INSECTICIDES IN THE URBAN ENVIRONMENT

T. C. MARRS
Department of Health, London

INTRODUCTION

Insecticides are used in the urban environment for much the same reasons as they are in the rural environment. Major differences however are that use on food producing crops is only on a very small scale, while use in public hygiene is much more extensive. Public hygiene use of insecticides presents specific problems in that the opportunity for human exposure may occur when subjects cannot leave the affected area (eg hospital wards), during treatment. Exposure can frequently be minimized however,by advising a reentry period, often 48h, and this can conveniently be done by treating at the beginning of a weekend. The use of non-volatile insecticides as poisoned baits presents less of a problem,where subjects cannot leave the area, but such use is liable to present a hazard to children and pets unless care is taken.

The main groups of insecticides are:-

1. Organochlorines (OCs)
2. Anticholinesterases (AntiChEs)
   A. Organophosphates (OPs)
   B. Carbamates
3. Pyrethroids
4. Compounds of natural origin, including antibiotics,avermectins and derris (rotenone).
5. Specific inhibitors of aspects of insect metabolism such as chitin synthesis.

The first three groups all act as insecticides by interfering with nerve transmission in insects. Unfortunately they also do so in man and, potentially, all will show effects on the mammalian central and/or peripheral nervous system.By contrast the last group interferes with metabolic processes in insects that do not occur or are unimportant in mammals.For example mammals, including man do not synthesize chitin. Therefore such insecticides are intrinsically safer.

ORGANOCHLORINES

The OCs are becoming less and less important: their biopersistance and persistence in the environment have led,in many countries, to revocation of use (eg DDT) or severe restriction of use (lindane). Nevertheless OCs are still sufficiently widely used for a knowledge of their toxic effects to be useful and it is important to be clear that, purely from the point of view of human safety, many of them are not particularly toxic. It was primarily environmental concerns that led to their restriction although their persistence in humans, as shown by the continuing presence of OCs in human milk (WPPR,1992) has also caused concern.

The OCs include DDT, HCH and lindane, the cyclodienes, dieldrin, endrin and heptachlor, and toxaphene.The most prominent effects of the OCs are those referable to the CNS. DDT produces tremor and incoordination in lower doses and convulsions in high doses, whereas HCH and the cyclodienes may produce convulsions as the first sign of intoxication, as well as fever, by a central effect. Chlorinated hydrocarbons produce microsomal enzyme induction and characteristic histopathological changes in the livers of experimental animals, and tumors are seen in rodents. These tumors do not appear to be in indicative of genotoxic carcinogenicity. There has been some concern over a possible association between lindane and aplastic anaemia.

There is no specific antidote for OC poisoning and it is treated symptomatically. Diazepam is usually used to deal with the convulsions.

Proceedings of the First International Conference on Urban Pests.
K.B. Wildey and Wm H.Robinson (editors). 1993

ANTICHOLINESTERASES

Two groups of anticholinesterases, the organophosphates (OPs) and the carbamates,are widely-used as insecticides. They are often more acutely toxic than the OCs. Their action is respectively to phosphorylate or carbamylate esterases, particularly the enzyme acetylcholinesterase, causing accumulation of the neurotransmitter, acetylcholine. A variety of cholinergic symptoms and clinical signs occurs in the parasympathetic system, such as bronchorrhea, salivation, constriction of the pupil of the eye and abdominal colic. Sympathetic effects can also ensue, together with signs of central nervous system involvement, initially confusion and sometimes convulsions. Where death occurs, it is usually due to respiratory paralysis, which may be of central or peripheral origin or both. However it is generally believed that, provided the patient survives, the symptoms and clinical signs of OP poisoning are reversible. The anticholinesterase effects of OPs and carbamates do not cause widespread pathological changes per se, morphological change being confined to the nervous system, skeletal muscle and heart muscle. However there is recognition that exposure to high doses of OPs and possibly also lower doses and carbamates may result in long term clinical and morphological effects in the central nervous system.

The numerous cholinesterases in the body show different magnitudes of sensitivity to inhibitors. Plasma cholinesterase is often the most sensitive cholinesterase to inhibition and reactivates slowly (Škrinjaric- Špoljar et al, 1973), making the plasma cholinesterase a useful marker of exposure. However, inhibition of this enzyme correlates poorly with cholinergic symptoms and signs, so that plasma cholinesterase inhibition is a marker of exposure and no more. Erythrocyte acetyl cholinesterase inhibition generally correlates better with cholinergic symptoms and signs, but unless blood samples are stored properly reactivation ex vivo may interfere with the validity of blood samples (Mason et al.1992).

Organophosphates

OPs include chlorpyrifos, propetamphos, acephate and diazinon. The OP anticholinesterases are derivatives of phosphoric, phosphonic or phosphorothioic or related acids. They are related to the chemical warfare nerve agents, which however are often phosphonofluoridates. Inactivation of cholinesterases by OPs occurs by a reaction in which one substituent group attached to the phosphorus atom, the leaving group, is lost producing a dialkylphosphoryl enzyme.Most insecticides produce a dimethylphosphorylated enzyme or a diethylphosphorylated enzyme and the kinetics of reactivation are the same for each derivative whatever the structure of the leaving group. Reactivation of the dimethylphosphorylated enzyme is considerably quicker than the diethylphosphorylated enzyme and will occur within a few hours (WHO, 1986). Aging is a reaction in which one alkyl group is lost to leave a monoalkylphosphoryl enzyme. Such derivatives are refractory to spontaneous or oxime-induced reactivation.The nerve agent soman (pinacolyl methylphosphonofluoridate) produces an unusual phosphorylated enzyme that ages with a half time of a few minutes. No pesticidal OP gives rise to a complex that ages at comparable speed,but unsuccessful use of oximes has been attributed to aging with certain OP insecticides (Glickman et al, 1984: Gyrd-Hansen and Kraul,1984).

Since the OP insecticides all have the same basic action, and this property is responsible for their acute toxicity, quantitative differences in toxicity are partly due to differences in absorption, distribution and metabolism. However the rates of formation of the OP-acetylcholinesterase complex, of enzyme reactivation and of the aging reaction (see above) must also be considered. One group of OPs, the phosphorothioates and phosphonothioates with a P=S group, differ from the other OPs in that they tend to be less toxic to man than other OPs. Pure preparations of this type of phosphorothioate only acquire toxicity after conversion of the P=S moiety to a P=O moiety.

A major difference between the OP and carbamate cholinesterase inhibitors is that certain OPs cause OP-induced delayed neuropathy (OPIDN). OPIDN is a sensory-motor neuropathy, tending to most severe in the long axons, occurring 7-14d after exposure to certain OPs, eg mipafox (Barrett et al, 1985). The most disabling feature is the paralysis of the legs which may result. The initial event in the pathogenesis of the syndrome appears to be inhibition of neuropathy target esterase (NTE).

Proceedings of the First International Conference on Urban Pests.
K.B. Wildey and Wm H.Robinson (editors). 1993

This is followed by an aging reaction similar to that described for soman with acetylcholinesterase above (Johnson 1975). However the structural requirements for inhibition of acteylcholinesterase and NTE are different (Gordon et al, 1983) and by the use of appropriate tests, it has been possible to avoid the use of neuropathic OPs as insecticides. OPs that have been associated with OPIDN include leptophos, EPN, cyanofenphos and trichloronat (el-Sabae et al, 1981).

A major concern with OPs is the possibility that the effects on the central nervous system may not be as reversible as was formerly thought. While it is generally recognized as likely that large, convulsive doses of OPs will produce effects that are not reversible, in the context largely of exposure to sheep dips, it has recently been suggested that OPs at lower doses might give rise to long term changes. At present this question is unresolved (for review see Marrs, 1993).

OPs have effects on many organs some of which are completely independent of their anticholinesterase effects. These include mutagenicity and carcinogenicity as well as organ specific toxicity to the heart and kidney and other organs (Ludomirski et al, 1982; Singer et al, 1987; Baskin, 1992; Pimentel and Carrington da Costa, 1992; Wedin, 1992). A myopathy has been described in experimental animals (Preusser et al, 1967; Wecker et al, 1978) and at autopsy of human poisonings (de Rueck and Willems, 1974). Lung damage,probably attributable to impurities, has been described with certain phosphorothioate pesticides (Aldridge and Nemery, 1984).

The treatment of OP poisoning involves symptomatic treatment and the use of antidotes. Atropine, an anticholinergic compound, and an oxime enzyme reactivator such as pralidoxime chloride (2-PAM) or obidoxime is used (von Bisa et al, 1964; Sanderson, 1985; Bismuth et al, 1992), while convulsions and muscle fasciculation respond to diazepam. Very large doses of atropine may be necessary (Hopmann and Wanke, 1966). The antidotal treatment is only effective against acute poisoning and there is no specific treatment for OPIDN or other long term effects.

Carbamates

Carbamates used for public hygiene purposes include fenoxycarb and bendiocarb.

In general the carbamates produce toxicity similar to that of organophosphates, but carbamate-inhibited cholinesterases reactivate more rapidly than enzymes inhibited by OPs, with the result that the effects do not last as long in carbamate poisoning.

PYRETHRINS AND PYRETHROIDS

Pyrethrins are photolabile natural insecticides produced from plants, such as pyrethrum and are esters of pyrethric or chrysanthemic acids. The synthetic pyrethroids are similar compounds rendered photostable by various substituent groups, such as chlorine, bromine or cyanide, on the basic structure. Because of their low mammalian toxicity, high insecticidal potency and lack of persistence in the environment, they have achieved widespread usage as household insecticides and in agriculture; very large amounts have been used in wood treatment in those parts of North America affected by termites. Synthetic pyrethroids hydrolyze rapidly in the mammalian body and in the environment. Therefore bioaccumulation does not occur, nor do they persist in soils. However, the pyrethroids can be allergens and allergic rhinitis, extrinsic allergic alveolitis and asthma have been reported (Bismuth et al, 1987).

The pyrethroids are neurotoxic by action on sodium channels (Vijverberg and van den Bercken, 1990). However, the neurotoxicity has nugatory morphological correlates and pyrethroids do not cause delayed neurotoxicity of the type seen with OPs (Aldridge, 1990). In experimental animals, synthetic pyrethroids produce central neurotoxicity, which may take the form of one or other of two syndromes. The CS syndrome consists of marked choreoathetosis, salivation, coarse tremor and convulsions and is a property of those pyrethroids with an α-cyano group (deltamethrin, cyfluthrin, cypermethrin, fenpropathrin, fenvalerate, flucythrinate and fluvalinate). The T syndrome is characterised by fine or coarse tremor, hypersensitivity to stimuli and aggressive sparring and is seen in those compounds without the cyano group (permethrin and resmethrin as well as the components of natural pyrethrum) (Aldridge, 1980). As well as central effects, in experimental animals, pyrethroids cause functional impairment of peripheral nerves (Rose and Dewar, 1983). Axonal

degeneration has been described at near lethal doses and there is no evidence that pyrethroids can produce delayed neuropathy of the OP type.

Despite the findings in the nervous systems of animals, in humans pyrethroids cause paraesthesia mainly in the face and little else. Pruritis with blotch erythema, lachrymation and itchy rhinorrhoea have also been described (Aldridge, 1990).

Specific treatment of the effects of synthetic pyrethroids is rarely necessary as systemic effects are practically unknown in humans.

INSECTICIDES OF BIOLOGICAL ORIGIN other than PYRETHRUM

Rotenone

The other insecticide of biological origin that everybody has heard of is rotenone, under the name derris (actually the name of an Asiatic plant). Rotenone blocks mitochondrial electron transport and in mammals this is responsible for the toxic effects in mammals, including humans. It can also cause dermatitis.

Avermectins

Abamectin is the common name for a mixture of avermectin B1a and B1b, macrocyclic lactone disaccharide antibiotics from *Streptomyces avermitilis*. Abamectin is used as an insecticide and acaricide, whilst the dihydro derivative, ivermectin, is used to control nematodes and arthropods (Wright, 1986). The insecticidal activity is based on action upon GABAergic nerve transmission; because mammals have GABAergic synapses only in the CNS, the mammalian blood/brain barrier ensures a degree of specificity. A notable feature of this group of compounds is their low mammalion toxicity however there is extensive human experience as ivermectin is used in the control of human onchocerciasis.

SPECIFIC INHIBITORS OF ASPECTS OF INSECTICIDE METABOLISM

The attraction of this group of insecticides is that they have no target organ or system in mammals.

The juvenile hormone analogs, which include hydroprene and methoprene are of low acute toxicity (LD50 c 5g/kg) and usually non-teratogenic and non-genotoxic (Hayes and Laws, 1991). Chitin synthesis inhibitors, such as diflubenzuron, are also generally of low toxicity.

CONCLUSION

All groups of insecticides have particular advantages and disadvantages in the urban environment, and it is particularly noteworthy that lability can be either advantageous or disadvantageous depending on the context. The OCs are not particularly toxic but are very persistent, while the OPs and carbamates tend to be more acutely toxic but less persistent. The specific inhibitors of insect metabolism act too slowly for many purposes. The synthetic pyrethroids are of low mammalian toxicity by most routes of administration and have a peculiarly satisfying "knock-down" effect. However, their lack of persistence may be a disadvantage in wood preservation.

DISCLAIMER—This paper represents the views of the author and not necessarily those of the Department of Health.

REFERENCES

Aldridge, W.N. and Nemery, B.(1984). Toxicology of trialkylphosphorothioates with particular reference to lung toxicity. *Fund Appl Toxicol.* 4:S215-S223.

Aldridge WN (1990). An assessment of the toxicological properties of pyrethroids and their neurotoxicity. *Crit Rev Toxicol,* 21, 89-103.

Barrett DS, Oehme FW and Kruckenberg SM: A review of organophosphorus ester-induced delayed neurotoxicity. *Vet Hum Toxicol* 27 (1985) 22-37.

Baskin SI and Whitmer MP (1992). Cardiac effects of anticholinesterases in clinical and experimental toxicology of organophosphates and carbamates ed B Ballantyne and T C Marrs.
Butterworth-Heinemann Oxford PP 135-144

Bismuth C, Baud FJ, Conso F, Frejaville JP and Garnier R (1987). *Toxicologie Clinique,* 4th Ed. Flammarion, Paris p424.

Bismuth C, Inns RH and Marrs TC (1992). Efficacy,toxicity and clinical use of oximes in anticholinesterase poisoning in clinical and experimental toxicology of organophosphates and carbamates ed B Ballantyne and T C Marrs. Butterworth-Heinemann Oxford PP 555-577

de Rueck J and Willems J (1975). Acute parathion poisoning: myopathic changes in the diaphragm. *J Neurol,* 208, 309-314.

el-Sebae AH, Soliman SA, Ahmed NS and Curley A (1981). Biochemical interaction of six OP delayed neurotoxicants with several neurotargets. *J Environ Sci Health,* 816, 465-474.

Glickman AH, Wing KD and Casida JE (1984). Profenofos insecticide bioactivation in relation to antidote action and the stereospecificity of anticholinesterase inhibition,reactivation and aging. *Toxicol Appl Pharmacol.* 73, 16-22.

Gordon JJ, Inns RI, Johnson MK, Leadbeater L, Maidment MP, Upshall DG, Gooper GH and Rickard RL (1983). The delayed neuropathic effects of nerve agents and some other organophosphorus compounds. *Arch Toxicol,* 52, 71-82.

Gyrd-Hansen N and Kraul I (1984). Obidoxime reactivation of organophosphate inhibited cholinesterase activity in pigs. *Acta Vet Scand.* 25, 86-95.

Hayes WJ and Laws ER (1991). Handbook of pesticide toxicology. Academic Press, New York, p612-613.

Hopmann G and Wanke H (1966). Höchdosierte Atropinbehandlung bei schwerer Alkylphosphatvergiftung. *Deutsche Med Wochenschr,* 99, 2106-2108.

Johnson MK (1975). Organophosphorus esters causing delayed neurotoxic effects. *Arch Toxicol,* 34, 259-288.

Ludomirsky, A., Klein, H.O., Sarelli, P. (1982). QT prolongation and polymorphous "torsade des pointes" ventricular arrhythmias associated with organophosphorus insecticide poisoning. *Am J Cardiol.* 49. 1654-1658.

Marrs TC (1993). Organophosphate poisoning. *J Pharm Therap in press.*

Mason H, Waine E and McGregor A (1992). In vitro studies on human cholinesterase (ChE) and biological effect monitoring of organophosphorus pesticide exposure. *Human and Experimental Toxicology* 11, 557.

Pimentel JM and Carrington da Costa RB (1992). Effects of organophosphates on the heart in clinical and experimental toxicology of organophosphates and carbamates ed B Ballantyne and TC Marrs, Butterworth - Heinemann, Oxford pp 145-148.

Preusser, H-J.(1967). Die Ultrastructur der motorischen Endplatte im Zwerchfell der Ratte und Veränderungen nach Inhibierung der Acetylcholinesterase. *Zeitschrift Zellforsch.* 80: 436-457.

Rose GP and Dewar AJ (1983). Intoxication with four synthetic pyrethroids fails to show any correlation between neuromuscular dysfunction and neurobiochemiocal abnormalities in rats. *Arch Toxicol,* 53, 297.

Sanderson DM (1985). Atropine or hyoscine in treatment of acute organophosphate poisoning? *Lancet* I 1168.

Singer AW, Jaax NK, Graham JS and McLeod CG (1987). Cardiomyopathy in soman and sarin intoxicated rats. *Toxicology Lett,* 36, 243-249.

Škrinjaric-Špoljar M, Simeon V and Reiner E (1973). Spontaneous reactivation and aging of dimethylphosphorylated acetylcholinesterase and cholinesterase. *Biochim Biophys Acta,* 315, 363-369.

Vijverberg HPM and ven den Bercken J, (1990). Neurotoxicological effects and the mode of action of pyrethroid insecticides. *Crit Rev Toxicol,* 21, 105-126.

von Bisa, K., Fischer, G., Müller, O., Oldiges, H. and Zoch, E.(1964). Die Antidotwirkung von Bis-(4-hydroxyiminomethyl-pyridinium methyl)-äther-dichlorid bei mit Alkylphosphat vergifteten Ratten. *Arzneimittelforsch.* 14. 85-88.

Wecker L, Kiauta T and Dettbarn W-D (1978). Relationship between acetylcholinesterase inhibition and the development of a myopathy. *J Pharm Exp Ther,* 206, 97-104.

Wedin GP (1992). Nephrotoxicity of anticholinesterases in clinical and experimental toxicology of organophosphates and carbamates ed B Ballantyne and TC Marrs, Butterworth - Heinemann, Oxford pp 195-202.

WHO (1986). Environmental Health Criteria 63. Organophosphorus insecticides:a general introduction. World Health Organization, Geneva. p 78.

Wright DJ.(1986) Biological activity and mode of action of avermectins. In *Neuropharmacology of pesticide action* ed MG Ford, 4GG Lunt, RC Reay and PNR Usherwood. Ellis Horwood, Chichester, England pp 174-202.

WPPR (1992). Working Party on Pesticide Residues Report 1990-1991. HMSO, London, Edinburgh and Belfast.