



# Medical aspects of work-related exposures to organophosphates

## Guidance Note MS 17

This guidance is issued by the Health and Safety Executive. Following the guidance is not compulsory and you are free to take other action. But if you do follow the guidance you will normally be doing enough to comply with the law. Health and safety inspectors seek to secure compliance with the law and may refer to this guidance as illustrating good practice.

### INTRODUCTION

1 The purpose of this guidance note is to inform doctors and other health professionals, particularly those concerned with occupational health, about the health effects which may arise from exposure to organophosphates and the role of biological monitoring and health surveillance of workers exposed to these compounds.

2 Organophosphates (OPs) are a broad group of chemicals which are widely used in agriculture as insecticides, therapeutic (including veterinary) medicine and in both domestic and public health applications. Within the group of OP compounds there is wide variation in human toxicity and not all are cholinesterase inhibitors. Although organophosphates were originally developed as pesticides they were adapted later for use in chemical warfare, and this has led to some anxiety that OP-based pesticides and medicines are more dangerous than they are. Chemical warfare agents have significant structural differences from commercially available OPs which markedly increase their toxicity to mammalian species.

3 OPs of occupational interest all act by blocking the normal function of the enzyme acetylcholinesterase at neuronal, autonomic effector organ or neuromuscular junctions and thus interfere with the normal transmission of nerve impulses.

4 Pesticides and veterinary medicines form the largest group of cholinergic organophosphates which are likely to pose risks to health in an occupational setting.

Guidance Notes are published under five subject headings:

### Medical

Environmental Hygiene

Chemical Safety

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General

5 Although OP pesticides are shorter-lived in the environment and in biological systems than the organochlorine pesticides which they replaced, short-term exposure at sufficiently high levels can produce harmful acute effects in humans and may result in long-term ill health. An association between long-term exposure at low doses and long-term ill health has been proposed but the evidence is not clear.

6 Another group of pesticides, the carbamates, are also used in agriculture and have similar pharmacological actions to the OP compounds. Exposure to both groups of chemicals produces similar symptoms of acute intoxication; the main difference lies in the speed of re-activation of the inhibited enzyme acetylcholinesterase. Recovery of the enzyme from carbamate inhibition is generally faster than recovery from OP inhibition, and repeated exposure does not tend to cause an incremental reduction in cholinesterase concentration.

### ROUTES OF ABSORPTION AND POTENTIAL OCCUPATIONAL SOURCES OF EXPOSURE

7 Any job which involves either direct or indirect contact with OP compounds constitutes a potential source of exposure. Workers at risk include those involved with OPs in:

- development, manufacture and packaging, including research and quality control;
- transport, storage and distribution;
- application and use, eg agricultural workers, pest control operatives, veterinary surgeons; and
- handling used containers or contaminated clothing, eg scrap recovery or ambulance workers.

8 Members of the public may be exposed to OPs accidentally, for example from spray drift or when they have a wasp nest destroyed in their garden.

9 The most common routes of absorption of OP compounds are via skin, respiratory tract and eyes. The low vapour pressure of the majority of commercial products (dichlorvos would be an exception) means that the major route of absorption is via the skin. However, the respiratory route of exposure may be important when formulations are used as sprays with the generation of finely divided aerosol. Under normal conditions of use ingestion is rare, although small amounts may be swallowed in contaminated saliva.

10 Some OP products are supplied as concentrates requiring dilution, eg sheep dip and agricultural pesticide formulations. Skin contamination with the concentrate may result in relatively high levels of exposure.

11 Good occupational hygiene practice is essential to minimise exposure. OPs formulated with organic solvents may permeate protective clothing unless contamination is washed off promptly. This is more important with concentrate exposure, when it is especially important to wear the correct gloves and to change them regularly. Poor occupational hygiene practices (eg trousers/leggings inside boots or too short a glove) may also result in contamination with chemicals migrating around the personal protective equipment. Damaged protective clothing must be replaced immediately.

## PHARMACOLOGY AND TOXICOLOGY

12 The chemistry of OP compounds is complex. The term is loosely applied to all carbon compounds which are derivatives of phosphorus containing acids. The basic structure is easily modified and there are many different OP compounds (at present some 200 OP insecticides are licensed around the world). Such a wide range of structure results in a wide range of physico-chemical properties. In turn these determine biological activity and possible species specificity.

13 The main enzymes known to be clinically important which are inhibited by OPs are cholinesterases. They can be divided into acetylcholinesterase and butyrylcholinesterase on the basis of their preferred substrate. The enzyme found in plasma is butyrylcholinesterase, which is sometimes known as pseudocholinesterase; the enzyme found in the nervous system and in muscle, and also in the erythrocyte, is acetylcholinesterase. Whilst acetylcholinesterase, as an enzyme, has a clear functional role, the role of butyrylcholinesterase is unclear.

14 Cholinesterases, inhibition of which by OPs gives rise to the acute clinical symptoms, are of the B-esterase group of enzymes. A-esterase enzymes which also hydrolyse, and so detoxify OPs, are not themselves inhibited in the process. Clinical symptoms of acute poisoning will be dependent on the relative amounts of the two groups of enzyme and on the affinity of the specific OP for each group.

15 OP anticholinesterases are esters of phosphoric, phosphonic, phosphorothioic or related acids. As an indicator, the majority (over 75%) of OP anticholinesterases

have one of the following elements in their approved names, *-pho-* or *-fos-* or *-vos-*, indicative of their phosphorus content (eg chlorfenvinfos,); *-thio-* or *-tho-*, indicative of their sulphur content (eg malathion). Important exceptions to this would include diazinon and demeton-S-methyl.

16 Many OP pesticides and veterinary medicines are phosphorothioates which contain P=S groups and as such require activation by the liver with conversion of the P=S (thion) moiety to the P=O (oxon) form in order to manifest their toxicity. Thus, for example, parathion is converted to paraoxon and malathion to malaoxon. This need for activation may not only delay the onset of clinical symptoms but also affect the clinical picture in that local effects at the site of exposure would not be expected with systemic toxicity being more prominent.

17 These features of activation metabolism and detoxification metabolism and the balance between them for any specific OP, together with inter-individual differences in respect of enzyme polymorphisms, will affect the relationship between exposure and acute toxicity.

18 Whilst inhibition of cholinesterase enzymes form a significant action of these OPs, other enzyme systems are affected. However, the potential clinical consequence of their inhibition, with the exception of neurotoxic or neuropathy target esterase (NTE), remains undefined.

19 The acute toxic effects produced by OP compounds in humans are generally considered to be due to inhibition of the nervous system acetylcholinesterase. In normal conditions, following hydrolysis of acetylcholine, there is a reactivation of acetylcholinesterase in less than a second. In the presence of an OP this reactivation is much slower (or non-existent) leading to effective enzyme inhibition and, in turn, a prolonged build-up of acetylcholine and clinical toxicity.

20 Acetylcholine acts as a neurotransmitter in many parts of the nervous system:

- preganglionic to postganglionic neurones (nicotinic):
  - parasympathetic;
  - sympathetic;
- postganglionic (muscarinic):
  - parasympathetic fibres to effector organs;
  - sympathetic fibres to sweat glands;
- motor nerves to skeletal muscle (nicotinic); and
- some nerve synapses in the CNS.

21 The level of inhibition of erythrocyte acetylcholinesterase ('true' cholinesterase) is generally correlated with the severity of acute OP poisoning symptoms, and by inference therefore with nervous system acetylcholinesterases, although the influence of toxicodynamics in the distribution of OP between blood, storage depots in fatty tissue and target nervous tissue is important in limiting the strength of this relationship.

22 Inhibition of cholinesterase is caused by phosphorylation of the active site of the enzyme by the OP. In causing this phosphorylation of enzyme the OP structure is split, with a 'leaving' group being displaced from the enzyme and the alkyl phosphate moiety of the OP attaching

