Chemistry and specifications of pesticides

Second Report of the WHO Expert Committee on Vector Biology and Control

Technical Report Series
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Geneva, 29 November – 5 December 1977

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CHEMISTRY AND SPECIFICATIONS OF PESTICIDES

Second Report of the WHO Expert Committee on Vector Biology and Control

The WHO Expert Committee on Vector Biology and Control [1] met in Geneva from 29 November to 5 December 1977 to study pesticide specifications and their use in public health, to establish new or revised specifications for the WHO manual *Specifications for pesticides used in public health*, and to provide guidance for improving the specifications of new types of formulations and active ingredients.

1. PESTICIDES FOR USE IN PUBLIC HEALTH

Chemical pesticides continue to be the mainstay of most public health vector control programmes. Although WHO is trying to develop biological control agents and environmental modifications for use in vector control, there is at present and during the immediate future an urgent need for safe and effective pesticides and thus for valid specifications for these pesticides.

The Committee therefore addressed itself to the task of revising the specifications and analytical methods for the pesticides currently being used in public health and of establishing specifications and analytical methods for newer pesticides that could prove safe and effective in vector control. In these deliberations account was taken of the recommendations made by the WHO Expert Committee on Insecticides in its nineteenth report [2] and in the report of the Scientific Group on the Chemical and Biochemical Methodology for the Assessment of Hazards of Pesticides for Man.[3]

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[1] The Committee was previously known as the WHO Expert Committee on Insecticides.

[2] WHO Technical Report Series, No. 475, 1971.

[3] WHO Technical Report Series, No. 560, 1975.

1.1 New pesticides and formulations

During the past 17 years WHO has conducted a research programme to develop pesticides for vector control. The programme was originally directed to finding residual insecticides for use in malaria control in those areas where DDT did not give control of the anopheline vectors. This is still an important aim of the programme today, but the research work has grown in complexity with the inclusion of research on other vectors and with the need for more information on the safety of pesticides and on the effects of these substances on the environment. As it happens, this intensification of research on new materials has occurred at a time when fewer and fewer candidate insecticides are available. Thus, in view of the problems faced by the malaria control programmes in many countries owing to the development of physiological resistance in anopheline mosquitos, it is essential that any new compounds that can be applied residually be continually examined.

The Committee was informed that the compounds bromophos, jodfenphos, chlorphoxim, and pirimiphos-methyl have been examined closely since the nineteenth meeting and merit consideration for the establishment of specifications. The Committee reviewed the chemical evaluations of the powder formulations of these materials carried out by a WHO research unit in Nigeria. The investigations included the determination of suspensibilities of the powders after accelerated storage treatment and after storage under local ambient conditions. The duration of local storage varied with each compound, but the measurements showed a correlation between accelerated and local storage and thus allowed the Committee to establish valid specifications for these materials.

The Committee was also informed of the intensive research being carried out to develop new insecticides for use in controlling larvae of the *Simulium damnosum* complex in the rivers of west Africa as part of the Onchocerciasis Control Programme in the Volta River Basin area.

Chlorpyrifos and fenthion are used extensively for the control of *Culex pipiens fatigans*, the main vector of Bancroftian filariasis, a disease widespread in both urban and rural areas of Asia and Africa.

Temephos, particularly as 1% on sand, is used extensively against *Aedes aegypti*, which breeds in containers of clean and potable water. This mosquito is the vector of yellow and dengue haemorrhagic fevers in south-east Asia and the western Pacific. The latter disease has acquired considerable importance in recent years.

1.2 Malathion

1.2.1 *Poisoning incident*

The Committee was given details of a poisoning incident that occurred in 1976 during the application of malathion water-dispersible powder during malaria control operations in Pakistan. Among 7500 field workers, cases of poisoning occurred in probably more than 2500, of whom five died. Staff of WHO and the Center for Disease Control, Atlanta, GA, USA, attributed the cause to organophosphorus poisoning, and subsequent chemical and toxicological investigations showed the presence of other organophosphorus compounds as impurities in some batches of the malathion powder. These impurities made the malathion exceptionally toxic. For almost 20 years it has been known from laboratory studies that a number of organophosphorus compounds can potentiate the toxicity of malathion in mammals by inhibiting the normal detoxification mechanism. This incident of poisoning in malaria control workers was a tragic demonstration that the phenomenon could be of critical importance for man under certain circumstances of field use of malathion.

1.2.2 *Some contributory factors*

The incident is believed to have been partly caused by failure to use elementary precautions during the handling and spraying of the formulation, and it thus shows that despite clear handling directions and package labels poor handling practices will occasionally occur in large-scale vector control programmes in developing countries. It is therefore necessary to improve and refine specifications continually so that all the factors that might cause problems during field use will have been determined, and limits will have been imposed in the specifications, before procurement. It was pointed out that odour was a limiting factor governing the acceptability of malathion water-dispersible powders in some malaria control programmes.

The recent increase in the use of malathion in malaria control programmes has coincided with an increase in the number of manufacturers of the insecticide—a result of the expiry of patents. This change from a single source of supply to several sources reinforces the need to pay careful attention to the specification requirements. Similar considerations apply to other insecticides. One example mentioned was fenitrothion, which is being increasingly used in public health programmes and is now made and formulated by several manufacturers.

In view of the possible increase in toxicity of a formulation after shipment or field storage, the Committee observed that there is a need for field methods of identifying active material and impurities in pesticide formulations. These methods should be simple, easy to use in developing countries, and if possible of a quantitative nature.

1.2.3 *Laboratory investigations*

The Committee reviewed the research that had been carried out as a result of the poisoning incident and agreed that there was a need to change to a new and specific method of analysis for specification purposes. It was considered worth while to summarize the steps undertaken in this research to show the basis for the new requirements and analytical methods.

After the poisoning incident and in collaboration with the various national malaria control programmes, WHO obtained samples of malathion water-dispersible powders from current malaria programmes for investigation of toxicity and presence of impurities. This urgent research was carried out by three laboratories in collaboration with WHO. The acute oral toxicity to rats was determined and the content of malathion and impurities was measured by gas-liquid chromatography. Forty-nine samples representing different manufacturers, dates of manufacture, and periods of field storage were collected and analysed, and the results allowed a correlation to be made between the presence of certain impurities and the degree of mammalian toxicity. From these investigations and from the literature [1, 2] it was concluded that the presence of an impurity (or perhaps more than one) was causing potentiation of the toxicity of the malathion itself.

1.2.4 *Effect of impurities*

From this investigation, isomalathion was implicated as the main cause of the increased toxicity because, although it occurs in technical malathion only in very low concentrations, it is formed in larger amounts in some of the powder formulations. Other investigations and information from manufacturers implicated certain of the inert diluents and perhaps even the surfactants as the agents causing isomerization of the malathion to isomalathion after manufacture and during shipment and

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[1] PELLEGRINI, G. & SANTI, R. *Journal of agricultural and food chemistry*, **20**: 944–950 (1972).

[2] UMETSU, N. ET AL. *Journal of agricultural and food chemistry*, **25**: 946–953 (1977).

field storage. As part of the research, several of the impurities found in and derived from malathion (including isomalathion) were prepared, and mixtures in various proportions with highly purified malathion were fed to rats. Pure malathion has an acute oral toxicity to rats of 10–13 g/kg of body weight and three impurities in addition to isomalathion were shown to produce potentiation. Isomalathion itself, however, was proved to be the dominant potentiator. The other components, which were present only in minor amounts and were not formed to any appreciable extent during storage of the powders, contributed only slightly to potentiation.

The Committee was informed of the very ready cooperation of the malathion manufacturers in solving this problem and in providing samples and methods for use in developing the new specifications. This cooperation and close working relationship resulted in improved formulations. A collaborating laboratory had developed gas-liquid chromatographic methods for malathion and for the isomerization product isomalathion, and these methods were tested collaboratively in nine laboratories including those of the manufacturers. An accelerated storage test at 55°C for 6 days was developed, and this was considered to be equivalent to field storage conditions in which isomalathion was likely to be generated.

Tests on samples of powder formulations of malathion from field programmes showed that all those that have been proved safe for indoor residual spraying have an acute oral LD_{50} to rats of at least 2 g/kg of body weight. The isomalathion content of those samples never exceeded 2% of the nominal malathion content. Thus impurities, including isomalathion itself, present in small amounts in good-quality malathion water-dispersible powder do not cause significant changes in the mammalian toxicity of the formulation, even though there is a large difference between the toxicities of such impurities and that of highly purified malathion. The samples with significantly increased mammalian toxicity had, as a rule, an isomalathion content 2–5 times greater than usual. An acceptable level of this contaminant, required for setting a limit to its presence in water-dispersible powder after accelerated storage, was then considered. The Committee was aware of uncertainties in the accuracy and precision of the analytical method for isomalathion. There is also uncertainty in the correlation of isomalathion formation during the accelerated storage treatment with that occurring under various field-storage conditions. However, it considered that a limit could be set that would be acceptable from an analytical point of view and that would ensure that the malathion passing this requirement in the labora-

tory would not cause problems in the field. The Committee considered that the limit for isomalathion should be 1.5–1.6% of the nominal malathion content. However, in view of the range of results obtained in a limited collaborative study and in view also of the possibility that the recommended accelerated storage test may be too severe as compared to field conditions, the Committee considered that a practical limit for isomalathion of 1.8% of the nominal malathion content should be the highest acceptable value (see Annex 1, section 6).

The Committee recommended that additional information be obtained from laboratory and field studies so that the isomalathion limit can be reviewed at a future date.

The Committee also recommended that research be continued on the analytical methods for determining isomalathion and on the development of the accelerated storage test so that the results obtained with it correlate closely with the field stability actually found for malathion water-dispersible powders formulated according to the new specifications.

1.3 Specifications for insecticides

The Committee reviewed the specifications for insecticides contained in the WHO manual *Specifications for pesticides used in public health* [1] and recommended a number of changes. It also considered the suitability for publication of several interim specifications.[2] A full account of the Committee's deliberations on this subject is given in Annex 1.

1.4 New insecticides

1.4.1 *Synthetic pyrethroids*

In its nineteenth report [3] the WHO Expert Committee on Insecticides noted the development of synthetic pyrethroids, which were then looked upon as replacements for the natural product for use in aerosols for space treatment. Since that time the situation has been completely changed by the discovery of pyrethroids that are both highly insecticidal and much more stable on exposure to light and air. They can be used for the control of agricultural and public health pests in situations where natural pyrethrum and the earlier synthetic pyrethroids would never have been considered.

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[1] *Specifications for pesticides used in public health*, 4th edition, Geneva, World Health Organization, 1973.

[2] Unpublished WHO document WHO/VBC/73.462.

[3] WHO Technical Report Series, No. 475, 1971, p. 18.

Their exceptional activity against insects is important because they are relatively expensive to manufacture and will therefore need to be used at dosage rates much lower than those used with other insecticides. This high activity may cause some difficulties in preparing formulations, in drawing up specifications, and in developing the necessary analytical methods.

The pyrethroids now being developed have both optical and geometrical isomers, the ratios of which vary with the source of the technical material. The stereoisomers vary in insecticidal activity and toxicity to mammals. Thus specifications will be required to define the ratio of these isomers, particularly the *cis-trans* isomers, and to describe analytical methods that can distinguish between them. Gas-liquid chromatography is the method of choice; it is already employed by manufacturers and users. There is no difficulty in obtaining stable standards, in contrast to the situation with natural pyrethrum. High-performance liquid chromatography is also likely to be used.

The new compounds are already available as the usual formulations of solutions, emulsion concentrates, and water-dispersible powders. To achieve low dosage rates, the formulations must contain low concentrations of active ingredient, and they must be more highly diluted before application. The low-concentration formulations may require changes in the accelerated storage tests and in the emulsion and suspension stability tests.

New members of this group of substances have properties that make them of great potential value in vector control. The Committee considered that, when field trials have shown which compounds and formulations are the most effective, support should be given to collaborative testing of analytical methods and the development of specifications.

1.4.2 *Insect growth regulators*

It is well known that some insect vectors have become so resistant to the standard insecticides that they cannot be controlled efficiently. The same insecticide can also be toxic to nontarget organisms and persist in the environment. There has therefore been great interest in a new strategy in which synthetic chemicals are used to interfere with the growth of the pre-adult stages of the insects. The chemicals may mimic the natural juvenile hormone so that their presence keeps the insects in the larval stages and prevents metamorphosis or, alternatively, they can inhibit the synthesis of chitin between larval stages or when the pupa is formed. They should be more specific than most insecticides because their sites of action are unique to the insect. Moreover, they are readily

decomposed. An isoprenoid hormone mimic and a chitin-inhibiting substituted urea have already been extensively tested for the control of mosquito larvae and have shown considerable promise.

Methods of analysis have already been published that would probably be suitable for inclusion in specifications. Gas-liquid chromatography is satisfactory for esters such as the isoprene-derived hormone mimics but not for the benzoylurea derivatives that are used to inhibit chitin formation. The latter have, however, been determined by high-performance liquid chromatography.

Hormone mimics cannot always be applied at exactly the time when the larvae are most susceptible, and since they are unstable in water it is often essential to use them in slow-release formulations such as granules or microcapsules.

Good control of mosquito larvae has been obtained with isoprenoid and substituted-urea compounds, which are safer to use and less polluting than more generally toxic insecticides. The Committee recommended that, if further trials confirm the suitability of these compounds for vector control, methods of analysis and specifications be developed.

1.4.3 *Controlled release formulations*

The main use of granules is now in agriculture, although they were originally developed as a way of applying mosquito larvicides and molluscicides. They are convenient and safe to handle, they reduce drift hazards, and they can be placed on the target more accurately than can conventional formulations. Most granules are based on inorganic materials such as clays, but organic polymers have also been used and all the new insecticides could certainly be prepared in this form. The choice of carrier, solvents, and binders provides control over wetting and breakdown and subsequent release of the active ingredient. Alternatively the granule may remain whole, with diffusion governing the release. Both these systems have been used with larvicides.

Another procedure is microencapsulation. The capsules containing insecticides are always much smaller than granules and can be prepared and stored as suspensions in water and diluted for spraying. As with water-dispersible powder formulations of solid insecticides, one great advantage of capsules is that the sizes of the individual units of pesticide are determined during manufacture and do not depend on mixing and application procedures. Some capsule walls may be designed to disintegrate and release the whole contents very quickly, but the greatest benefits from this formulation are obtained if the wall remains and is used to control the rate at which the chemical leaves. This control

depends mainly on choice of polymer, degree of cross-linking, capsule size, and wall thickness. Other factors include the nature of the core (i.e., whether it comprises technical grade material, a solution, or a suspension) and the effect of diffusion of water or air inwards. Chlorpyrifos and pirimiphos-methyl are being developed as encapsulated formulations, and if these formulations prove effective specifications will be prepared. The properties of capsules should ideally be tailored for a particular use. In the case of *Simulium* larvae, for example, important features would be density, a size range that would allow the capsules to be ingested by the larvae, and a wall material that remains intact while the capsules are suspended in the river but disintegrates once they are ingested by the larvae. Mosquito larvicides or the hormone mimics should be released from the capsule at a constant rate all the time they are immersed.

1.5 Rodenticides

Because most of the rodenticides used in public health are the same active materials and formulations as those used in agriculture, a joint FAO/WHO informal consultation of rodenticide experts was convened at FAO headquarters in Rome from 8 to 12 December 1975. The report of the consultation [1] outlined the major chemical and physical characteristics of effective rodenticides and described analytical methods needed to determine them.

The Committee recommended that newly available technical details, including some analytical methods, be inserted in the report, the data being obtained from national laboratories and the industry itself, and that, if resources were available, the revised version, for use in both public health and agriculture, be published separately from the manual on pesticides in collaboration with FAO.

1.6 Molluscicides

The Committee did not recommend any changes in the established specifications and analytical methods for molluscicides. No new molluscicides for public health use had been developed. It was understood that development of slow-release formulations of existing molluscicides is under way and that some new molluscicides are being tested. When these products are sufficiently developed, interim specifications will be prepared.

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[1] Unpublished WHO document VBC/76.3.

1.7 Impurities in pesticide formulations

It has been known for some time that impurities in organophosphorus pesticides can cause major changes in their biological properties.[1] Other groups of pesticides can also contain impurities of very high biological activity. It is the Committee's view that the determination of impurities by sensitive and specific analytical techniques may be of great importance in some instances. The research carried out in connection with the development of improved specifications for malathion has brought to light that some simple thiophosphate esters may be present in commercial malathion and perhaps in other organophosphorus pesticides. The Committee was informed about work on these compounds now being carried out and recommended that such studies be strengthened by the further development of analytical techniques that would help in evaluating the biological effects of these compounds and in assessing their potential hazard to man.

The Committee understood that the general problem of impurities in pesticides and their toxicological significance is under review and recommended that it should be considered in detail by the WHO Expert Committee on the Safe Use of Pesticides in 1978.

2. METHODS, STANDARDS, AND SAMPLING

2.1 Methods for general use in specifications

The Committee reviewed the methods of work described in the WHO manual *Specifications for pesticides used in public health*[2] and recommended a number of changes. These are recorded in Annex 2.

2.2 Standards for use in analytical procedures

A basic element in most procedures for the specific analysis of pesticides is the use of a standard. The Committee was informed that for the assistance of national laboratories WHO provides standard materials (such as *p,p'*-DDT, dichlorvos, malathion, and the alpha and gamma isomers of HCH) in small lots without charge. At present

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[1] ALDRIDGE, W. N. & REINER, E. *Enzyme inhibitors as substrates*. Amsterdam, North Holland, 1972 (Frontiers of biology, vol. 26), pp. 30–33.

[2] *Specifications for pesticides used in public health*, 4th edition, Geneva, World Health Organization, 1973.

these few standards are obtained through the generosity of the various pesticide manufacturers.

The Committee supported this effort but noted that with the need for better standards and a wider variety of them (as exemplified by the new procedure for malathion, which requires high-purity malathion and isomalathion) this aspect of the use of WHO specifications may become difficult to manage from the viewpoint of source of supply and storage of stocks of known purity. In addition the highly pure standards may not have the reproducibility required to maintain a constant level of standardization over a period of time.

This is now a significant problem for control laboratories supplying the large variety of materials needed for the quality control of pesticide formulations used in agriculture. Because of the limited number of pesticides used in vector control, the problem is not yet so great for public health programmes. It is likely to become so quite rapidly, however, with the development of more specific methods and with the increasing need for methods of identifying and quantifying impurities that may endanger the user or contaminate the environment.

In reviewing this subject the Committee considered several categories of standards used in pesticide analysis. Primary analytical pesticide standards used for calibrating secondary standards have a purity of more than 99%, as determined accurately with sophisticated instruments and techniques. Secondary pesticide standards are usually in the 90–98% purity range and are generally used for calibration of the analytical methods for pesticides in technical-grade and formulated products. Technical pesticide standards are materials without a definite chemical composition but with a definite range of elemental composition (e.g., chlordane and campheclor); they are used in some qualitative analytical procedures for the assay of technical-grade and formulated products. Standards for pesticide degradation products, by-products, and metabolites usually have purities of 90% or more, as determined by the use of sophisticated instruments and techniques. Internal standards are usually common laboratory reagent-grade organic chemicals for calibrating and quantifying the analytical procedures when using gas-liquid and high-performance liquid chromatography.

The Committee recommended that, when an analytical procedure for a pesticide is developed, the standard be specified and the method of determining the purity be defined before the acceptance of the procedure for inclusion in a specification. In making this recommendation the Committee was aware of the difficulties of applying it to established pesticide specifications; it therefore urged that all ways and means be

explored to improve the descriptions of existing standards and the definition of their purities. The Committee noted that WHO had designated some national laboratories as centres for standardizing various materials in the past and suggested that this possibility be further explored.

On being informed that FAO had been requested by various national laboratories to assist in obtaining pesticide standards, the Committee recommended that FAO and WHO collaborate in developing a better reference service.

2.3 Gas-liquid and high-performance liquid chromatography

The Committee noted the rapid expansion in the use of gas-liquid chromatography for all types of pesticide analysis in the past few years. The reproducibility of the results obtained by different laboratories with this technique was confirmed by the collaborative trials carried out on malathion and the contaminant isomalathion (see section 1.2.4). It was further noted that the Association of Official Analytical Chemists, Washington, DC, USA, has been studying the use of gas-liquid chromatography and has issued the report of the Committee on Gas Chromatography of Pesticide Formulations,[1] which gives general guidelines for the use of this technique. In addition, several collaborative analytical trials have been completed and published in the journal of the Association. On the grounds that this technique is now becoming more common and that reliable results can be easily obtained with relatively modest equipment, the Committee considered that its use can be recommended for those pesticides for which no simpler technique of specific analysis is available or for which there is a special need for detection of minor components. The Committee recognized that in many laboratories, especially in developing countries, such equipment is not available and that there is need to develop simple but specific analytical methods. This aspect of the problem of pesticide analysis is discussed in section 2.5.

The development of high-pressure liquid chromatography was noted to be progressing rapidly, and the Committee considered that the method should be acceptable for routine analysis in the future, with the drawback that equipment may be lacking in laboratories in developing countries. However, the Committee considered that it would be of much value where specificity is essential and where thermally labile materials are being investigated. The Committee noted that this analytical procedure has been included in the draft rodenticide specifications as an alternative to the ultraviolet analysis of many anticoagulant compounds.

[1] *Journal of the Association of Analytical Chemists*, **59** : 420 (1976).