

PESTICIDES AND THE ENVIRONMENT^{1, 2}

A Review of the Changing Profile of Pesticides' Effect on Human Health

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There is an increasing tendency to use organophosphate insecticides in place of the more persistent organochlorines. This article discusses organophosphate poisoning—diagnosis, treatment, and preventive measures. It also covers the pollution problems of organochlorine pesticides and recommends fuller international surveillance through development of pesticide protection teams.

Introduction

The qualitative characteristics of the spectrum of chemicals being used for pest and vector control in agricultural and public health activities is continually undergoing change. Changes in pest infestations, resistance to selected pesticides, alterations in crop production economics, and the impact of these chemicals on non-target species are some of the many factors influencing the choice of chemicals used for agricultural and public health purposes.

Over the last three or four years, the change has been away from the more persistent organochlorine pesticides, with a switch to the faster-acting and generally more toxic organophosphate and carbamate groups. The United States pesticide production figures for 1960-1968 are shown in Table 1; these figures illustrate the type of changes taking place.

Human health problems can be anticipated

from such changes. The organophosphates, because of their toxicity, and the organochlorine pesticides, because of their persistence, present different medical problems. Today's physicians and veterinarians are increasingly being called upon to manage a wide variety of pesticide intoxications, and at the same time to give advice on pollution problems created by persistent pesticides.

In trying to review these several changing problems of pesticide exposure, this paper will first discuss the clinical aspects of human toxicity resulting from organophosphate exposure. Second, it will review the potential for training and surveillance of the exposed worker. And third, it will summarize the epidemiology of DDT residues in man. A possible plan for international surveillance through development of pesticide protection teams will also be discussed.

Human Pesticide Intoxication with Organophosphates

Organophosphates are implicated in more human poisonings than any other pesticide group, and ethyl parathion is the member most often known to produce accidental, occupational, and epidemic poisoning. The ensuing illness can mimic several more common medical emergencies, such as myocardial infarction,

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TABLE 1—Annual pesticide production in the United States of America (in thousands of pounds).

Compound	1960	1962	1964	1966	1968	1970
Calcium arsenate	6,590	4,660	6,958	2,890	3,398	1,418
Lead arsenate	10,062	9,990	9,258	7,328	9,016	9,142
Copper sulfate	116,000	79,968	83,768	103,416	87,568	101,136
Aldrin-toxaphene group*	99,671	106,276	105,296	130,470	115,974	107,311
Benzene hexachloride†	37,444	12,022	—	—	—	—
DDT	164,180	167,032	123,709	141,349	139,401	123,103
Methyl bromide	12,659	12,757	16,994	16,345	20,454	20,033
Methyl parathion	11,794	16,156	18,640	35,862	38,163	50,572
Parathion	7,434	8,786	12,768	19,444	—	—
Ferbam	2,529	2,966	1,838	1,379	1,900	—
Nabam	2,978	4,216	2,251	2,053	—	1,938
Zineb	—	—	6,664	4,721	3,081	—
2,4-D acid	36,185	42,997	53,714	68,182	79,263	47,077
2,4,5-T acid	6,337	8,369	11,434	15,489	17,530	4,999
Other organic pesticides‡	277,229	348,967	437,943	577,816	698,253	729,210

* Includes the chlorinated compounds aldrin, chlordane, dieldrin, endrin, heptachlor, and toxaphene.

† Gross production (gamma isomer content was 7.7 million pounds in 1961, 3.4 million pounds in 1962, and 1.8 million pounds in 1963); no data since 1963.

‡ Includes such materials as dithiocarbamate fungicides, malathion, methoxychlor, captan, TDE, organic rodenticides, etc.; does not include all fumigants.

Source: U.S. Department of Agriculture, *Agricultural Statistics*, 1968 and 1970.

encephalitis, and pulmonary edema. In children, the condition has been confused with asthma, epilepsy, and pneumonia. The physician will not always be able to obtain a clear history of exposure, and there are several reports of parathion poisoning incurred through very bizarre exposure mechanisms.

For example, a number of children in Florida were recently poisoned by exposure to illicitly sold parathion powder. The peddler, most frequently visiting poorer residences, would sell this pesticide in unlabelled paper bags and advocate its use in the home as a roach killer (1). On another occasion the material was sold in a barber shop; elsewhere, children have been poisoned by wearing contaminated jeans or by eating dirt previously contaminated by a parathion spill (2, 3). Another common poisoning mechanism is the pesticide container, which only too frequently is sold in the open market after use, or is brought home from the fields and used as a garbage container or a receptacle for mixing and storing food.

Mention should also be made of the poisoning potential of pesticide warehouses when they fall into disrepair. Pesticide spillage occurs frequently, and if the floors are not concrete



Used pesticide containers being sold in open market.

there may be serious soil contamination. Later, if the area becomes flooded, the contaminated soil might be washed down the road and seep into adjoining food warehouses. Situations such as these can account for epidemic pesticide poisonings that may not be easily recognized if diagnostic facilities are not available.

The Illness

Symptoms usually appear two to four hours after skin exposure and 15-60 minutes after ingestion. They are due to cholinesterase inhibition, and the effects are both muscarinic and nicotinic, developing because of the accumulation of acetylcholine.

The muscarinic effects include nausea, vomiting, abdominal cramps, involuntary defecation, diarrhea, sweating, salivation, pain in the chest, and a blurring of vision due to miosis. The nicotinic effects include weakness, fasciculation, twitching, and flaccid paralysis. When the breathing muscles are involved respiratory embarrassment occurs, leading to apnea and death. Death is due to respiratory failure, which may be the result of paralysis of the muscles of respiration or blockage of the bronchial tubes with secretions and constriction of the smaller bronchioles.

The patient is anxious, restless and may soon develop convulsions and coma. At first he is pale, sweating, frothing at the mouth; he usually has pinpoint pupils, though in some instances the pupils may be dilated. Cardiovascular signs include tachycardia and hypertension; several abnormal electrocardiographic changes have also been reported. Neurological abnormalities include flaccid paralysis and electroencephalographic changes. If hypoxia is not quickly corrected, these changes in the central nervous system may become permanent.

Laboratory Diagnosis

It is important to emphasize that the physician's or veterinarian's diagnosis of organophosphate poisoning must be made on clinical grounds, as there is not sufficient time to wait for laboratory results before commencing treatment. The laboratory, therefore, provides confirmatory evidence. Low readings of red blood cell cholinesterase and plasma cholinesterase strongly suggest organophosphate poisoning.

There are several laboratory methods for measuring these enzyme levels, but the automated pH stat and Michel electrometric

methods are the ones most frequently used. The normal value ranges for the Michel method are 0.39-1.02 Δ pH/hr for male red blood cell cholinesterase and 0.44-1.63 Δ pH/hr for male plasma cholinesterase (4). Females have slightly lower levels. For the pH stat, the range is 8-17 μ M/ml/min for red blood cell cholinesterase and 1.2-5.5 μ M/ml/min for plasma cholinesterase (5). Several colorimetric test kits are available, and the subject has been well reviewed by Witter (6).

Most organophosphate pesticides reduce both plasma and red blood cell cholinesterase, but with Dursban (R) only plasma cholinesterase is inhibited. In the case of carbamates there is rapid reactivation of the cholinesterase, and sometimes by the time samples are analyzed the results are within normal ranges.

It is very important to collect the blood for cholinesterase testing before oximes are introduced, since these antidotes produce rapid reactivation of the blood cholinesterase and information on the baseline value is lost. The blood should be collected in a heparin tube and should be refrigerated.

Both red blood cell and plasma cholinesterase levels can be lowered by a wide variety of other conditions. Thus, plasma cholinesterase can be reduced in liver disease, malnutrition, and myocardial infarction, as well as after administration of certain drugs. Also, a few otherwise normal persons have a genetic anomaly producing reduced plasma cholinesterase activity and an unusual sensitivity to quaternary ammonium esterase inhibitors. Such persons may have difficulty with succinyl choline anesthesia. Red blood cell cholinesterase inhibition occurs in disseminated sclerosis, paroxysmal nocturnal hemoglobinuria, and in the newborn.

Laboratory measurement of pesticide metabolite levels can also provide valuable information about pesticide poisonings. Thus paranitrophenol (PNP), which is a urinary metabolite of parathion, chlorothion, and EPN,⁴ will more specifically identify the chemi-

⁴O-ethyl-o-p-nitrophenyl benzenethiophosphonate.

cal characteristics of the intoxicant, and will provide useful clinical information as to the magnitude of initial exposure and the need for continued atropine medication.

Alpha-naphthol and iso-propoxyphenol are examples of the urinary metabolites of carbaryl and OMS-33 (Baygon)⁵ respectively, which can be readily detected in poisonings with these carbamate insecticides. Their identification provides additional information on poisonings by these agents.

Gas chromatography, one of the most sensitive diagnostic procedures that the laboratory can perform during a poisoning incident, is the final diagnostic laboratory test. With the use of multiple column analysis and the flame photometric detector, the exact nature of the pesticide can be determined by examining the patient's gastric content, blood, and other tissues.

Treatment

The four major essentials of treatment are (1) restoration of the airway and the correction of hypoxia; (2) atropine and oxime therapy; (3) decontamination; and (4) investigation at the scene of the poisoning.

Airway restoration and hypoxia correction. The mouth and pharynx should be cleansed of secretions with a finger, or by suction, and an airway inserted; endotracheal intubation may be required. The cuff should be inflated before gastric lavage is attempted, so as to avoid aspiration of vomitus. Positive pressure methods of artificial respiration or 50 per cent oxygen via a nasal catheter should be used to correct the hypoxia.

Atropine therapy. Atropine is life-saving and should be administered as soon as possible. This therapy should be continued until pupillary dilation is achieved. Treatment should be prompt and vigorous. Afflicted patients are usually tolerant to atropine and large doses may be required.

Initially 2-4 mg are given intravenously, and

this is repeated every 5 to 10 minutes. Pupillary dilation and a pulse rate of 140 beats per minute are the most important end-points of treatment. Proportionately smaller doses are administered to children, but here again atropinization is the desired state in all cases. Goetsche, describing a severe case of poisoning in an adult sprayman who required atropine therapy for 18 days, reported the largest daily dose to be as high as 445 mg (7).

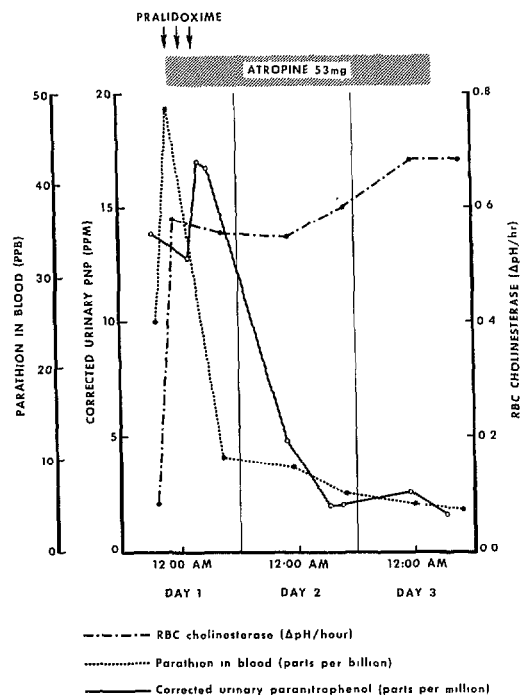
It is justifiable to commence atropine therapy in the field so long as this step is the prelude to subsequent admission to a hospital or clinic. It is totally unjustifiable to give one or two doses in the field and then allow the worker to go home. When administered as a first-aid measure in the field, and on the understanding that such a procedure is in preparation for hospitalization, the World Health Organization has recommended the use of automated atropine injectors in the field. Supplies of these should be made readily available during the spraying season.

When laboratory facilities are adequate, it is possible to monitor a severely poisoned victim by three toxicological parameters: cholinesterase measurements, urine metabolite excretion levels, and blood levels of the pesticide. Figure 1 shows the toxicological dynamics of a case of parathion poisoning in a 45-year old sprayman; the rapid rise of the red blood cell cholinesterase should be noted following administration of pralidoxime (2-pyridinium aldoxime methiodide).

Oxime therapy. Pralidoxime is the oxime most frequently used in treating organophosphate poisoning in the United States. It is particularly helpful in relieving generalized muscle weakness and respiratory muscle weakness. It should be given in conjunction with atropine, and as early as possible. The usual adult dose is 1 g administered intravenously, preferably as an infusion of a 250 cc saline solution given over a 30-minute period. If this is impracticable, a slow intravenous injection of a 5 per cent solution in water over a period of not less than two minutes can be given. A second dose can be given in one hour. The dose

⁵*o*-isopropoxyphenyl methylcarbamate.

FIGURE 1—Red blood cell (RBC) sequential cholinesterase, blood parathion, and urine paranitrophenol (PNP) changes in a severe case of oral ingestion of parathion treated with three 1-gram doses of pralidoxime and 53 mg of atropine.



essential. The first wash should be preserved for toxicologic studies.

Scene investigation. Appropriate health and agricultural authorities should always be notified of serious pesticide poisoning, as the subsequent field visits by these authorities will often prevent further intoxications. Health education can be given to other workers, and if there is serious contamination in a home the inhabitants can be shown how to decontaminate the home environment with caustic soda.

Training and Surveillance of the Pesticide Worker

The occupational hazards of the pesticide worker can be largely overcome by judicious pre-employment education. The nature of the chemicals and their potential for absorption through the skin, the mouth, and the lungs should be emphasized. Instruction should be given on the need for careful washing of hands and subsequent changing of clothes; the benefits of protective clothing should be stressed.

As workers shift from using the organochlorine pesticides to the more toxic organophosphates, they often fail to fully recognize the hazards of these latter chemicals. These hazards should be explained and stressed, and the importance of avoiding skin contamination should be strongly emphasized. Bare feet or canvas shoes should be discouraged, gloves and masks which leak should be destroyed, and the particularly great hazards involved in handling the concentrate should be emphasized.

The potential hazards of the empty pesticide container to the community also need to be stressed; the worker should be told to rinse out the drum when it is empty, perforate the base with a pickaxe, and then bury it in the field. Several industrial chemical firms recently started to put polyethylene bags inside the metal containers, thereby reducing the hazards somewhat if such containers should later be taken and used in other ways.

On the national level, multiple poisoning incidents may be prevented if serious thought and planning is devoted to all phases of

in children is proportionately lower, and 0.5 g is the usual dose for a 10-year old child.

These oximes act on the binding of organophosphate pesticides with a cholinesterase moiety, breaking up this union and making free cholinesterase available. They are not uniformly active against all the organophosphates and are not recommended for use in cases of carbamate poisoning. However, supplies of this very valuable antidote should always be available in those hospitals and clinics responsible for the care of spraymen working with organophosphate insecticides.

Decontamination. Clothing should be removed and the skin thoroughly washed with soap and water, paying particular attention to the hair and removal of debris from under the nails. Following oral ingestion, gastric lavage is



Leaking pesticide drums containing concentrated parathion.

pesticide transportation, shipping, and storage. Special care should be exercised at dockside to avoid damaging any pesticide drums. The chemicals should then be stored in a concrete building, off the ground on a firm trestle, and separate from food supplies. When being transported from the warehouse, the drums should be firmly secured and kept separate from any food.

With regard to labelling, instructions should be clear and printed in the language of the country of use, preferably with descriptive warning symbols to help the illiterate. In the field, pesticides should always be stored in their original containers; the practice of transferring them to alternate receptacles, such as soft drink or liquor bottles, should be discouraged and the hazards publicized through the mass media.

Apart from these measures designed to promote safer handling, regular cholinesterase and urine testing programs will provide added health protection for the worker. In cholinesterase testing programs it is usually advisable to remove the worker from further organophosphate pesticide exposure if he shows a reduction in his baseline cholinesterase values of 50 per cent or more.

When baseline data are not available, it has been our practice in Florida to remove persons who have a red blood cell cholinesterase level of $0.40 \Delta \text{pH/hr}$ or less (Michel) from further

exposure to organophosphates. Over a five-year period of study we have seen many workers who are asymptomatic at that level and below, but time, has proven the reliability of this standard of $0.40 \Delta \text{pH/hr}$.

We usually recheck the blood after a three-week period, during which the individual is employed handling other chemicals such as fertilizers. After this interval of time, it is usually safe to allow him to return to his previous work.

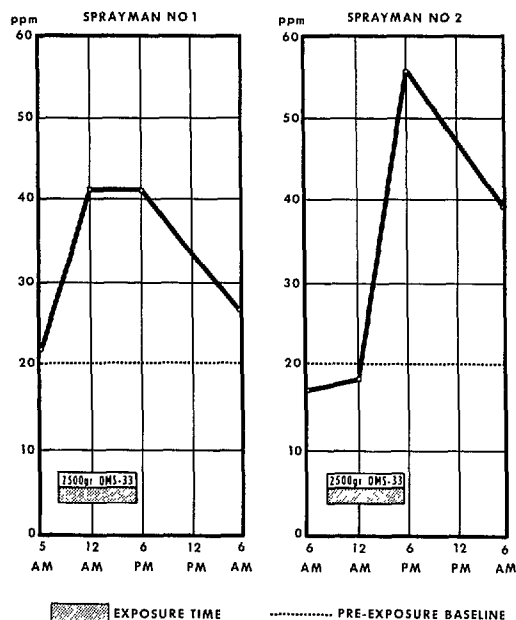
Urine metabolite surveillance affords another approach to occupational surveillance by helping to quantify occupational exposure. Several reports available in the literature describe the use of paranitrophenol in surveillance of the occupationally exposed worker (8, 9). In the case of carbamate exposure the urinary metabolite technique has special, distinct advantages over cholinesterase surveillance—because of the *in vitro* and *in vivo* reversibility of cholinesterase inhibition with this class of insecticide (10).

During the field testing of OMS-33 (Baygon) for the World Health Organization in El Salvador, the potential urinary excretion by exposed spraymen of iso-propoxyphenol, the metabolite of this pesticide, was investigated by the author. Figure 2 shows the urine output of iso-propoxyphenol in two spraymen after their occupational exposure to Baygon. The interrupted line shows the spray team's overall baseline level of phenols before Baygon spraying commenced. The solid line shows the iso-propoxyphenol excreted after spraying eight hours per day for two days with a 20 per cent emulsifiable Baygon concentrate.

The Epidemiology of DDT

In contrast to the organophosphates, DDT (dichloro-diphenyl-trichloro-ethane) has presented no serious human toxicity problems. Use patterns have changed primarily because of insect resistance and the environmental consequences of trace amounts of this insecticide in non-target species, especially fish and birds. In man, the only unequivocal effect of long-term

FIGURE 2—Urinary output of iso-propoxyphenol by two spraymen after exposure to a 20 per cent emulsifiable OMS-33 (Baygon) concentrate (El Salvador, 13-14 March 1967).



incidental exposure has been acquisition of the human pesticide residues. With development of analytical capabilities for measuring this pesticide and its metabolite, in blood as well as in fat, considerable information has been obtained on the distribution of these residues in the population at large.

The organochlorine pesticides are soluble in fat, and trace amounts of a growing list of chemicals can now be detected in the human body. Blood concentrations of DDT and its metabolites are significantly correlated with adipose data; these biological indices are measures of exposure rather than toxicity. In blood, residues of DDT tend to reflect recent exposure, whereas residues of DDE, the major metabolite of DDT, are more indicative of an individual's lifelong exposure. These biological indices have been used to measure national prevalences in man and to make international comparisons; changes observed in national surveys over time have been used to express secular changes in pollution.

For the United States of America, DDT residues in fat and blood are greater in blacks than in whites and increase with time up to 20 years of age (11). They then appear to level off in older age groups, as might be expected in view of the 22 years or so that have elapsed since this pesticide first became generally available.

With respect to the general U.S. population, levels of DDT and its metabolites in fat are greater in the warmer states than in the cooler states (12). On both sides of the Atlantic the prevalence of DDT and its metabolites tends to relate to the specific climatic characteristics of the country involved (13).

In a recent survey of serum DDE levels in the general population of Dade County, Florida, higher levels were found in the poorer and more congested communities (14). Clustering of serum DDE residues by families has also been observed (12).

These several geographic and social differences suggest that in warmer climates non-dietary sources of DDT may be as important as dietary sources in producing incidental human exposure. House dust surveys support this idea. The individual domestic pest control measures which leave these dust residues may thus be an important non-dietary source of human DDT residues—at least in tropical regions (15).

Within Dade County's general population, using the Hollingshead Two-Factor Index, it was found that the average level of DDE in more affluent whites was 22 parts per billion (ppb); among poorer whites it was 34 ppb. For blacks, the average level was 33 ppb in Social Class I and 50 ppb in Social Class V. (In this index, professionals are included in Social Classes I and II and semi-skilled and unskilled workers in Classes IV and V.) (16) Other studies of occupationally exposed workers showed average serum DDE levels of 43 ppb in whites and 103 ppb in blacks.

These and other community surveys noted no adverse health effects from these orders of magnitude of DDT residues. Poland *et al.*, in a case control study of 18 persons with a five-year history of heavy exposure to DDT in a

DDT-manufacturing plant (who had average serum levels of 573 ppb DDT and 586 ppb DDE), noted that the only biochemical changes observed were a 57 per cent increase in urinary 6-beta hydroxycortisol and a 19 per cent reduction in the half-life of serum phenylbutazone (17).

The Future

Because of changes in pesticide use patterns, the dangers of human pesticide intoxication, and the continued need for general population and food residue surveillance, a strong case can be made for international development of multidisciplinary pesticide protection teams. Such teams should have the combined expertise needed for agricultural crop and plant protection, as well as for human, animal, and environmental surveillance. This would join the special skills of agriculture with the needs and priorities of human and animal health practices, and would realistically meet future environmental protection needs. Such teams would give advice on the correct and safe use of appropriate pesticides, document the incidence and causes

of human intoxication, identify prevention methods, and investigate episodes involving death of non-target fish and other wildlife; they would also constitute a basic network for future environmental and human monitoring on a world-wide basis.

A suitable composition for such a team would be: (1) a person trained in crop protection; (2) a public health worker; (3) a chemist; and (4) a biologist. Team members would need a preliminary basic training course, possibly utilizing several centers of expertise which already exist in different parts of the world. However, it would be neither difficult nor time-consuming to prepare such individuals for their respective roles.

This multidisciplinary team would contribute greatly to assuring the safe and judicious handling and monitoring of pesticides in the future. The very real dangers posed by toxic organophosphate insecticides and the need for international monitoring of residues in food and man suggest that development of such an approach is essential if we are to successfully cope with the special challenges of chemical technology in the years ahead.

SUMMARY

Popular organophosphate insecticides such as parathion pose serious health hazards for man; exposure can rapidly prove fatal, because vital cholinesterase activity is blocked. The immediate cause of death is usually respiratory failure stemming from muscle paralysis or bronchiolar constriction. Important elements of treatment are airway restoration and hypoxia correction, atropine and oxime therapy, decontamination, and investigation of the place where the poisoning occurred.

Extreme caution is needed to minimize exposure of workers and others where organophosphates are being used, and to monitor workers for signs of undue exposure. Suggested

measures include proper training of workers, use of protective clothing, and a regular program for testing workers' levels of urine residues and blood cholinesterase.

In contrast, studies of DDT have uncovered no serious human toxicity problems. (The prime reasons for rejecting organochlorates are patterns of insect resistance and potential adverse effects on some fish and birds.)

Small international teams organized to assure safe use of pesticides could contribute greatly to DDT residue surveillance and to prevention of organophosphate poisoning in man.

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