Work with pesticides and organophosphate sheep dips

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Pesticides are an important hazard in agriculture. In developed countries their use is strictly regulated. Risk assessment for new pesticides includes comparison of the potential exposures of spray operators and other farm workers with a reference value. Usually, this is derived from toxicological studies in animals with allowance for the uncertainties in extrapolating between and within species. Older pesticides undergo periodic reviews, for which epidemiological data may also be available. Unintentional fatal poisoning by pesticides is extremely rare in Britain. Documented reports of non-fatal acute poisoning are also uncommon, but there may be substantial under-ascertainment of minor incidents. Pesticides have been linked with various chronic diseases, but few associations have been clearly established. A particular concern recently in Britain has been the possibility that organophosphate insecticides can cause chronic neuropsychiatric illness.

Key words: Organophosphates; pesticides; poisoning; regulation.

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Introduction
Among the many occupational hazards encountered in agriculture, pesticides have been subject to the most extensive scientific investigation. Pesticides are chemical or biological substances that are used to kill or control harmful living organisms in our environment. They include herbicides, fungicides, insecticides, rodenticides, soil sterilants and wood preservatives, all of which may find use on farms. In addition, some insecticides are formulated as veterinary medicines, such as sheep dips.

Regulatory risk assessment
By definition, pesticides are biologically active, and this renders them intrinsically more hazardous than most other classes of industrial product. In the UK and other developed countries, they are therefore subject to strict regulation. This includes an assessment of risks to operators who apply them and to workers who may be nearby when an application is being made, or who handle crops and other materials that have been treated with pesticides [1].

For new pesticides, this risk assessment is based principally on toxicological studies in vitro and in animals. The data obtained are used to characterize potential toxic effects and to establish the ‘no observed adverse effect level’ (NOAEL) for each outcome in experimental animals (i.e. the highest dose, measured in mg/kg body weight, at which the effect did not occur). An acceptable operator exposure level (AOEL) is then determined by applying an ‘assessment factor’ to the most appropriate NOAEL (usually that for the most sensitive toxic end-point in the most sensitive species when exposed over a relevant time period). The assessment factor, most often 100, is to allow for uncertainties in the extrapolation from animals to humans and for possible differences in sensitivity from person to person. The potential exposures of operators and other workers are estimated (taking into account any engineering controls or personal protective equipment that will be required as a condition of use) and they are compared with the AOEL to establish whether they will be acceptable.

Risk assessments are also carried out at intervals for
pesticides that are already on the market. Re-examination of a product may be stimulated by the emergence of new scientific information suggesting a risk not previously taken into account, but more often it is carried out as part of a routine review programme. As well as toxicological data from animals and in vitro experiments, such risk assessments also take into account any human evidence that is available, e.g. from case reports and epidemiological studies of people exposed in the manufacture or use of the pesticide.

Over the years, the regulation of pesticides in the UK has become progressively more precautionary. In other words, the government now requires more positive reassurance that exposures will be acceptable before a specified use is permitted. As a consequence, when older pesticides are reviewed, approval holders (usually the manufacturers) are often required to generate new scientific data in order to provide the additional reassurance of safety that is now expected.

Monitoring for adverse health effects

As an adjunct to the regulation of pesticides, regular monitoring is necessary to ensure that control measures are satisfactory. In Britain, the Health & Safety Executive (HSE) systematically reviews and classifies all reports that it receives of incidents in which a pesticide is alleged to have caused ill-health [2]. Similarly, notifications of illness that might be related to the use of veterinary medicines are collated by the Veterinary Medicines Directorate [3]. Reports of severe acute poisoning from occupational exposure to pesticides or veterinary medicines are extremely rare. This is borne out by national data on occupational mortality for England and Wales, which indicated only three deaths from pesticide poisoning among male farmers during the 11 year period between 1979–1980 and 1982–1990, as compared with 127 from injury by machinery, 28 from electrical injury and 17 from injury by animals or plants [4]. The incidence of non-fatal poisoning is not so well defined. Over 12 months during 1998–1999, a total of 72 alleged ill-health incidents from pesticides were recorded by the HSE, although not all involved occupational exposure and not all were classified by the HSE as ‘definitely’ or ‘probably’ attributable to pesticides [2]. However, there is almost certainly under-reporting of mild cases and in a cross-sectional survey of 84 agricultural workers from south-west Hampshire, 13 participants (15%) reported that they had at some time suffered an accident or health problem involving the use of an agricultural chemical [5]. They included four workers who had consulted a doctor as a consequence.

In theory, the occurrence of non-fatal acute poisoning could be more reliably determined if reporting systems were improved, and the HSE is currently exploring the feasibility of collecting information through selected general practitioners. A greater challenge is the identification and quantification of longer-term health effects, especially if these are not specific to pesticide exposure. In some cases, it may be possible to link disease and exposure by clinical investigations. For example, a number of pesticide products have been shown, by means of patch testing, to cause allergic contact dermatitis [6]. More often, however, it is necessary to seek epidemiological evidence that the risk of a disease is increased in those exposed to the pesticide.

Problems arise in the epidemiological investigation of pesticides because of the number and variety of products with which people may have worked. Many case–control studies have attempted to ascertain past exposure to pesticides as a class and positive associations have been reported with a wide range of diseases. However, such findings can be difficult to interpret. As with medicines, different classes of pesticide have quite distinct toxicological profiles and it seems unlikely that the same disease will be caused by more than a minority of all pesticides. If this is correct, then any causal associations are likely to be diluted when all pesticides are analysed together as a group, biasing estimates of relative risk towards unity. The fact that, despite this dilution, risk estimates from case–control studies are often higher than those obtained from cohort studies of workers with relatively heavy exposure to pesticides, suggests that the former are commonly exaggerated by recall bias.

To the extent that they incorporate better data on exposure, cohort studies provide more reliable information on the health effects of pesticides than case–control investigations. A good example is the possible association of non-Hodgkin’s lymphoma with phenoxy herbicides, such as 2,4-D, 2,4,5-T, MCPA and MCPP, and structurally related chlorophenols (which have been used as wood preservatives). An early case–control study in Sweden [7] found an odds ratio of 6.0 [95% confidence interval (CI) = 3.7–9.7], but in a later study of 21,863 exposed workers from 36 cohorts in 12 countries [8], the risk estimate for non-Hodgkin’s lymphoma was much lower and not statistically significant (standardized mortality ratio 1.27, 95% CI = 0.88–1.78).

Pesticides have been postulated as causing a wide range of chronic diseases, including various types of cancer, aplastic anaemia, Parkinson’s disease, peripheral neuropathy and congenital malformations, although only rarely has the link been clearly established (e.g. lung cancer caused by arsenical compounds and neurotoxicity caused by methyl bromide). Nevertheless, in some cases the suspicion and uncertainty have generated significant public concern. In Britain, there has been much debate in recent years about possible chronic neurotoxic effects from low-level exposure to organophosphate insecticides.
Organophosphates

The organophosphates are a group of compounds containing carbon and phosphorus, which inhibit the enzyme acetylcholinesterase. They were developed as insecticides during the 1950s and 1960s, and in Britain they rapidly found extensive application in agriculture, tending to replace organochlorine compounds such as DDT and dieldrin. They have also been widely used in sheep dips. More recently, their use has declined, in part because of replacement by synthetic pyrethroids.

The organophosphates have well-recognized acute toxic effects, arising from their capacity to inhibit acetylcholinesterase in the central nervous system, in the autonomic nervous system and at the neuromuscular junction. Symptoms of poisoning include giddiness, anxiety, restlessness, headache, confusion, salivation, sweating, watering eyes, blurred vision, diarrhoea and muscle fasciculation, followed by weakness and paralysis. Management may include the administration of atropine to antagonize effects at muscarinic sites and treatment with agents such as pralidoxime to reactivate acetylcholinesterase where it has not been damaged irreversibly.

Some organophosphates can also inhibit the enzyme neuropathy target esterase, giving rise to a sensorimotor polyneuropathy, mainly affecting the lower limbs, that begins 1–4 weeks after the poisoning. However, these compounds have not been used in the UK for some years.

Another short-term effect of organophosphates, only documented more recently, is the intermediate syndrome. This is characterized by transient muscle weakness of the limb, neck and respiratory muscles, which begins 1–4 days after a poisoning incident and may continue for up to several weeks.

These well-established acute and sub-acute toxic effects have only been demonstrated after clearly excessive exposures that should not occur if organophosphate pesticides and sheep dips are used in the approved manner. A more controversial issue is the possibility that organophosphates cause long-term illness, perhaps even when there has been no obvious acute toxicity. In particular, a syndrome of chronic organophosphate-induced neuropsychiatric disorder (COPIND) has been proposed, including personality changes, impulsive suicidal thoughts, cognitive impairment, language disorder, alcohol intolerance, heightened sense of smell, deterioration of handwriting, sensitivity to organophosphates on re-exposure and decreased exercise tolerance [9].

Investigation of this hypothesis is not straightforward. Many of the alleged health effects are subjective or semi-subjective, making them difficult to ascertain without bias. Also, for some of the postulated health outcomes, there is a possibility of reverse causation. For example, it is not inconceivable that workers who start out with lower levels of cognitive function tend to incur higher exposures when working with pesticides. Another problem is that people whose illness is severe may leave the workforce and thus be excluded from studies that are restricted to workers who are in exposed jobs at the time research is carried out.

Nevertheless, a substantial number of relevant studies have been conducted and these were reviewed by the Department of Health’s Committee on Toxicity in 1999 [10]. The committee concluded that neuropsychological abnormalities probably can occur as a long-term complication of acute organophosphate poisoning, especially if the poisoning is severe. However, the effects reported had been mainly on sustained attention and mental agility, whereas long-term memory appeared not to be affected. The evidence available also indicated that as well as the peripheral neuropathy caused by inhibitors of neuropathy target esterase, persistent peripheral neuropathy can sometimes follow acute poisoning by other organophosphates, although not to a degree that would normally cause symptoms. In contrast, the balance of evidence did not support the occurrence of peripheral neuropathy or clinically significant impairment in neuropsychological tests from low-level exposure to organophosphates in the absence of overt acute poisoning. Nor was such exposure thought to be a major factor in the excess mortality from suicide that has been demonstrated in British farmers [11].

Several outstanding gaps in knowledge were identified, including uncertainty as to whether low-level exposure to organophosphates might cause disabling neuropsychological dysfunction.

### Table 1. Approaches to controlling the risks from occupational exposure to pesticides in agriculture

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<th>Substitution</th>
<th>Use of alternative methods of pest control such as optimal crop rotation</th>
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<td>Use of ‘lower-risk’ pesticides</td>
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<td>Engineering controls</td>
<td>Formulation of products to minimize exposures (e.g. as granules)</td>
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<td>Use of closed transfer systems for loading spray equipment</td>
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<td>Use of wide-necked containers for pesticide concentrates to reduce spillage</td>
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<td>Enclosed cabs on tractors</td>
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<td>Automated pesticide application in glass houses</td>
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<td>Respirators</td>
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<td>Training</td>
<td>In Britain, pesticides may only be used in agriculture by or under the supervision of a person with appropriate formal training or experience</td>
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logical illness in a small minority of exposed persons who for some reason, either genetic or environmental, are unusually sensitive to these chemicals. In support of this, farmers with chronic illness that they attributed to work with sheep dips have been found to differ from controls in the prevalence of a polymorphism of the enzyme paraoxonase, which is involved in the metabolism of organophosphates [12].

Methods of reducing risk to workers

As with all occupational hazards, steps should be taken to control the risks from exposure to pesticides as far as is reasonably practicable. The main approaches used are summarized in Table 1.

Conclusion

Because of their intrinsically hazardous nature, the use of pesticides must be carefully controlled. However, provided that they are regulated properly and applied in an appropriate manner, pesticides can make a valuable contribution to public health and to our quality of life.

References