# Medical aspects of work-related exposures to organophosphates

HSE
Health & Safety Executive

Guidance Note **MS 17**

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## 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.

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

to a serine amino acid within the enzyme active site.

23 After inhibition by an OP, acetylcholinesterase can undergo two fates. One leads to an 'aged enzyme' where, after a molecular rearrangement of the alkyl phosphate group attached to the serine residue, the enzyme is irreversibly inhibited and enzyme activity can only return by replacement of 'aged enzyme' by newly synthesised enzyme. On the other hand the inactivated enzyme can spontaneously reactivate back to the normal active enzyme. These two reactions have different rates of reaction which are said to depend on the nature of the alkyl phosphate group of the OP.

24 For the erythrocyte enzyme, the replacement of any 'aged enzyme' is dependent on the lifetime of the erythrocyte in the circulation (approximately 120 days) while the replacement rate of butyrylcholinesterase is considerably faster, the reported half-life being about 12 days.

## CLINICAL MANIFESTATIONS OF ORGANOPHOSPHATE (OP) POISONING

### Acute

25 The diagnosis of acute OP poisoning may not be easy. Some signs and symptoms can be clearly defined, whereas others, particularly those of central nervous system origin, may be variable and not easily detected. The pattern of signs and symptoms that develop will depend not only on the particular OP compound but also, to some extent, upon the route of absorption.

26 Some OPs require metabolic activation before they inhibit cholinesterase and active metabolite may continue to be formed for some time after absorption. Similarly redistribution from lipid or fat storage depots may affect the development of symptoms. The picture will also be complicated by OP affinity towards acetylcholinesterase and butyrylcholinesterase and subsequent ageing and reactivation.

27 Repeated absorption of small doses, as may occur from wearing contaminated clothing, may result in progressive, cumulative inhibition of nervous tissue cholinesterase. This happens when the repeat exposures occur within the cholinesterase recovery period. A further small exposure may then precipitate the symptoms of acute OP poisoning. This is distinct from chronic toxicity as described below.

28 With repeated exposure to OPs the induction of tolerance may result in the loss of cholinergic symptoms and signs despite continued inhibition of acetylcholinesterase.

29 The signs and symptoms of acute OP poisoning include:

- those related to excessive activity of the autonomic nervous system: miosis (pin-point pupils), blurred vision, lacrimation, excessive salivation, cold sweats, bronchorrhoea, cardiac arrhythmias/bradycardia with decreased cardiac output and hypotension;
- those related to over-reactivity of voluntary muscle: tremors, impaired co-ordination; and
- non-specific symptoms: headache, giddiness, loss of appetite, nausea and diarrhoea.

30 Other signs and symptoms may include:

- urinary incontinence, abdominal pain, vomiting and bronchoconstriction caused by over-activity of smooth muscle;
- glycosuria and hyperglycaemia, leucocytosis, low grade fever; and
- central nervous system effects:
  - depression of the respiratory centre accompanied by a low arterial oxygen saturation and metabolic acidosis, and in severe cases seizures and convulsions;
  - various non-specific psychomotor effects, eg apprehension, anxiety, restlessness, irritability, mental confusion, depression, sleep problems such as insomnia and dreaming, hallucinations, expressive language defects, changes of mood, lack of concentration, memory impairment, slowed reaction time.

31 Acute poisoning may have any combination of the above signs and symptoms and may be variable. However, the pattern of signs and symptoms may depend upon the route of absorption of the OP compound. Following inhalation, the earliest effects may be rhinitis and chest tightness (this has been described particularly following exposure to dichlorvos); and following ingestion the early features may include intestinal colic, nausea, vomiting and diarrhoea.

32 Acute poisoning by an OP may lead to death from respiratory failure due to paralysis of respiratory muscles, aggravated by central depression of the respiratory centre, bronchoconstriction and bronchorrhoea, but this would require exceptional exposure.

33 There has been reference, specifically in relation to sheep dipping, to a short-lived flu-like illness known as 'dipper's flu'. Symptoms include runny nose, headache, aching limbs and malaise occurring shortly after the time of dipping and persisting for up to 48 hours. The cause of this condition is unknown and an OP effect cannot be ruled out.

34 When poisoning occurs with a proprietary formulation of OP pesticide or veterinary medicine, the presence and influence of the solvent should not be forgotten. Local skin effects (irritation) will almost certainly be due to the solvent. In severe cases the presence of an organic solvent may contribute to the development of CNS toxicity either through facilitating the absorption of the OP or through a direct toxic effect of the solvent itself.

### Post-acute

35 A number of well-recognised chronic conditions may follow acute OP poisoning although, because of the complex pharmacology and toxicology of this group of compounds, not all OPs will give rise to these complications.

36 The intermediate syndrome occurs typically one to four

days following an acute poisoning. It is considered to be a dose-related phenomenon. The individual develops a proximal muscle weakness which may affect the facial, neck and respiratory muscles, leading to respiratory failure. The effects are self-limiting, generally lasting between one and three weeks. The underlying basis of the intermediate syndrome is unknown but muscle end plate necrosis may be implicated. It is possible that adequate doses of pralidoxime may prevent the onset of the condition.

37 OP-induced delayed polyneuropathy (OPIDP) is associated with inhibition and ageing of the enzyme neurotoxic or neuropathy target esterase (NTE). This may be accompanied, 10 to 14 days after the acute toxic poisoning, by a selective 'dying back' pattern of degeneration of long and large fibre tracts of the spinal cord and peripheral nervous system. This neuropathy affects the motor and sensory nerves particularly to the lower limbs with resultant weakness, clumsiness, tingling and ultimately paralysis. Although there may be some recovery, initially in the sensory system, residual signs and symptoms are not uncommon. OPIDP has been described in species other than human and the current standard pre-marketing neurotoxicity screening test for OP compounds is whether or not the substance inhibits NTE in hens with associated clinical and histopathological endpoints. If this test is positive the product is not authorised/approved.

38 Other less clearly defined neurobehavioural effects subsequent to acute OP poisoning have been ascribed to cerebral hypoxia during the toxic episode. There are, however, a number or reports which indicate that such effects may follow an acute poisoning where there has been no evidence of seizures or convulsions and therefore no justification for an hypoxic aetiology. In this situation both the clinical picture and the underlying aetiology may overlap with the chronic effects outlined below.

**Chronic**

39 A number of reports have indicated that exposure to OPs at levels which have not resulted in acute toxic symptoms with cholinesterase depression may give rise to chronic, and in some cases disabling, health effects. These effects have been described as neurobehavioural, neurological, neurophysiological and autonomic.

40 Published reports in the literature are, however, inconsistent in their findings and the objective changes found are, in the majority of studies, subtle and of a magnitude below the threshold of clinical manifestation. An additional difficulty is the absence of any well-defined exposure assessment when, in practice, individuals may have been exposed over time to a variety of formulations and undetermined concentrations.

41 Many of the symptoms attributed to chronic ill health from OP exposure are indeterminate and non-specific (headache, fatigue, tiredness, irritability, loss of concentration) and there are no clearly defined patterns which are sufficiently robust as to enable a case definition for epidemiological study. Furthermore, there is no identified mechanism which can currently account for the occurrence of chronic effects. However, the possibility needs be considered that effects can exist other than those related to the inhibition of cholinesterase enzyme systems.

42 Depression with suicidal intent, chronic fatigue and multiple chemical sensitivity are syndromes which have claimed to be associated with exposure to pesticides and veterinary medicines, including OPs. A number of other conditions have also been reported including cardiomyopathy, osteoporosis, malignancy and developmental abnormalities.

43 A recent report[1] concluded that the balance of evidence did not support the view that low level exposure to OPs, in the absence of overt toxicity, caused clinically significant neurophysiological effects or peripheral neuropathy. However, the possibility that OPs cause disabling disease in a small sub-group of exposed persons could not be ruled out.

44 An earlier report[2] on the clinical aspects of long-term low-dose exposure to OP sheep dip concluded that 'whilst the symptoms and distress... are genuine, and can continue for a long time, to elucidate the role of OPs in these symptoms would require further study'.

45 Any diagnosis of chronic ill health effects will currently, therefore, derive from a history of exposure together with a combination of appropriate signs and symptoms when all other diseases have been excluded.

## REQUIREMENTS OF COSHH

46 Under the Control of Substances Hazardous to Health Regulations 1994 (COSHH)[3] an employer or self- employed person must assess the risks to health from work involving hazardous substances.

47 The prime purpose of the risk assessment is to determine the measures required to prevent ill health. If there is a risk, employers are required to decide on the action needed to prevent or minimise that risk and protect the health of employees and others who may be affected by the work activity.

48 Wherever it is reasonably practicable to do so, COSHH requires that exposure to substances known to cause ill health should be prevented by the use of alternative substances or processes and by minimising the numbers exposed. Where it is not reasonably practicable to prevent exposure, employers have a duty to ensure that any exposure is adequately controlled and the health of employees is protected.

49 Detailed advice on the control measures, other than health surveillance, required under COSHH are beyond the scope of this guidance note. Practical guidance on the Regulations themselves is given in the COSHH general *Approved Code of Practice.*[4] HSE has also published a general guide on *Health Surveillance under COSHH: Guidance for Employers.*[5]

50 Specific requirements and recommendations about control will be set out as approval conditions under specific pesticide and medicines legislation and will appear on product labels or pack inserts.

51 Where valid and suitable occupational hygiene methods are available and any deterioration in control might otherwise not be detected sufficiently quickly, exposure should be monitored to detect failure or deterioration of adopted control measures.

52 Where the employer's assessment has revealed a risk to health which cannot be eliminated, then health surveillance of exposed employees may be required under COSHH to identify possible cases.

## BIOLOGICAL MONITORING - THE MEASUREMENT OF OP METABOLITES AS AN INDEX OF EXPOSURE

53 The Health and Safety Executive (HSE) has produced general guidance on the practical application of biological monitoring in the workplace for the assessment of chemical exposure.[6] Biological monitoring by the measurement of the alkyl phosphate/phosphorothioate metabolites of OPs in the urine provides a relatively non-invasive means of investigating exposure, although at the current time there are few laboratories which can offer this as a routine service.

54 There is a relatively small number of the alkyl phosphate/phosphorothioate metabolites compared to the potential number of different OPs. A measure of six of these 'alkyl phosphates' will cover about 85% of likely encountered OPs and can be quantified in a single GC analysis run after derivatisation with pentafluorobenzylbromide using a flame photometric detector.

55 The method is very sensitive and is capable of detecting increased levels of 'alkyl phosphates' well below OP exposures that cause cholinesterase inhibition. Low levels of some urinary metabolites can be found in seemingly unexposed subjects. However, even though OPs are ubiquitous in the environment the exact origins of such background levels has yet to be determined.

56 Urinary 'alkyl phosphates' have a relatively short half-life of around 10-14 hours in urine after a single exposure and therefore any urine sample has to be taken close to the time of OP exposure.

57 Urinary metabolites have a potential role in the practical investigation of isolated subacute accidental exposures and as a research tool, eg in the investigation of the effectiveness of personal protective equipment, such as gloves and clothing in preventing exposure.

58 Urinary metabolite measurements may also prove useful in monitoring workers with a potentially high risk of exposure (eg formulators, sheep dip contractors) or to establish that control measures are adequate where there are changes in working practices. In effect a local baseline can be established, from measurements made at a time when controls are known by independent observation to be good, against which change can be assessed.

59 The relationship between urinary metabolites and cholinesterase inhibition (and hence acute toxicity) has not been defined but because of the wide range of OP potencies (ie enzyme affinity) this relationship is likely to be specific to each OP. At the present time urinary metabolites remain an indicator of exposure and cannot be interpreted in health terms.

60 Because OPs are readily absorbed through the skin, inhalation-based occupational exposure limits[7] and the use of environmental monitoring for OPs do not provide an adequate basis for assessing exposure.

## BIOLOGICAL EFFECT MONITORING - THE MEASUREMENT OF CHOLINESTERASE ACTIVITY AS AN INDEX OF OP UPTAKE AND EFFECT

61 Although different OP compounds inhibit neural, erythrocyte and butyrylcholinesterases to varying extents, and with differing time courses, the measurement of erythrocyte ('true') acetylcholinesterase and plasma ('pseudo') butyrylcholinesterase activity provides an indication of the uptake of these compounds. Such measurements have therefore found a place in monitoring workers exposed to OP compounds.

62 In their active oxon form OPs are widely different in their affinities for erythrocyte acetylcholinesterase and butyrylcholinesterase. The differences *in vitro* may be as great as a thousandfold at the concentrations which cause a significant depression. Thus the dose response relationship, as with the measurement of urinary alkylphosphates, will be specific to each OP.

63 Large inhibitions in butyrylcholinesterase have been noted in the absence of any significant symptoms of toxicity to the cholinergic nervous system and suppression of this enzyme is considered to be a more sensitive indicator of OP exposure than of toxicity. The level of erythrocyte acetylcholinesterase, on the other hand, appears to correlate reasonably well with the severity of acute OP poisoning cholinergic symptoms.

64 The correlation of erythrocyte cholinesterase with symptoms is particularly high when measured early, at least within 48 hours, following exposure. Symptoms have, however, also been recorded with no clear evidence of erythrocyte acetylcholinesterase depression.

65 Several spectrophotometric assays for the measurement of butyryl- and acetylcholinesterases are available. The units in which activity is expressed and the normal range will depend on the substrate used, but the differing methods will not affect the sensitivity to detect OP-induced depressions.

66 Both erythrocyte acetylcholinesterase and butyrylcholinesterases have a wide range of values in normal unexposed individuals, although in any one individual activity varies little with time. Interpretation of measurements in exposed subjects is greatly assisted if pre-exposure levels are available for both enzyme activities. In the absence of such baseline measurements, true falls in enzyme activity may remain undetected, although where serial measurements are taken, a change outside the normal expected variation (a 20% fall) may be indicative of a likely OP effect.

67 Depression in butyrylcholinesterase activity may, in particular, be associated with:

- physiological variation (eg pregnancy);
- disease (eg cancer, liver disease);
- iatrogenic (eg plasma inhibition or reduced synthesis by drugs);