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## **Is there an association between exposure to chemicals and chronic fatigue syndrome? Review of the evidence.**

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## **ABSTRACT**

**Background:** Chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) is characterised by persistent or recurrent incapacitating fatigue which can have a considerable impact on the function of the patients. A number of chemical substances have been reported to be associated with fatigue. However, it remains uncertain whether exposure to chemicals at levels usually considered safe is related to chronic fatigue. This paper provides an overview of the existing evidence of association between chemical exposures, particularly in low levels, and CFS/ME.

**Methods:** The Pubmed and the Scopus databases were searched using combinations of relevant terms, including 'chronic fatigue', 'chronic fatigue syndrome', 'chemicals', 'toxicants' and the names of specific 'toxicants' and classes of toxicants. Standard toxicology textbooks were also reviewed.

**Results:** The existing studies were in small number and had many limitations. Most studies were descriptive and only a handful of analytic studies were located, which seldom compared cases of CFS/ME with healthy controls. None of them was prospective and they were commonly prone to selection and information biases. The results are presented under the subheadings: organophosphates and other pesticides/insecticides; carbon monoxide (CO); heavy metals; solvents, ciguatera and other chemicals; and multiple exposures, including in Gulf War troops.

**Conclusions:** The existing evidence remains inconclusive as to the association between exposure to chemicals and chronic fatigue syndrome, and there is therefore a need for further well designed epidemiological studies.

## Introduction and search methods

Fatigue is a subjective and common symptom in daily life and may be a prominent long-term feature of a number of medical and psychiatric conditions. Chronic fatigue syndrome or myalgic encephalomyelitis or encephalopathy (CFS/ME) is characterised by persistent or recurrent incapacitating fatigue, which is not lifelong and lasts for at least 6 months, leading to substantial reduction in previous levels of occupational, educational, social and personal activities (1). Fatigue has a central origin, as opposed to peripheral muscle fatigue, is typically sustained following physical or mental exertion and is accompanied by a number of symptoms such as muscle pain, headaches and cognitive dysfunction. The diagnosis of CFS/ME presupposes the exclusion of known medical causes of chronic fatigue (1).

The public health impact of CFS/ME has probably been largely underestimated, each person with CFS/ME costing on average around £15,000 per year to the UK economy (2). The prevalence is estimated at around 2-4/1000 population (3). It affects both males and females, of all age groups from 5 years olds, and from a wide range of ethnic and socio-economic backgrounds, although most of it presents in young women. It often results in moderate to severe disability (4) and poor quality of life (5).

Population exposure to a number of environmental and man-made substances with the potential to affect bodily functions is increasing, as is the report of a wide range of 'unexplained' illnesses. Media and public interest on CFS/ME and chemical exposures have been high and helped to fuel controversies on the nature and aetiology of the condition. These justify the appropriateness of investigating whether chemicals can cause diseases such as CFS/ME, to ascertain the existing scientific evidence of such possible association and to guide the need for future studies addressing this topic.

A number of chemical substances have been reported to be associated with fatigue, particularly following high levels of exposures (6), as evidenced mainly from studies in occupational health or following high levels of environmental exposures, and animal studies. However, exposures to toxicants are often difficult to establish and not recognized, particularly beyond the acute phase of intoxication. Therefore it is possible that at least some patients diagnosed with CFS/ME actually have the effects of unrecognised chemical toxicity. Nevertheless, whether exposure to chemical substances at levels usually considered safe (particularly if prolonged) can cause chronic fatigue is uncertain.

This paper examines the plausibility and the existing evidence of association between chemical exposures (particularly in low levels) and disease that presents clinically as CFS/ME. It ends with the public health and research implications of the current state of knowledge about the subject. The literature was reviewed from standard textbooks in toxicology and chronic fatigue syndrome; all editions of the Journal of chronic fatigue syndrome; and using 'Pubmed' and 'Scopus' databases. The following key terms were entered: 'chronic fatigue', 'chronic fatigue syndrome' AND 'toxicants' 'chemicals' and the names of specific 'toxicants' or classes of toxicants. The search also included references cited by the articles examined.

## RESULTS

### **The plausibility of the association between chemical exposures and CFS/ME**

It is important to distinguish the effects of 'toxic' from that of lower levels of chemicals. Situations in the former category have been well described and there is no doubt some chemicals can cause fatigue, sometimes prolonged, amidst a number of other symptoms characterizing the effects of unsafe exposure to toxicants. The existing literature on the various chemicals confirms the plausibility of such associations provided a 'source-pathway-receptor' 'cycle' can be established for sufficient amounts of chemicals (7).

The effects of lower doses of chemicals have been much less studied and it is much harder to attribute health outcomes to exposures to lower and continuous levels. If these take place, then it is also possible that the mechanisms leading to health effects would be different from those that occur after higher levels of exposure, and they may be under a higher influence from individuals' susceptibilities than by the agents' primary toxicity.

A range of chemicals are capable of causing ill-health. The mechanisms involved vary according to the specific toxicant, dose, exposure route, absorption, distribution and individual susceptibility factors. Those substances may directly or indirectly affect cellular function, e.g. through mechanisms such as oxidative stress, lipid peroxidation, ischemia, enzyme inhibition, changes in membrane structure and permeability, depletion of ATP and other factors (7). Many of these biological processes have been shown in CFS/ME, although not consistently (8).

## **The evidence of association between exposure to chemicals and CFS/ME**

### *Organophosphates and other pesticides/insecticides*

Organophosphates (OP) are known neurotoxicants with well described long-term neurological effects (9). Pyrethroids, organochlorines, and carbamate pesticides are also toxic to the nervous system (7).

In 1996, Behan described farmers exposed to organophosphate insecticides with behavioural and neuro-endocrine abnormalities identical to patients with typical CFS/ME (10). Thamaz et al. (11) observed a direct relationship between chronic fatigue (CF) scores and levels of exposure to organophosphate pesticides. Kennedy et al. (12) also described patients meeting the diagnostic criteria for CFS/ME following exposure to OP. However, these patients presented lower levels of chronic fatigue, muscle and joint pain and psychiatric morbidity compared to Gulf War (GW) veterans exposed to OP insecticide sprays in the same study. Fernández-Solà et al. (13) described 26 patients meeting the CDC- CFS/ME criteria following work exposure to insecticide products. These patients corresponded to 67% of those attending a toxicology clinic following reported exposure to insecticide products. Exposures were to OP (n=9), pyrethroids (Pi) (n=8) and OP + Pi (n=9), and occurred through fumigation (n=23) or accidental inhalation or skin contact (n=3). Crucially, acute intoxication symptoms were not present, indicating the potential for chronic effects following exposure to low doses. These patients presented acute upper inflammatory symptoms following exposure by fumigation, but no muscarinic or nicotinic manifestations, with later development of CFS/ME. This suggests the mechanism involved in CFS/ME symptom development is independent from acetylcholinesterase inhibition, but rather may involve cholinergic action on more sensitive brain proteins(14).

Richardson (15) described 4 cases of CFS/ME following pesticide poisoning, who in this study presented with acute symptoms. A case control study in the US (16) found exposures to herbicides, pesticides, or insecticides more commonly in CFS/ME cases (of gradual onset) (n=17) than in controls. Another case-control study by Dunstan et al. (17) reported higher levels of serum DDT in CFS/ME patients than in controls without CFS/ME.

Carbon monoxide (CO) poisoning is a recognized cause of fatigue and other symptoms often found in CFS/ME, such as headache, dizziness, nausea and flu-like symptoms (18, 19), which may occur following chronic, often undetected exposures (20). Report and severity of cognitive symptoms have been directly related to levels of CO found in home environments (21).

## *Heavy metals*

Mercury and lead are well known neurotoxicants, which have been linked to CFS/ME.

**Mercury:** Mercury toxicity has been described in occupational groups such as dentists (22) and also in coastal and riverine populations in areas of high levels of fish contamination (23). An association of amalgam filling and mercury has been claimed, and severe fatigue identified in 32% of patients with chronic mercury toxicity in one study (24). However, the burden of evidence indicates a lack of association between amalgam fillings and CFS/ME (25).

**Lead:** Lead is another neurotoxicant which has been claimed to be associated with CFS/ME (26). Their effects on cognitive function, particularly in children have been widely reported and continue to cause public health concerns.

**Nickel:** A relationship between heavy metals and CFS/ME is supported by the finding of nickel allergy assessed by patch testing in 36% of patients with CFS/ME, particularly in women (n=50), which was significantly higher than in controls (19%, n=73) (27). Furthermore, a history of contact dermatitis has been obtained from 52% of 204 women with chronic fatigue and no signs of immune disorders (28).

## *Solvents, ciguatera and other chemicals*

Racciatti et al. (29) found more severe immune abnormalities (significantly lower CD4/CD8 ratios and reduced NK CD56+ cell counts) in 5 cases of CFS/ME following work related exposure to solvents and other chemicals (n=3) or ciguatera poisoning (n=2), compared with 5 cases of CFS/ME without history of exposure to toxins. However, association between solvents and CFS/ME has not been confirmed in a small case control study in the metropolitan area of Atlanta (US) (16). Ciguatera poisoning had been previously described to be associated with a chronic condition which is indistinguishable from CFS/ME (30).

## *Multiple exposures, including in Gulf War troops*

Many of the studies investigating the association between CFS/ME and chemicals assessed multiple exposures and were not able to depict the effect of individual substances. For example, psychiatric patients with CFS/ME (n=33) from a private clinic were rated as having significantly higher levels of exposure to toxic substances than controls without CFS/ME matched by age, gender and psychiatric diagnosis (n=79) (31). Interestingly there were 8 (17%) fine art painters in the CFS/ME group and 4 (5%) in the control groups, suggesting a potential role for specific exposures.

In another study, 46 patients (cases) with neurological symptoms and a history of long term exposure to biocides, organic solvents and/or heavy metals were compared with 50 patients with neurological diseases but without such exposures (controls) (32). The neurological symptoms, including fatigue, difficulty concentration and pain were more severe in patients with history of exposure than in those without exposure history (n=96) (32).

Troops deployed to the Gulf War represent a sizable group of individuals with multiple exposures to environmental factors, including a number of toxicants. During the Gulf War, troops have been exposed to complex chemical mixtures, including organophosphate pesticides, anti-nerve agents, carbamates and possibly nerve and blister agents (33). This group of previously healthy young adults have experienced an excess of ill health (34). Chronic fatigue syndrome, as defined by CDC-criteria was identified in nearly 16% members of the Veteran Affairs' Gulf War Registry (35). Ozakinci et al. (36) reported that a large number of US troops deployed to the Persian Gulf continued to suffer from ill-health years after deployment, including various symptoms that are found in CFS/ME. However, the aetiology of their illness has been controversial and no evidence for a single toxic agent causing their symptoms has been found. Their exposures to intense physical and particularly emotional stress has been claimed to explain at least part of their symptoms (34). This illustrates the difficulties in determining causality in situations of multiple exposures, where mild traumatic brain injury and emotional stress may act as strong confounders or effect modifiers.

## DISCUSSION

The recent UK NICE guidance established diagnosis and management guidelines for CFS/ME, but acknowledges the scarcity of evidence, particularly in relation to its causes and treatment (3).

The existing literature links ill health to a number of toxicants, and a small number of reports have claimed symptoms that are indistinguishable from CFS/ME following exposure to chemical substances. However, the existing studies are in small number and have many limitations. Most are descriptive and only a handful of analytic studies were located, which seldom compared cases of CFS/ME with healthy controls. None of them was prospective and they were commonly prone to selection and information biases.

The studies reviewed relied by and large on patients' reports of exposure, sometimes occurring years before the study, rather than on objective measurements. This may have led to bias, as recall may be influenced by the diagnosis given or perception of association between ill health and exposure. In addition subjects have often been exposed to multiple agents, making it difficult to isolate the effects of single substances. Control of confounding was usually not possible. Most studies were not population based, had small sample sizes or achieved very small response rates. In addition, the diagnostic criteria have varied across studies, making generalisability and comparability between studies difficult.

The present evidence provides only weak suggestions of association and is insufficient to confirm a causal role for low doses of chemicals on CFS/ME. Environmental exposures are often difficult to measure, and further research on the ascertainment of these exposures is essential. For many of the chemicals, exposure measurements are appropriate in the acute phase, but chemicals such as OP and solvents are usually rapidly metabolised and do not appear in the blood after the immediate exposure phase. Studies of CFS/ME have also been made difficult due to the absence of an objective measurement of fatigue and of a biological marker that would avoid diagnosis misclassification. These inherent difficulties in studying environmental factors and epidemiology have often been aggravated by weak study designs and methodology.

The current level of evidence does not suggest the need for any specific environmental public health action. However, safe limits of environmental exposures to general population and specific groups, e.g. occupational groups, should continue to be reviewed regularly. It is important to recognize vulnerable individuals and groups within the populations, who may be at higher risk from the effects of environmental toxicants; these may include for example, children, women, people in certain occupations and those with genotypes that increase their susceptibilities to environmental exposures.

Observation of safety procedures in occupational settings is paramount, and, similarly to general population levels, limits of occupational exposure need to be reviewed on a continuous basis. Safety regulations need to be strictly followed. This means ensuring good work layouts and ventilation, use of protective equipments as appropriate and use of other mechanisms to limit exposure, added to the early recognition and management of any symptoms or abnormalities. Of note is that cases of CFS/ME have been reported in situations when occupational standards have not been followed (13). The importance of minimizing and managing stress at work and indeed at population level cannot be underestimated. Life styles and societal structures (including work structures) that are compatible with optimum population physical and emotional well being should be encouraged, aiming to reduce potential causes of stress.

There is a need for well designed epidemiological studies investigating the association of environmental chemicals and chronic fatigue, including the use of reliable exposure and outcome measurements, large sample sizes and good data on confounding factors. The weakness of the definitions of CFS/ME have been recognised (4) and is now urgent the use of better and more specific disease definitions that consider sub-group of patients, so as to avoid future heterogeneity in cases recruited to studies. In particular, distinctions between psychiatric and other medical causes of chronic fatigue are important and studies should restrict recruitment to cases of CFS/ME that have been clinically diagnosed using internationally accepted criteria, with the application of strict exclusion criteria that will avoid 'contamination' of the studies with non-cases.

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## **Conflicts of interest**

The authors declare no conflict of interest.

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