Guidance Note MS 17 from the Health and Safety Executive

# Biological monitoring of workers exposed to organo-phosphorus pesticides

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## INTRODUCTION

1 The term 'pesticide' as used in this Guidance Note applies to preparations used to control or destroy any forms of living organism interfering with man's agricultural, environmental or amenity requirements.

2 Organo-phosphorus (OP) pesticides include phosphates, phosphites, phosphonates, phosphoramides, pyrophosphates and their sulphur analogues. Formulations are usually either liquids or powders which are mixed with water and applied as sprays, or are directly applied in granule form. A list of commonly used approved chemicals will be found in the booklet *Approved Products for Farmers and Growers* published annually by the Ministry of Agriculture, Fisheries and Food. This booklet is available from HMSO.

3 The production and use of OP pesticides has increased rapidly in recent years, because they are more short-lived in the environment and in biological systems than the organo-chlorine pesticides which they are replacing. However, OP pesticides can produce harmful effects effects in man following acute and subacute exposure, and repeated exposure at lower doses may cause insidious cumulative toxicity.

4 Another class of chemicals, the carbamates, are also used as pesticides for agricultural purposes and have similar pharmacological actions to the OP compounds. Symptoms of acute intoxication, arising from exposure to both groups of chemicals are similar, the main difference lying 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

## POTENTIAL OCCUPATIONAL SOURCES OF EXPOSURE

5 Any job which involves contact with OP pesticides, either directly or indirectly, is a potential source of exposure. These occupations range from laboratory workers undertaking research on OP pesticides to ambulance workers who, during the course of their duties may come into contact with injured operators or their contaminated clothing.

6 The majority of workers occupationally exposed are involved with OP pesticides in:

(a) manufacture and packaging;

(b) transport, storage and distribution;

(c) application and use;

(d) contamination from used containers, e.g. scrap recovery.

## ROUTES OF ABSORPTION

7 Depending upon the circumstances of use, the possible sites of contamination with OP pesticides are skin, respiratory tract and eyes. Under normal conditions of use, ingestion is rare, although small amounts may be swallowed in contaminated saliva. In agricultural practice, the usual route of absorption is via the skin, with inhalation being less important. OP preparations based on organic solvents are liable to diffuse through protective clothing unless prompt action is taken to wash off contamination. Contamination of the eyes may produce local effects and subsequent disturbance of vision.

## BIOLOGICAL EFFECTS

8 When poisoning with proprietary formulations of organo-phosphorus compounds occurs, the presence and influence of the solvent should not be forgotten. Local skin effects will almost certainly be due to the solvent; in exceptional and severe cases the progress of the intoxication can be seriously affected by the presence of an organic solvent.

9 The toxic effects produced by OPs in man are generally considered to be due to an inhibition of the cholinesterase group of enzymes. The two major functional enzyme types are acetylcholinesterase (AChE) and 'plasma' cholinesterase. Both occur in various tissues but in relation to OP toxicology the two most important sites are blood and the nervous system.

(a) *Nervous system* The prime toxic effects of OPs arise mainly from their ability to inhibit AChE in nervous tissue which permits an abnormal accumulation of the neuro-transmitter acetylcholine, particularly at cholinergic synapses and neuro-effector regions.

(b) *Blood* Erythrocytes (red blood cells) have AChE activity whereas blood plasma contains a non-specific cholinesterase. The biological function of these 'plasma' and red blood cell esterases is uncertain, but measurement of their activities forms a convenient means of biological monitoring for exposure to OP pesticides.

## CLINICAL MANIFESTATION OF ORGANOPHOSPHORUS POISONING

10 The diagnosis of OP poisoning is not 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.

11 Repeated absorption of small doses, as may occur from saturated clothing, have cumulative effects resulting in progressive inhibition of nervous tissue cholinesterase. The addition of a small extra exposure may then precipitate the classical condition of OP poisoning. These signs and symptoms do not generally appear until whole blood AChE activities have fallen to about 50% of normal pre-exposure values. The erythrocyte cholinesterase values may be considerably lower, e.g. 80% inhibition.

12 Symptoms of poisoning include those which are:

(a) non-specific:
headaches, giddiness, loss of appetite and nausea;

(b) those related to over-reactivity of voluntary muscle:
tremors and impaired co-ordination;

(c) those related to excessive activity of the autonomic nervous system:
miosis (pin point pupil), blurred vision, excessive salivation and sweating, increased bronchial gland secretion, slowing of the heart rate with decreased cardiac output and hypotension (low blood pressure) and running eyes and nose.

13 Other symptoms include:

(a) urinary incontinence, abdominal pain, vomiting and broncho-constriction (tightness of the chest) caused by over-activity of smooth muscles;

(b) central nervous system effects:

(i) depression of the brain stem respiratory centre;

(ii) various non-specific effects have been described following short-term or chronic low-level exposure, e.g. apprehension, anxiety, restlessness, irritability, depression, sleep problems, e.g. insomnia and dreaming, hallucinations, expressive language defects, mood swings, difficulty in concentration, memory impairment, slower speed of reaction and lapses of attention.

14 The pattern of signs and symptoms as they develop will to some extent depend upon the route of absorption of the pesticide. Thus following inhalation, the most notable effects will be miosis, running nose and tightness of the chest; the general systemic signs of poisoning will develop later. Following ingestion, intestinal colic is often a prominent and early feature. Following skin absorption miosis, running nose and chest tightness may not develop.

15 Death can occur in acute OP poisoning from respiratory failure due to paralysis of respiratory muscles aggravated by central depression of respiration, broncho-constriction and increased bronchial secretion.

## INHIBITION OF BLOOD CHOLINESTERASE ACTIVITY AS AN OBJECTIVE INDEX OF ORGANOPHOSPHORUS ANTICHOLINESTERASE POISONING

16 Although enzyme inhibition in tissues is not exactly parallel to that in blood, the most convenient choice of enzyme activity for measurement is that of blood cholinesterase.

17 The degree of differential inhibition of erythrocyte AChE and 'plasma' cholinesterase varies with the chemical structure of the OP and time. Thus with some OPs, the 'plasma' enzyme gives an earlier indication of absorption of the compound; with others the erythrocyte enzyme is inhibited to a greater extent, and others inhibit AChE and 'plasma' cholinesterase to similar degrees. The choice of enzyme activity to be measured will depend upon the chemical nature of the OP used. However, as there may be occupational exposure to several OPs over a period of time, it is more appropriate to measure the activities of both enzymes. With whole blood measurements, erythrocytes contribute 92% of AChE activity and plasma 8% of this activity. In the field there may be difficulty in separating erythrocytes and plasma; under these conditions it is possible to make measurements on whole blood although this diminishes the amount of information obtained.

18 In interpreting the results of cholinesterase activity determinations, the methodology used must be considered. Only when a single laboratory is involved in the cholinesterase activity measurements can results be compared over a period of time. Because of differences in the physical nature of effects measured, e.g. changes in colour or pH, the detection limits, sensitivity, units and 'normal values' vary. It is essential that for any group of observations there is consistency of methodology.

19 Numerous methods are available for measuring cholinesterase activity in biological fluids, the principal ones being based on titrimetric, manometric, radiometric, spectrophotometric and electrometric methods. All, except for the titrimetric method, are accurate and sensitive. The most appropriate and convenient method is spectrophotometry, in particular the Ellman technique described in *A new and rapid colourimetric determination of acetylcholinesterase activity* (G L Ellman, K D Courtney, V Andres and R M Featherstone, *Biochemical Pharmacology*, 1961, Vol. 7, pp 88–95.

20 Cholinesterase activity in normal whole blood and plasma varies between individuals. In order to interpret the significance of a measurement on a sample taken

during or after occupational exposure of a worker, it is essential to be able to relate this to control measurements made in that individual during a time when he was not exposed to OPs. In the absence of such base line measurements a minor, but genuine, degree of cholinesterase inhibition due to OP exposure may be missed.

21 No method of biological monitoring based on serial measurements of body fluid constituents is entirely adequate. The main limitations in measuring blood cholinesterase activity as an index of exposure to OPs are as follows:

(a) Blood cholinesterase activity, and its changes, may not necessarily be an index of the activity of the enzyme in nervous tissue. This is related to such factors as variations in permeability of the blood-brain barrier for different OPs and to differences in the kinetics of interactions of OPs with blood and neural enzymes.

(b) The method attempts to quantify the direct effect of the OP, i.e. inhibition of cholinesterase. It does not measure the pharmacological actions which give rise to the toxic effects, i.e. acetylcholine accumulation and related functional impairment.

22 In spite of its limitations as an index of functional disorder, the technique has found considerable practical usefulness as a monitor for exposure to OPs.

## HEALTH SURVEILLANCE

23 The success of any system of surveillance designed to detect or avoid early toxic effects depends upon the following:

(a) the availability of adequate pre-exposure information;

(b) carrying out the procedure on a regular basis using appropriate technology, suitably trained staff and with the full co-operation of employees and management.

24 Regular surveillance is not required for occassional users of OPs, e.g. garden use. However, it does become desirable for those regularly exposed to large quantities of OPs, e.g. pilots involved in aerial crop spraying and contract operators involved in ground spraying. For such employees a reasonable and practical scheme for monitoring workers would include:

(a) pre-exposure medical assessment, to confirm fitness for such work and to detect individuals with increased risk, e.g. those with liver disease or nervous disorders. At the same time advice can be given regarding safe methods of using OP pesticides and the recognition of early signs of poisoning;

(b) biological monitoring, which may continue with periodic medical assessment, to detect any early symptoms or signs of poisoning, in conjunction with blood tests to determine cholinesterase activities. When signs of toxicity occur before the set time for biological monitoring, this is an indication for immediate appropriate tests.

25 An effective biological screening programme based on measurement of blood cholinesterase activities would include:

(a) the measurement of both whole blood AChE and 'plasma' cholinesterase activities. It should be noted again that for comparability of serial results, one laboratory should be used for all the tests;

(b) the determination of 'pre-exposure base lines' following a period of at least 60 days without known exposure to any cholinesterase inhibiting compounds;

(c) the taking of blood samples at periodic intervals during occupational exposure to ensure the detection of cumulative toxicity at the earliest possible time. The time interval between consecutive samples depends upon the nature of the work being carried out. A reasonable time interval for the majority of workers with repeated exposure would be four to five weeks. In those occupations where early symptoms such as blurred vision and impaired co-ordination could present a particular hazard to the worker, other employees or the general public, e.g. pilots involved in regular aerial spraying during the seasonal period, a shorter interval between consecutive samples should be considered. Clinical measurement of accommodation and visual acuity may also prove helpful.

26 If depressions of cholinesterase activity are detected and the level of whole blood AChE has fallen to 65% or less of pre-exposure value, or the 'plasma' cholinesterase to 50% or less, then the worker should be medically examined. The medical officer may then, at his own discretion, taking into account the nature of the work involved and the clinical symptoms, recommend that the worker be removed from further exposure to OPs until such time as the affected person is considered fit to resume his occupation. The rate of recovery of blood enzyme activity varies with the chemical structure of the OP pesticide(s) to which the individual is exposed. The return of the enzyme complement requires up to 100 days. The erythrocyte cholinesterase returns to normal more slowly than the 'plasma' cholinesterase; this difference provides a useful confirmation of the diagnosis. It is not necessary for pre-exposure levels to be reached before an individual is considered fit to resume work. The medical officer should base his decision upon both clinical evidence and the results of biological monitoring.

### Electrophysiological monitoring

27 There are the following advantages and disadvantages in electrophysiological monitoring techniques:

(a) Electromyograph (EMG) measurements have been used in recent years to screen workers for occupational over-exposure to OPs. The method most frequently employed is based on measuring electrical activity over the adductor pollicis muscle resulting from stimulation of the ulnar nerve at the wrist. Although apparently a sensitive and early indicator of neuromuscular dysfunction, EMG has the disadvantage that

the method is not specific for OP anticholinesterases. No indication is given of central nervous system involvement and the relevance of changes to impairment of skilled movements has not been clearly defined.

(b) EMG measurements do provide an assessment of functional neural impairment and complement the assessment of target enzyme imparment measured by cholinesterase activity. A combined approach, using both techniques, yields information of considerable value in assessing OP exposure, and interpreting its significance in relation to health hazards. The EMG technique remains a research method requiring further evaluation. Subject to the availability of trained staff, and the necessary equipment, EMG records can be taken at the time of blood sampling with little additional inconvenience or loss of time.

## EMERGENCY TREATMENT

28 If a worker is suspected of having OP poisoning, medical attention should be sought as soon as possible.

29 Recommended first aid treatment:

(a) Stop the patient working, remove him from the exposure area into protective cover and keep him at rest.

(b) Remove all protective clothing and any other clothing that may be contaminated by chemical, taking care to avoid contaminating your own skin. Wash the affected skin with soap and water. Cover the patient with clean blankets, rugs or coats, etc.

(c) If breathing ceases or weakens, make sure the breathing passages are clear, remove false teeth or other obstructions from the mouth, and apply artificial respiration by whatever means are available (the Mouth to Mouth or Mouth to Nose methods should *not* be used). If the patient's eyes are affected, wash them out with clean running water for several minutes. When transporting the patient to hospital, see that he is placed in the recovery position, with his head down and tongue forward to prevent inhalation of vomit.

(d) Remember to tell the hospital and the doctor the name of the chemical which the patient has been using and show them any available leaflet or label regarding the chemical, or give them a note showing the name copied from the container. The free leaflet MS(B)7 *poisoning by Pesticides*, published by the Health and Safety Executive gives details of treatment.

30 A sample of the patient's blood should be taken as soon as possible after exposure and separated (if possible). The sample should then be stored at 4°C until such time as cholinesterase activities can be measured. 'Plasma' cholinesterase can be measured at most hospitals, but erythrocyte AChE analysis requires specialist laboratories.

31 A medical officer should treat a patient presenting signs of OP poisoning with atropine (2mg intramuscularly or subcutaneously). If the condition is severe, atropine may be given intravenously. When symptoms are not promptly relieved, the dose may be repeated every 15 to 30 minutes until the patient is fully atropinised. Victims of OP poisoning can tolerate doses of atropine which are very large by conventional standards. Pralidoxime mesylate (P2S), available from poison centres, is the specific antidote. The DHSS can provide a list of hospitals which have facilities for an antidote and treatment. Both atropine and P2S are most effective during the first 24 hours after poisoning and an assessment of the need to continue with atropine should certainly be made after 24 hours. The heart rate is a useful guide and a rate between 70 and 80 beats per minute should be the target. When muscular activity and convulsions are a feature, diazepam, by injection, will be of considerable value.

## NOTIFICATION

32 OP poisoning is a notifiable disease under the Factories Act 1961 and also a prescribed disease under the National Insurance (Industrial Injuries) Act 1965. When an agricultural worker is suspected of suffering from OP poisoning due to a substance specified in the Health and Safety (Agriculture) (Poison Substances) Regulations 1975, the local Agricultural Inspectorate should be informed.

## FURTHER INFORMATION

This Guidance Note is produced by the Health and Safety Executive. Further advice on this or any other publications produced by the Executive is obtainable from Baynards House, 1 Chepstow Place, London W2 4TF, or from Area Offices of the HSE.

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