data, report more previous solvent exposure.

Inevitably questions can be raised in each study about the quality of the information relating to diagnosis and/or solvent exposure, particularly in social and legislative climates where CTE or a similar condition is readily acknowledged. Again, the weight of the evidence tended to support the existence of an effect. However, the particular nature of this was difficult to define.

Conclusions of the systematic review

20. The following conclusions were drawn by Dr Spurgeon in relation to the objectives set:

Objective (i): Whether evidence exists for the development of chronic adverse effects on cognitive functioning or psychiatric disorders following long-term occupational exposure to organic solvents.

21. Taking simply a “weight of evidence” approach the results of studies which involve neurobehavioural testing, and symptom reporting, as well as results from cohort and case-referent studies, suggest that long-term occupational exposure to organic solvents can result in adverse effects on the central nervous system. However, a number of qualifications to this conclusion should be made. These are noted in relation to objectives (ii), (iii) and (iv) below.

Objective (ii): Whether the size and nature of any identified chronic adverse effects, together with valid and reliable methods of assessment be defined from the current literature.

22. Although the published literature on this subject is very large it is difficult to be specific about the nature of any adverse effect beyond a general statement relating to effects on cognitive functioning and mental health.
23. Neurobehavioural studies are the most numerous in this field but the results of these are the least persuasive. These studies use a wide variety of tests and no consistent pattern in the results can be discerned. Most differences in performance between exposed and control groups are very small and their biological or social significance is unclear. Neurobehavioural studies in this field are essentially “broad brush” investigations which can only suggest the possibility of effects, which then require further investigation. It is not possible for studies of this type to provide any more precise information on the nature of cognitive changes which may occur in response to solvent exposure, since this requires a much more detailed theoretically-based approach. No studies using such an approach have so far been carried out.
24. It should also be noted that the dataset contained only one useful longitudinal study. The results of this study suggested effects which were (a) associated with high levels of past exposure and/or (b) interacting with age to produce greater cognitive decline in older workers.
25. Studies which investigate reported symptomatology have provided most consistent evidence of effects when questionnaires developed specifically to screen for neurotoxicity were used. Data on the sensitivity and specificity of these questionnaires (notably the Q16 which has wide application) is currently limited

however. Studies which use questionnaires designed to identify particular types of psychiatric disturbance have produced less consistent results. Case-referent studies appear to have fairly consistently demonstrated an increased risk of general psychiatric disorders in those with previous solvent exposure, but less consistently an association with specific conditions. Information from case series similarly indicates rather general and inconsistent effects on cognitive functioning and mental health.

26. Attempts to reach international consensus on case definition and diagnostic criteria have met with limited success in the sense that recent surveys have indicated wide variation in their application and interpretation. Similarly, there is no universal agreement on appropriate methods of assessment. Unsurprisingly, therefore there are large differences in the number of diagnosed cases in different countries in the European Union.

Objective (iii): Whether the duration and level of exposure associated with any identified chronic adverse effects could be determined from the current literature.

27. The identification of the level or duration of solvent exposure required to produce adverse effects presents considerable difficulties. Criteria agreed at the international workshops included a requirement for at least 10 years exposure for a diagnosis of solvent-related CTE. However, it is difficult to find an evidential basis for this in the literature. For example, effects appear to have been demonstrated in some workers exposed for less than 5 years. The influence of

exposure level versus duration, and how these 2 aspects may interact, is currently unclear. While many studies have demonstrated exposure-effect relationships using a cumulative exposure index (level and duration), it is not possible to discern an adverse effect level from these data.

Objective (iv): Whether it was possible to determine the size of the risk of developing adverse effects on cognitive functioning or psychiatric disorders, associated with long-term occupational exposure to organic solvents.

28. The majority of studies in this field do not present data in terms of the relative risk of developing particular effects. In this respect the only informative studies are the cohort and case-referent studies and the cross-sectional study of symptom reporting carried out by Chen *et al* (1999). The results are suggestive of an increased risk of psychiatric disorders in workers with previous solvent exposure. The results are inconsistent in terms of the size of the risk, with relative risks ranging from less than 2 to more than 5 in some studies. There are numerous methodological aspects of these studies, notably in relation to case identification and exposure classification, which may account for these inconsistencies. Further, the general category of psychiatric disorders is very broad. The question of the influence of the social and legislative climate in the countries concerned on the pattern of disability awards has also been raised. There is little convincing evidence of an association between solvent exposure and an increased risk of Alzheimer's disease and the original Danish investigations (Mikkelsen, 1980; Olson, 1980) remain the only studies to identify an association with "dementia".

The characteristics of this condition, as defined in the Danish context, are unclear but are not regarded as synonymous with Alzheimer's disease.

Chronic exposure to specific single solvents

29. The Council published its Command paper "Conditions due to Chemical Agents" in February 2002 (Cm. 5395) as part of its review of the scheduled list of prescribed diseases. In this report, reference was made to the possible neuropsychiatric effects of benzene, tetrachloroethane, methyl bromide, carbon tetrachloride, trichloromethane and chloromethane. The Council has reviewed the current scientific evidence relating to these specific solvents and has encountered similar problems to those highlighted in Dr Spurgeon's review of solvent mixtures. Whilst the evidence suggests chronic exposure to the solvents mentioned above may result in neurobehavioural effects, these effects were ill-defined and findings were inconsistent between studies.

30. The Council did not find evidence that exposure to any of the solvents resulted in a doubling of risk for any occupational group and so is not recommending prescription for chronic exposure to benzene, tetrachloroethane, methyl bromide, carbon tetrachloride, trichloromethane or chloromethane.

Conclusions of the Council

31. The purpose of this Commissioned paper was to review evidence about chronic, long-term occupational exposure to solvents as possible causes of adverse neurobehavioural changes and psychiatric disorders. To this effect, the Council commissioned a systematic review of the current literature to inform its decisions,

the conclusions of which form the basis of this paper. After a rigorous screening process 162 research articles were selected, including studies using neurobehavioural tests, studies using symptom questionnaires, case-referent studies and cohort studies.

32. The Council concludes that:

- Whilst evidence exists to suggest that impairment of cognitive functioning may occur after long-term occupational solvent exposure, there remains a lack of consistent epidemiological evidence as to the type, duration and amount of exposure to solvents necessary to cause neurobehavioural disorders. Furthermore, there is no consensus on disease definition, causing difficulties with diagnosis for prescription purposes.
- Due to these inherent difficulties the Council is unable to recommend prescription of the neurobehavioural effects of solvent exposure in any occupational group.