EDITORIAL

Adverse health effects after low level exposure to organophosphates

Acute poisoning with organophosphate based pesticides is a notable cause of morbidity and mortality in the developing world, but much less common in the United Kingdom. However, the potential for frequent low level exposures to organophosphates exists for many occupational groups including agricultural workers, sheep dippers, and pesticide sprayers. Over the past decade an increasing number of people began to suspect that repeated low level exposure to organophosphate compounds was causing adverse effects on their health. The worst affected were sheep farmers who dipped their flocks in organophosphate based dips, although other circumstances of exposure were also implicated. A broad range of symptoms was associated with exposure but none of these were sufficiently specific to indicate a possible physiological or toxic mechanism. Few patients presented with robust clinical signs so that clinical investigation was difficult and a diagnostic marker was not identified.

Some studies did suggest that long term effects on the central and peripheral nervous systems might be associated with frequent but low level exposure to organophosphate.[1 2] These neurological effects were different from those associated with the delayed neuropathy known to follow acute poisoning with those organophosphate compounds that were already acknowledged to be neurotoxic and consequently had been banned from use. The new neurotoxic effects in humans ranged from neurobehavioural and electroencephalographic changes to increases in the variability of action potential latencies in skeletal muscles (the "jitter" of neuromuscular transmission measured in humans by single fibre electromyogram (SFEMG)). Neuropsychiatric disorders had been described previously in industrial workers exposed to organophosphates. The clinical findings included anxiety and depression, irritability, subtle effects on memory and concentration, and a decrease in alertness. Mild poisoning in crop spraying pilots was linked to subsequent lapses of attention, often leading to accidents.

Other investigators found no health effects in comparable occupational groups. Rodnitzky *et al*[3] studied 23 subjects (12 farmers and 11 pesticide sprayers) and a control group, with various psychometric tests and found no abnormalities. Levin *et al*[4] found increased levels of anxiety in commercial organophosphate sprayers but not in farmers.

All the epidemiological studies were limited by a nearly universal lack of historical comparative exposure data and the absence of a validated diagnostic test.

In this edition, Pilkington *et al* report the results of an extensive epidemiological study of the relation between exposure to organophosphate pesticides, indices of change in peripheral nerve function, and neuropsychological abnormalities in United Kingdom sheep farmers and dippers.[5] The inevitable paucity of individual data on historical exposure was rectified by an ingenious method to estimate exposure. Buchanan *et al* describe this method in their separate paper on the estimation of cumulative exposure to organophosphate sheep dips.[6] This hygiene study concluded that handling concentrate was the principal source of exposure, as measured by urinary concentrations of organophosphate metabolites. The authors noted that data from a few subjects had a major influence on the exposure models. It is also worth noting that very few of the dippers wore the recommended personal protection equipment.

The results of this epidemiological study suggest an association between exposure to organophosphate concentrate and symptoms of adverse neurological effects, although this finding was dependent on the inclusion of the few people with very high levels of exposure. Also, this association was not confirmed by objective measurement of sensory thresholds, except for a suggestion that thresholds were higher in concentrate handlers and that cold thresholds were higher in sheep dippers than in non-dipping farmers. The authors concluded that long term health effects might result primarily from exposure to high levels of organophosphates associated with the handling of concentrate rather than from prolonged exposure to diluted dip.

This study also shows the difficulties faced by environmental epidemiology when accurate historical exposure data are not available, there is no diagnostic marker, and the development of ill health may depend on susceptibility factors. Methodological developments in molecular epidemiology may help resolve some of the difficulties with exposure metrics, but further resolution of the health issues will depend on focused investigation of the toxic mechanism. Mechanistic studies have suggested that long term effects of organophosphates may be mediated by cholinergic mechanisms or phosphorylation of neuronal protein sites, and other mechanisms may be important as genetic differences in detoxification enzymes and non-specific binding account for some of the variations between people in susceptibility to anticholinesterases. It is probable, therefore, that the development of long term health effects has a genetic component[7] but susceptible people will be difficult to identify without a very large study population, good comparative exposure data, and knowledge of the toxic mechanism.

In these circumstances, it may be that epidemiological techniques are not sufficiently sensitive to identify susceptible people. Mechanistic research may identify more clearly the pathophysiological effects that can be investigated in the individual patient and will be informative for future epidemiological studies. If there are subpopulations of people specifically susceptible to the toxic mechanism and who may, therefore, develop a clinical effect, then this study suggests that only a few of the subgroup may be sufficiently exposed to be actually affected. It is no wonder in such circumstances that it may be difficult for epidemiological studies to identify these people.

It is difficult to extrapolate the results of this latest study to public or general occupational exposures. High dose

acute organophosphate poisoning can result in long term neurological effects, changes in behaviour, deficits in neuropsychological performance, and alterations in the electroencephalogram. Information on low dose exposure, either acute or chronic, in an occupational setting or otherwise, remains unclear, but there is now sufficient evidence from this study to suggest that populations that have exposure to concentrate should be investigated for changes in neurobehavioural variables and neuromuscular electrophysiology (including SFEMG). Similarly, epidemiological studies of exposed occupational groups should include validated monitoring of urinary metabolites to identify those most at risk. Further studies in animals and humans will identify the toxic mechanism, and hopefully help the development of a diagnostic marker.

The nervous system is not a homogeneous single function organ and there are neuron specific differences in biochemistry, electrophysiology, and function. It is possible that a single toxic mechanism could produce various symptoms, depending on the extent and level of effect, which range from subtle behavioural changes to frank neurological deficits. The long term toxicity of organophosphates is an important public and occupational health issue. This latest study provides a further indication that some people do develop long term effects after exposure to organophosphates but the mechanism and the clinical relevance remain unresolved.

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