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PESTICIDE RESIDUES IN FOOD

Report of the 1968 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues

Geneva, 9-16 December 1968

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Geneva, 9–16 December 1968

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PESTICIDE RESIDUES IN FOOD

Report of the 1968 Joint FAO/WHO Meeting

A Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues was held in Geneva from 9–16 December 1968. The meeting was opened by Dr P. Dorolle, Deputy Director-General of the World Health Organization, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. The FAO Working Party of Experts on Pesticide Residues had already met from 4 December to 7 December 1968 in Geneva in preparation for the Joint Meeting.

1. INTRODUCTION

In the modern world the use of pesticides is essential. By their very nature these compounds are toxic to a variety of forms of life. Consequently, for whatever purposes they are required, they must be properly employed so as to avoid hazard to man and contamination of the environment. Recognizing this fact, a Joint Meeting of an FAO Panel of Experts on the Use of Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues in 1961 (FAO/WHO, 1962) recommended that studies be undertaken to evaluate this hazard on the basis of the toxicological and other pertinent data on those pesticides known to leave residues in food, even when used in accordance with good agricultural practice.

Subsequently, joint meetings of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues were held in 1963 and 1965. The reports of these meetings (FAO/WHO, 1964; FAO/WHO, 1965a), which were concerned primarily with the recommendation of acceptable daily intakes, and the supporting documents (FAO/WHO, 1965b and c) were then considered by the FAO Working Party on Pesticide Residues with a view to recommending tolerances and appropriate methods of analysis for certain pesticides used on cereals (FAO, 1966).

To minimize the delay in recommending acceptable daily intakes, tolerances and methods of analysis for additional pesticides, joint meetings of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues (referred to hereafter as " Joint FAO/WHO Meetings on Pesticide Residues ") were held in 1966 and 1967. In the reports of these meetings (FAO/WHO, 1967a, 1968a), the recommended acceptable daily intakes and tolerances for a number of pesticides

are given. The supporting documents (FAO/WHO, 1967b and 1968b) contain detailed monographs on the pesticides which were considered and include comments on analytical methods.

The present Joint FAO/WHO Meeting on Pesticide Residues was convened to consider a further number of pesticides, together with requests of both a general and specific nature contained in the report of the third session of the Codex Committee on Pesticide Residues held in September/October of 1968 (FAO/WHO, 1968c).

During the present joint meeting the FAO Working Party undertook:

(*a*) to review relevant data on certain pesticide residues;

(*b*) to propose pesticide residue tolerances and, where appropriate, practical residue limits;

(*c*) to recommend methods of analysis for pesticide residues.

The WHO Expert Committee undertook:

(*a*) to review toxicological and related data on certain pesticide residues;

(*b*) to propose, where possible, acceptable daily intakes for man for those residues.

Furthermore, each of these groups made recommendations designed to initiate, stimulate and co-ordinate necessary research.

2. GENERAL CONSIDERATIONS

2.1 Modification of the agenda

Endrin was deleted from the agenda because available information indicates that a considerable amount of work is currently in progress and the results will not become available until 1969.

2.2 Definitions

The glossary published as Appendix I to the report of the 1967 Joint FAO/WHO Meeting on Pesticide Residues (FAO/WHO, 1968a) was reviewed, and the meeting agreed to continue using the terms defined therein. In addition, the definitions of the "regulatory method" and "referee method" were discussed and agreed upon (see page 10).

2.3 Principles adopted

As with previous meetings, this meeting took account of the principles enumerated in the first and second reports of the Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on

Pesticide Residues (FAO/WHO, 1964 ; FAO/WHO, 1965a) and also those set out in the second and fifth reports of the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO, 1958 ; FAO/WHO, 1961). The meeting endorsed these principles and agreed to adhere to them in the toxicological assessments.

Further, the report of the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives (WHO, 1967) was reconsidered. It was again recognized that the proposals made therein would prove valuable in dealing with some of the problems confronting the present Joint Meeting, notably those concerning the margin of safety and the establishment of temporary acceptable daily intakes and temporary tolerances.

In addition, the following general principle was agreed: If the main metabolites present in the residues in the edible portions of farm animals, animal products or plants to which the pesticides were applied are identical with the main metabolites in experimental animals, then the ADI applies to both the pesticide and its metabolites ; if the main metabolites are not identical, then the ADI applies only to the original pesticide, and separate studies on the main metabolites in the residues will be necessary for assessment of their toxicological properties.

2.4 Variability of the composition of certain pesticides

Certain pesticides are of unknown or variable composition, e.g., toxaphene and other chlorinated terpenes and technical grades of BHC (HCH). Consequently, the Meeting was unable to relate the existing toxicological data on these compounds to the products in actual agricultural use. This situation is likely to occur more frequently in the future as patent protection of various compounds expires, permitting them to be produced by a number of different manufacturers. If toxicological evaluations are to be applicable to products whatever their source, it is essential for such products to conform to specifications that ensure reasonable identity of composition. In this connexion, attention is drawn to the WHO and FAO programmes concerned with the development of specifications for pesticides and it is recommended that priority be given to specifications for pesticides that may result in residues in food. The Meeting emphasized that, for pesticides that are variable mixtures, it would be desirable, at some future date, to have reference standards readily available from some central source.

2.5 Use of fumigants and fumigant mixtures

The Meeting noted the importance of halogenated hydrocarbons and other fumigants in developing countries, especially for use on farms.

Earlier meetings had recommended tolerances for inorganic bromide resulting from the use of methyl bromide and ethylene dibromide but had stressed the importance of avoiding or eliminating detectable residues of unchanged fumigants such as ethylene dibromide ($CH_2Br \cdot CH_2Br$), methyl bromide (CH_3Br) and carbon tetrachloride (CCl_4).

This matter had been referred through FAO to the Pesticide Section of the International Union of Pure and Applied Chemistry (IUPAC) with a view to obtaining more precise information on the residual levels of unchanged fumigants. Experiments in which whole wheat grain was fumigated with a mixture of carbon disulfide, carbon tetrachloride, trichloroethylene (C_2HCl_3) and methyl bromide indicated that detectable residues of carbon disulfide and carbon tetrachloride might persist for months despite aeration, milling, baking, etc. (IUPAC, 1969).

Therefore, the Meeting wished to draw the attention of member governments to the need for further work on the toxicity of these unchanged fumigants and on their levels in food under various practical conditions of use.

2.6 Disappearance of pesticide residues

The Meeting noted that IUPAC was at present engaged in determining the nature of terminal residues of pesticides and of establishing methods of analysis within the framework of a co-operative programme. The Meeting felt however that there was a considerable lack of knowledge of the fate of pesticide residues from the time of harvesting to the time of consumption of the treated commodity.

Investigation of these problems should be encouraged and supported, and programmes including the use of radioisotope-labelled compounds should be established. The Meeting recommended the designation of collaborating laboratories on pesticide residues in food in order that the work at present being undertaken in this field might be co-ordinated as far as possible. These laboratories might undertake studies on the rate of disappearance of pesticide residues and on the toxicity of the terminal residues. The distribution of work and its assignment to individual laboratories should follow priorities to be agreed among the participants.

2.7 Pesticide residues in animal feedstuffs

The Third Session of the Codex Committee on Pesticide Residues (FAO/WHO, 1968c) recommended that the Codex Alimentarius Commission should request FAO to convene a meeting of the FAO Working Party on Pesticide Residues, in conjunction with interested divisions of FAO, to consider the problem of pesticide residues in animal feedstuffs and their effect on tolerances and practical residue limits now being recommended

for meat, milk, milk products and eggs. The present Meeting strongly endorsed this recommendation.

2.8 Environmental contamination

The Meeting noted that certain practical residue limits of pesticides were unduly high owing to environmental contamination. They therefore recommended that the sources of such contamination should be identified and investigated. Two possible sources are the appearance of pesticides in animal feedstuffs and the widespread use of aerosol dispensers, pressurized or hand sprayers, hand vapourizers, etc., in homes, restaurants and other places where food is prepared for sale or consumption. That elimination of these sources, as far as practicable, would reduce the background level of pesticide residues is evidenced by some recent surveys of the levels of organochlorine insecticides in the human body (Egan et al., 1965; Abbott et al., 1968).

The Meeting expressed concern over the extent of use of certain persistent pesticides. This resulted in contamination of the environment by these substances and the meeting suggested replacing them, wherever possible, by pesticides, the residues of which are less undesirable toxicologically.

The Meeting was also concerned about the entry of arsenic and lead from many sources into the diet of man. These sources include the intentional use of materials containing these elements in industrial food processing and agricultural practices. The Meeting recommended that, where possible, satisfactory substitutes be used, in an effort to decrease the dietary intake of these compounds.

2.9 Matters relating to the establishment of ADI's

Because some pesticides are closely related chemically and toxicologically, it was suggested that the desirability of establishing acceptable daily intakes for groups of such pesticides should be considered by a future meeting. This procedure might be extended to include further consideration of the interaction of pesticides belonging to different groups.

The major criterion for evaluation of some organophosphorus compounds and carbamates is the *in vivo* inhibition of cholinesterase and aliesterase. There are difficulties, however, with regard to methodology and interpretation of the results. The Meeting therefore recommended that WHO convene a future meeting of experts in this field in collaboration with IUPAC and other interested organizations to clarify the nature of the enzymes, the methods of determining them, and the interpretations of the results obtained, so as to ensure uniformity of assessment.

The Meeting re-emphasized that the magnitude of the safety factor used in establishing the ADI depends on a number of considerations.

Adequate data from observations in man are of prime importance and could allow the use of considerably smaller safety factors, with obvious consequential advantages.

2.10 Methods of analysis

The Meeting noted the comments on methods of analysis in the report of the third session of the Codex Committee on Pesticide Residues (FAO/WHO, 1968c, paragraphs 86-96), particularly the request for guidance on methods for use in cases of dispute. After general discussion, the following definitions of *regulatory method* and *referee method* were adopted.

1. A *regulatory method* is one used for the determination of residues in the course of the administration of legislation relating to the subject.

> For this purpose, it is often necessary to identify the nature of the residue as well as to determine its level. Subject to any expression of requirements in the particular law, the accuracy, precision and sensitivity of a regulatory method need be sufficient only to demonstrate clearly whether a tolerance level has been exceeded. Usually regulatory methods are not specified in pesticides legislation and at any given time there may be a number of methods available for a particular purpose.

2. A *referee method* is one that has been specified, or agreed upon, for use in the event of a dispute.

> Referee methods are mainly required to settle disputes concerning the level of a residue but procedures for identification of a residue may sometimes have to be included in such methods. Referee methods lay special emphasis on accuracy and precision, even if this may involve equipment and experience not normally available in laboratories undertaking regulatory work. Nevertheless some regulatory methods are suitable for use as referee methods, although their evaluation by interlaboratory comparisons is desirable before they are adopted as such.

In recommending referee methods for pesticide residue analysis, the Codex Committee on Pesticide Residues is advised by the Joint FAO/WHO Meeting on Pesticide Residues, and the latter in turn refers problems to the Pesticide Section of the International Union of Pure and Applied Chemistry. To consider such problems, the Pesticide Section has established two Commissions : one on methods of pesticide residue analysis and the other on the nature of terminal residues. The subsequent reports of these Commissions are published and made directly available to FAO and WHO. In this connexion, the Joint Meeting recognized that extensive collaborating work between laboratories is desirable before referee methods can be established and recommended that, if possible, IUPAC undertake this activity.

While recognizing the value of such collaborative work in determining the extent of the differences in the results obtained by different laboratories, the Meeting drew attention to the fact that these differences might be reduced but are not likely to be eliminated by specifying more precisely the details of the analytical methods. This is because the results obtained in different laboratories are also dependent on variations in basic techniques, as well as on other factors. In legislation and in commercial contracts this problem is sometimes recognized by designating particular analysts or laboratories for referee purposes; in some but not all such instances the referees must use specified techniques.

For the above reasons, the Meeting agreed with the proposal made at the third session of the Codex Committee on Pesticide Residues (FAO/WHO, 1968c) that tolerances may be recommended for particular uses of pesticides without necessarily making recommendations for specific referee methods. When considering individual pesticides, the Meeting attempted in each case to advise on methods suitable for regulatory use or, after further evaluation where necessary, for referee purposes.

Multidetection systems of residue analysis

Particular attention was paid to multidetection systems of analysis, which are now widely used for regulatory purposes for residues of organochlorine compounds and, to an increasing extent, for residues of many organophosphorus compounds. Some available systems (United States, 1968) can be used to detect and measure residues of many compounds in many food products at levels ranging from 0.05 ppm down to 0.001 ppm. Other systems are becoming available for a range of unchanged halogenated fumigants (Bielorai & Alumot, 1966). Such systems can be adapted to suit individual regulatory problems, for example by selecting specific or non-specific detectors or by changing the column fillings or operating conditions. Nevertheless, some pesticides are difficult or impossible to fit into broad general schemes.

A number of collaborative studies of individual multidetection systems have been made. Difficulties have been encountered in such studies, but there is no reason why they should not be further explored where it is desirable to establish the acceptability of such systems for referee purposes. Multidetection systems have the great advantage that, if correctly used, they provide evidence of identity and afford means of measuring one or more of a wide range of residues.

2.11 Submission of scientific information to FAO and WHO

The Meeting emphasized the great value of publishing experimental results. Publication in the scientific literature ensures that the work will be subject to scientific examination and criticism and affords the possibility

for refutation or confirmation of the results. Consequently, greater weight will usually be given to published than to unpublished work. If reports can be submitted only in unpublished form, they must be the result of work supervised by an expert, whose name must be given. Furthermore, the Meeting drew attention to the necessity for providing descriptions of experimental techniques that are sufficiently clear to allow checking and assessment of the validity of the results.

2.12 Reference publication

The Meeting recommended that FAO/WHO consider issuing a single volume containing monographs of all pesticides evaluated up to and including the present meeting. This publication would facilitate reference to individual compounds and would be of advantage to authorities who have to make use of the information provided.

3. RELATIONSHIP OF ACTUAL INTAKES OF PESTICIDES TO THEIR ACCEPTABLE DAILY INTAKES AND TO TOLERANCES *

Use of " Acceptable Daily Intake " in assessing risks to consumers

It is essential for the protection of health that the amount of a pesticide consumed by an individual should not exceed the acceptable daily intake, which is established by considering relevant toxicological and related data and is expressed in terms of milligrams of pesticide per kilogram of body-weight of the consumer. To assess the possibility that a particular consumer is at risk, it is necessary to express his actual intake in terms of milligrams of pesticide residue per kilogram of his body-weight per day and to compare this figure with the acceptable daily intake. For this purpose, it is necessary to measure precisely the amount of pesticide in the food he actually consumes over a suitable period of time.

A few actual intake studies of this kind have been undertaken ; they are very laborious and time-consuming. Although they provide very valuable information, these studies do not permit a rapid assessment of the risk to the population from residues of a particular pesticide. To assess this risk, *estimates* must be based, in practice, upon information concerning the residues that could possibly occur in individual foodstuffs or in groups of foodstuffs and upon suitable figures for the amounts of each kind of food

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* See FAO/WHO, 1968 a, Appendix I.

likely to be consumed. Reports of the Joint FAO/WHO Meetings on Pesticide Residues have contained selected data for food consumption from surveys and residue data from various sources, including determinations of residues in experimental material.

In some of these calculations the " high consumption " (ninth decile) figures obtained from consumer intake studies in the USA have been used (FAO/WHO, 1967, 1968a). These figures were also used in the evaluations made by the present Meeting. However, they are higher than the average consumption figures and their use has been questioned on the ground that the usual dietary variation within a given population has already been incorporated in the safety factor used in establishing the acceptable daily intake. Furthermore, since there is wide variation in dietary pattern among different countries, and since high consumption figures are available from only one country, they cannot be used on a world-wide basis. Average consumption figures, on the other hand, are available from almost all countries and consequently can be used with more confidence. The Meeting therefore recommended that a pilot study be done for individual countries for which average food consumption figures compiled by FAO are available for the calculation of the daily intake of a pesticide and that the computer programme already developed by WHO for food additives be expanded for use in this study. When the results of this pilot study become available, they should be compared with those derived from the use of high consumption figures and the advantages and disadvantages of the two systems carefully assessed.

The residue levels used in making the estimates referred to above should be those determined at the moment of consumption. If such data are inadequate however, it is permissible to use residue levels based on figures for the raw commodities, taking into account any available information on the disappearance of residues of the pesticide during normal storage and processing of the product (including cooking) prior to eating.

There is a need for more fully co-ordinated experiments to determine the quantitative and qualitative relationship of a known pesticide residue, under conditions of " good agricultural practice ", to the terminal residue at ingestion.

" *Tolerances* " *and their relationship to actual intakes*

To protect the consumer against the health hazards of exposure to a new pesticide it is not sufficient for the authorities to wait until it is widely used and then undertake quantitative surveys of the residues occurring at the moment of consumption. Not only is this too late but such diet studies, although of great value, require very considerable amounts of time and effort. It is therefore necessary, in the interests of the consumer, to impose tolerances for food products at some stage prior to consumption,

such as at harvesting, at the first point of marketing or, with an imported product, at the point of discharge within the country. The " tolerances " recommended at Joint FAO/WHO Meetings on Pesticide Residues, are accompanied, as far as possible, by statements concerning the stage at which they are intended to apply.

In several instances the " tolerance " figures proposed might seem to be relatively high, because if they were taken as levels at the time of consumption, they might lead to excessive intakes. However, in order to relate such figures to the acceptable daily intakes, which are assessed on the assumption that the residue will be consumed daily over an entire lifetime, several factors have to be considered :

Firstly, the tolerance for a particular food item reflects the maximum level of a residue that may be required by good agricultural practice, but this level is often not reached. On the other hand, although the level might on occasion be exceeded, these instances are so infrequent in practice that the average intake over a reasonable period of time is not appreciably affected. The acceptability of a food item containing pesticide residues in excess of the tolerance is a matter for national authorities to decide.

Secondly, the tolerance is based on the assumption that the particular pesticide is used on all foods in the class in question, whereas in fact this will only rarely be the case.

Thirdly, a substantial loss of residue will usually occur during storage, processing and cooking, thus leading to a much lower level at the time of consumption.

Value of national total diet studies

The various calculations made to assess the risks likely to be encountered from a pesticide include various safety factors and involve assumptions. The risks can best be determined by measuring the amounts of the pesticides being consumed at any time by the population under consideration.

Such studies have been carried out for a number of widely used and important pesticides of different classes in several countries (Swackhamer, 1965 ; Duggan & McFarland, 1967 ; United Kingdom, 1968). In most cases, the actual daily intakes were found to be far below the " acceptable daily intakes ". Similar studies on food at the time of consumption should be undertaken *periodically* and extended to other countries as well. The Meeting emphasized that, for such studies to yield useful results they must be adequately planned and properly executed.

4. EVALUATION OF DATA FOR ADI'S

Because further information is expected to become available on organomercurial compounds, the Meeting decided to postpone consideration of these pesticides until a future meeting.

Chloropropylate, dicofol and toxaphene were evaluated for the first time by a Joint FAO/WHO Meeting on Pesticide Residues. The data submitted for dicofol was considered satisfactory, and an acceptable daily intake was set for this compound. In the case of chloropropylate, a temporary acceptable daily intake was set, because of uncertainty about the nature of the metabolites, and the availability of only one completed long-term study. An acceptable daily intake for toxaphene could not be established because of lack of information on the identity of the material at present in use.

Re-evaluations were made of BHC (technical grades) and chlorobenzilate. An acceptable daily intake for BHC (technical grades) could not be established because of variability in the proportions of the various isomers and known differences between the toxicology of these isomers in the various marketed products. An acceptable daily intake was established for chlorobenzilate on the basis of data previously submitted, supplemented by the results of a two-year study in a second species, which had been carried out at the request of the 1965 Joint Meeting.

A total of five organophosphorus compounds were considered for the first time. Coumaphos was given a temporary acceptable daily intake, pending review of further toxicological data on the metabolic products. In establishing the acceptable daily intakes for four other organophosphorus compounds, the further work considered desirable was noted. In the case of crufomate, adequate animal data were available, but observations in man were limited. For dioxathion there was a lack of toxicological data on the substances making up the 30% of impurities known to be present in the technical product, while for fenchlorphos there was some concern about the toxicity of its metabolite, 2,4,5-trichlorophenol. In addition, it was noted that both dioxathion and fenchlorphos had a greater effect on aliesterase than on cholinesterase. For ethion, an absence of long-term studies and omission of cholinesterase estimations in the reproduction studies were noted.

Three organophosphorus compounds were re-evaluated. The Meeting confirmed the evaluations made in 1965 and 1967 for phosphamidon and azinphos-methyl respectively. Recent data on reproduction and teratogenicity studies on parathion-methyl caused concern. A temporary acceptable daily intake, at a lower level than that suggested in 1965, was established, conditional upon receipt of further data on these subjects.

The Meeting was unable to re-evaluate oxydemeton-methyl, although a monograph on this compound had been prepared in 1967. Scrutiny of the available information revealed that the toxicological information provided could not be related to a single defined compound, nor was there precise knowledge of the materials actually used in agricultural practice. Furthermore, no long-term data on any substance belonging to this group were available for evaluation. The Meeting therefore recommended that the acceptable daily intake established at the previous meeting should no longer be considered valid. The further work required to allow full assessment to be made must contain specification of the compound (or compounds) in actual agricultural use, including studies to compare the metabolic fate in plants, animals and man, investigation of the cholinesterase inhibition in man, and adequate long-term studies in two species.

Lead and calcium arsenates were both re-evaluated. No acceptable daily intake could be established because of lack of long-term studies and because of doubts about the possibility that arsenic could be a carcinogen.

Ethylene oxide was re-evaluated. Since no further data were available on its toxicity, and since insufficient data were available on reaction products with food components, the 1965 decision to set no acceptable daily intake was confirmed.

Because a no-effect level could not be demonstrated in long-term studies in the rat, no acceptable daily intake was set for oxythioquinox.

An acceptable daily intake was established for endosulfan on the basis of adequate long-term studies and supporting data.

The third session of the Codex Committee on Pesticide Residues had requested a further interpretation of the ADI previously established for malathion with respect to its applicability to malaoxon. The ADI for malathion may now be held to provide also for trace amounts of malaoxon.

The acceptable daily intake values established by the Meeting are listed in Annex 2.

5. EVALUATION OF DATA FOR TOLERANCES AND PRACTICAL RESIDUE LIMITS

In the course of evaluating evidence on residues of the various pesticides the Meeting considered information on patterns of use, on supervised trials, on methods of analysis, and on the fate of residues during storage and processing. Any available evidence on the occurrence of residues in foods in commerce or at the time of consumption was taken into account.

Some of the pesticides had not been considered by previous Joint FAO/WHO Meetings on Pesticide Residues and certain others had been previously considered from the standpoint of acceptable daily intakes but not evaluated for tolerances or practical residue limits. The Meeting also reviewed, and in some instances amended, certain of the recommendations made at previous meetings.

Of the compounds being considered for the first time by the Meeting, temporary tolerances were recommended for coumaphos, fenchlorphos and crufomate in certain meats and animal products ; for dioxathion and ethion in certain animal and plant products ; and for chlorobenzilate, chloropropylate and dicofol in certain plant products. The first three of these are products used against pests of farm animals and the last three are acaricides used on plants. The further information that would enable these recommendations to be reviewed is indicated in each case (see Annex 3). No recommendations for tolerances were made for oxythioquinox since no ADI had been established for this compound (see p. 16). Other compounds that were considered at this meeting were azinphos-methyl, lead and calcium arsenates, ethylene oxide and phosphamidon. Although there were still certain doubts concerning the identities of the terminal residues of azinphos-methyl and phosphamidon, temporary tolerances for these compounds in various plant products were recommended. For the arsenates, however, although there are many data on residues in commerce, the Meeting could not recommend tolerances, since no acceptable daily intakes for arsenic or lead had been established. No recommendations for tolerances were made for ethylene oxide, because of lack of information on the amounts of ethylene chlorohydrin formed during the commercial use of the fumigant as a bactericide or an insecticide.

Parathion-methyl, endosulfan, BHC (technical grades), toxaphene and oxydemeton-methyl were also considered at this meeting. Special difficulties were encountered with oxydemeton-methyl, owing to the wide range of commercial products. The precise compositions of these products are not known and it is probable that they lead to different terminal residues. Therefore, no recommendations were made for tolerances for oxydemeton-methyl. Similarly, in view of the widely varying compositions of BHC (technical grades) from various sources, the Meeting was not prepared to recommend tolerances for this product. Again, no recommendations were made for toxaphene, because of inadequate information concerning the composition of the marketed product and because of the unreliability of the methods of analysis for the residues. For parathion-methyl and endosulfan, however, temporary tolerances for various plant products were recommended.

The Meeting also considered various matters that had been referred to it by the third session of the Codex Committee on Pesticide Residues (FAO/WHO, 1968c). As a result, certain amendments or additions were

incorporated into the *Summary of recommended acceptable daily intakes, tolerances, temporary tolerances and practical residue limits* (Annex 2) and the individual monographs concerned with HCN, carbaryl, lindane, diazinon, DDT, dieldrin, malathion, bromide ion (from use of methyl bromide or ethylene dibromide) and heptachlor. These additions include recommendations for tolerances or practical residue limits in certain instances.

Special considerations were given to the analytical methods available for different purposes (see section 2.10). Alternative methods of expressing amounts of residues in products with a substantial fat content, such as meat and milk, were also considered. It was agreed that tolerance values in milk should normally be expressed on a whole-milk basis for the more polar pesticides, which include many of the organophosphorus compounds and their metabolites as well as all the carbamates. Where residues of these compounds occur, they will generally be found in both the aqueous and the non-aqueous phases of milk and milk products. On the other hand, some of the organochlorine pesticides are relatively non-polar in character and their residues in milk or milk products will occur almost exclusively in the fat phase. For these products, residues of organochlorine compounds are normally expressed on the basis of the content in fat, i.e., by stating the residue content in ppm of the non-polar component in the food product as determined by extraction with a non-polar solvent. The same considerations generally apply to other products, such as meat and meat products.

6. FUTURE WORK

It was suggested that a future meeting should consider the following items:

1. All compounds listed in the priority IV group of the report of the third session of the Codex Committee on Pesticide Residues (FAO/WHO, 1968c), namely, binapacryl, captan, dichlofluanid, difolatan, dinocap, diphenylamine, ethoxyquin, folpet, formothion, hexachlorobenzene (b), orthophenylphenol and its sodium salt, quintozene, thiabendazole, and thiometon (parathion-methyl and toxaphene were considered in 1968).

2. Fenitrothion, as suggested, at the 1967 Joint Meeting.

3. The possibility of establishing acceptable daily intakes or negligible residue levels for a number of fumigants that may persist in the unchanged form after processing treated food products, namely, carbon disulfide, carbon tetrachloride, ethylene dibromide, ethylene dichloride, and trichloroethylene.

4. The desirability of establishing acceptable daily intakes for groups of related pesticides.

7. RECOMMENDATIONS TO FAO AND WHO

1. In the interests of public health and agriculture, further joint meetings of the FAO Working Party and the WHO Expert Committee on Pesticide Residues should be convened to review and evaluate additional pesticides that are used extensively in agriculture and to review those already evaluated in the light of additional data and of the advances in toxicology and related sciences. It is desirable that these meetings be held annually.

2. WHO should conduct a pilot study using the appropriate average and high food consumption figures for the calculation of the daily intakes of pesticides. It is expected that such a study would provide additional assurance that, when pesticides are used in accordance with good agricultural practice, their residues in foods fall within the limits recommended in this report and do not exceed the acceptable daily intakes.

3. A meeting of experts in the field of methodology should be convened, possibly in collaboration with IUPAC and other interested organizations, to clarify the nature, methods and interpretations of the results obtained in cholinesterase and aliesterase inhibition measurement.

4. Programmes, including the use of radioisotope-labelled compounds, to investigate (*a*) the rate of disappearance of pesticide residues between harvest or slaughter and consumption and (*b*) the nature and toxicity of the terminal residues, should be encouraged and supported as much as possible.

5. Priority should be given to the development and publication of specifications for pesticides that may result in residues in food. Attention is drawn to the respective FAO and WHO programmes concerned with the development of specifications for pesticides.

6. Consideration should be given to publishing a single volume containing monographs of all pesticides evaluated up to and including the 1968 Joint Meeting.

8. RECOMMENDATIONS TO MEMBER GOVERNMENTS

1. Noting that the occurrence of unintentional residues in a number of food items and animal feedstuffs is partly a result of environmental contamination, the Meeting recommends that efforts be made to discover the sources of such contamination and, where possible, to eliminate them, in order to reduce the background level of pesticide residues.

2. In view of the concern over the extent of the use of certain persistent pesticides, the Meeting recommends that they be replaced, wherever

possible, by pesticides, the residues of which are less undesirable toxicologically.

3. Noting that arsenic and lead enter into the diet of man from many sources including the intentional use of materials containing these elements in industrial food processing and agricultural practices, the Meeting recommends that, where possible, satisfactory substitutes be used in an effort to decrease the dietary intake of these compounds.

4. Noting that the results of recent investigations indicate the presence of residues of unchanged fumigants in treated food products after processing, the Meeting recommends that further work be undertaken on the toxicity of these unchanged fumigants and their levels in food under various practical conditions of use.

5. The Meeting recommends that further total diet studies be carried out, particularly in those countries where such work has not been undertaken so far, and emphasizes the need for adequate planning and proper execution of such studies.

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Annex 1

INDEX TO DOCUMENTATION ON SPECIFIC COMPOUNDS

Compound	*FAO/WHO Publication and year* [1]	*Compound*	*FAO/WHO Publication and year* [1]
Acrylonitrile	1965c	Endrin	1965b
Aldrin	1967b, 1968b	Ethion	1969
Allethrin	1965b	Ethylene dibromide [3]	1967b, 1968b
Azinphos-methyl	1969	Ethylene dichloride	1965c, 1968b
BHC (technical grades)	1969	Ethylene oxide	1965c, 1969
Bromide ion [2]	1969	Fenchlorphos	1969
Calcium arsenate	1969	Ferbam	1965b, 1968b
Captan	1965b	Heptachlor	1967b, 1968b, 1969
Carbaryl	1967b, 1968b, 1969	Hydrogen cyanide	1965c, 1969
Carbon disulfide	1965c, 1968b	Lead arsenate	1969
Carbon tetrachloride	1965c, 1968b	Lindane [4]	1967b, 1968b, 1969
Chlorbenside	1965b	Malathion	1967b, 1968b, 1969
Chlordane	1968b	Mancozeb	1968b
Chlorfenson	1965b	Maneb	1965b, 1968b
Chlorobenzilate	1969	Methoxychlor	1965b
Chloropicrin	1965c	Methyl bromide [3]	1967b, 1968b
Chloropropylate	1969	Mevinphos	1965b
Chlorpropham	1965b	MGK 264	1968b
Chlorthion	1965b	Nabam	1965b, 1968b
Coumaphos	1969	Oxydemeton-methyl [5]	1968b
Crufomate	1969	Oxythioquinox	1969
DDT	1967b, 1968b, 1969	Parathion	1965b, 1968b
Demeton	1965b, 1968b	Parathion-methyl	1969
Diazinon	1965b, 1967b, 1968b, 1969	Phenylmercuric acetate [6]	1967b, 1968b
		Phosphamidon	1965b, 1967b, 1969
Dichlorvos	1967b, 1968b	Phosphine [7]	1967b, 1968b
Dicofol	1969	Piperonyl butoxide	1967b, 1968b
Dieldrin	1967b, 1968b, 1969	Propham	1965b
Dimethoate	1968b	Pyrethrins	1967b, 1968b
Dimethrin	1965b	Thiram	1965b, 1968b
Dioxathion	1969	Toxaphene	1969
Diphenyl	1967b, 1968b	Triphenyltin compounds	1965b
DNOC	1965b	Zineb	1965b, 1968b
Endosulfan	1968b, 1969	Ziram	1965b, 1968b

[1] Unless otherwise stated, the first-mentioned date refers to the first complete, or completely revised, monograph. Succeeding dates refer to addenda to that monograph. Where a monograph has been completely revised, no mention is made of any earlier, obsolete monographs that may have been published. The complete list of references is to be found on pp. 20 & 21.

[2] Addendum only; previously evaluated under " ethylene dibromide " or " methyl bromide ".

[3] See also " bromide ion ".

[4] Previously referred to as " gamma-BHC ".

[5] Previously referred to as " demeton-S-methyl sulfoxide ".

[6] Plus other organomercurial compounds.

[7] Also referred to as " hydrogen phosphide ".

Annex 2

SUMMARY OF RECOMMENDED ACCEPTABLE DAILY INTAKES, TOLERANCES, TEMPORARY TOLERANCES AND PRACTICAL RESIDUE LIMITS AS OF DECEMBER 1968 *

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
ıldrin	0.0001			See dieldrin
ırsenic (as calcium or lead arsenate)	None	None recommended		Considered further but no tolerance recommendations possible in absence of ADI.
ızinphos-methyl	0.0025	● Apricots, grapes. 4.0 *c* ● Other fruit. . . . 1.0 *c* ● Vegetables . . . 0.5 *c*		
3HC (technical mixture of isomers)	None	None recommended		Considered but no recommendations possible (see Monograph)
Total inorganic bromide from all sources including bromine-containing fumigants	1.0	Dried eggs, spices, herbs . . . 400 *a* Raw cereals . . . 50 Dried figs . . . . 250 *a* Avocados . . . . 75 *a* Dried raisins, dried dates . . 100 *a* Dried peaches . . 50 *a* Dried prunes . . 20 *a* Other dried fruit. 30 *a* Citrus fruit, strawberries. . . . . 30 *a* Other fresh fruit. 20 *a* Whole-meal flour 50		Pending possible establishment of maximum acceptable daily intake of unchanged fumigant, inorganic bromide residues must not be associated with unchanged fumigant Definition of bromide residue now modified with respect to source
;aptan	0.1	None recommended		This compound was not considered further
;arbaryl	0.02	Tree fruit including citrus fruit, small fruit and berries, leafy vegetables, brassicas, olives, shelled nuts, cucurbits, melons 10 *a* Other vegetables, poultry, cotton seed. . . . . 5 *a* Rice. . . . . 2.5 *a*		Poultry residues largely concentrated in the skin

* Explanatory notes are given at the end of the table on page 29. For further details concerning these recommendations, see FAO/WHO (1969) *1968 evaluations of some pesticide residues in food.* FAO/PL : 1968/M/9/1 ; WHO/Food Add./69.35.

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
carbaryl (*cont.*)	0.02	● Meat of cattle, goat and sheep. 1.0 *a* ● Whole milk . . . 0.02 *a*		
carbon disulfide	None	None recommended		
carbon tetrachloride	None	None recommended		Considered further but no ADI, toler ances or practica residue limits established or recommended
chlorbenside	0.01	None recommended		This compound wa not considered further
chlordane	0.001	Large root crops, leafy and stalk vegetables . . . 0.3 *a* Small root crops (except carrots), cucurbits, pine-apple . . . . . 0.2 *a* Sugar-beets, whole pods of pod vegetables, berries, toma-toes and related garden crops, sweet corn and popcorn . . . . 0.1 *a*	Raw cereals . 0.1 *a*	Residue to be measured as alpha plus gamm chlordane Tolerances to appl to residues tha result from soi treatment only (See p. 50 of 196 Monograph for definitions of large and small root crops)
chlorobenzilate	● 0.02	● Apples, pears (whole fruit ba-sis) . . . . . 5.0 *c* ● Citrus fruit (whole fruit basis). . . 1.0 *c* ● Almonds, walnuts (shell-free basis) 0.2 *c* ● Melons, canta-loups . . . . . 1.0 *c*		
chloropropylate	● 0.01	● Apples, pears, cit-rus fruits (whole fruit basis). . . 3.0 *c* ● Tomatoes, canta-loups . . . . . 1.0 *c*		
coumaphos	● 0.0005 *c*	● Eggs (on a shell-free basis) . . 0.05 *c* ● Meat, including poultry, (on a fat basis) . . . . . 0.5 *c*		Residues to be de termined as cou maphos and it oxygen analogue and expressed a coumaphos Tolerances for mea and poultry to b applied at slaughter
crufomate (Ruelene)	● 0.1	● Whole milk . . . 0.05 *c* ● Meat (on a fat ba-sis) . . . . . 1.0 *c*		Tolerance for mea to be applied a slaughter

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
DDT	0.01	Apples, pears, peaches, apricots, small fruit (except strawberries), vegetables (except root vegetables), meat, fish or poultry (on a fat basis) . . . 7.0 *a* ● Nuts (shelled) . . 1.0 *a* Strawberries, root vegetables. 1.0 *a* Cherries, plums, citrus fruit, tropical fruit . . . 3.5 *a*	● Whole milk . 0.05 *a* ● Milk products (on a fat basis) . . . . 1.25 *a* ● Eggs (on a shell-free basis) . . . 0.5 *a*	The limits apply to DDT, DDD and DDE singly or in any combination
Demeton	0.0025	None recommended		This compound was not considered *per se*
Diazinon	0.002	Peaches, citrus fruit, cole crops and leafy vegetables . . . . . 0.7 *a* Other fruit and vegetables . . . 0.5 *a* ● Meat (on a fat basis. . . . . 0.75 *a*		Tolerance for meat to be applied at slaughter
Dichlorvos	0.004	Raw cereals . . . 2.0 *a* Cereals products and fresh vegetables . . . . . 0.3 *a* Canned and frozen vegetables, fruit other than citrus fruit . . . 0.1 *a*		Content of dichloracetaldehyde (DCA) to be reported where possible
Dicofol	● 0.025	● Fruit, hops, vegetables, tea (from a particular estate) for blending only . . . . 5.0 *c* ● Tea (blended) . . 1.0 *c*		
Dieldrin	0.0001	Vegetables and fruit (other than citrus fruit) . . 0.1 *c* Citrus fruit, rice . 0.05 *c*	Raw cereals . 0.02 *c* ● Eggs (on a shell-free basis) . . . 0.1 *c* Milk products (on a fat basis) . . . . 0.125 *c* Meat (on a fat basis) . . . 0.2 *c* Whole milk . 0.005 *c*	Practical residue limit in shell-free egg is equivalent to 0.25 ppm in egg yolk. The limits apply to aldrin and dieldrin singly or in any combination and are expressed as dieldrin

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
dimethoate	0.02	Tree fruit (including citrus fruit). 2.0 *a* Vegetables (except tomatoes and peppers) . 2.0 *a* Tomatoes and peppers . . . . 1.0 *a*		Residues to be determined as dimethoate and its oxygen analogue and expressed as dimethoate
dioxathion	● 0.0015	● Pome fruit. . . . 5.0 *c* ● Grapes . . . . . 2.0 *c* ● Citrus fruit . . . 3.0 *c* ● Meat, excluding poultry, (on a fat basis) . . . . . 1.0 *c*		Residues of *cis* and *trans* isomers of principal active ingredient to be determined and expressed as sum of both Meat tolerance to be applied at slaughter
diphenyl	0.125	Citrus fruit . . . 110		
dithiocarbamates, dimethyl (ferbam, thiram and ziram)	0.025 *b*	None recommended		Acceptable daily intake applies to parent compounds and to their sum if more than one is present
dithiocarbamates, ethylene bis-[mancozeb, maneb and zineb (including zineb derived from nabam plus zinc sulfate)]	0.025 *b*	None recommended		Acceptable daily intake applies to parent compounds and to their sum if more than one is present
endosulfan	● 0.0075	● Fruit, vegetables 2.0 *b*		Residues should be measured and reported as total of endosulfan A and B, and endosulfan sulfate
endrin				Consideration deferred pending completion of current investigations
ethion	● 0.00125	● Grapes . . . . . 2.0 *c* ● Other fruit. . . . 1.0 *c* ● Vegetables . . . 0.5 *c* ● Tea (from a particular estate) for blending only . 7.0 *c* ● Tea, blended . . 1.0 *c* ● Meat (on a fat basis) . . . . . 1.5 *c*		Meat tolerance to be applied at slaughter
ethylene dibromide	None	None recommended		See also entry under total inorganic bromide. Considered further but no change from previous report

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
hylene dichloride	None	None recommended		Considered further but no change from previous report
hylene oxide	None	None recommended		Considered further but no ADI, tolerances or practical residue limits established or recommended
nchlorfos	● 0.01	● Whole milk . . . 0.04 *c* ● Egg yolk. . . . . 0.05 *c* ● Meat (on a fat basis) . . . . . 7.5 *c*		Residues of fenchlorfos and its oxygen analogues to be determined and expressed as fenchlorfos Tolerance for meat to be applied at slaughter
ptachlor	0.0005	● Root vegetables (other than potatoes and carrots), cole crops, and other leafy vegetables 0.1 *a*	Whole milk . 0.005 *a* Milk products (on a fat basis) . . . . 0.125 *a* Meat (on a fat basis) . . . 0.2 *a* Raw cereals . 0.02 *a* Vegetables except carrots . . . . 0.05 *a* ● Carrots . . . 0.1 *a*	Combined residues of heptachlor and its epoxide to be determined and expressed as heptachlor Tolerances apply to residues resulting from application to seed and soil only
drogen yanide	0.05	Raw cereals . . . 75 Flour 6		Considered further but no change from previous report
drogen phosphide	Not necessary	Cereal products (only items to be cooked), dried vegetables and spices . . . . . 0.01 Raw cereals . . . 0.1		See report of 1967 meeting (FAO/WHO, 1968 a), p. 17, for restrictions
d (as lead rsenate)	None	None recommended		Considered further but no tolerance recommendations possible in absence of ADI
dane	0.0125	Raw cereals . . . 0.5 *a* Vegetables . . . 3.0 *a* ● Cranberries, cherries, grapes, plums and strawberries . . 3.0 *a*	Whole milk . 0.004 *a* ● Eggs (yolk) . 0.2 *a* Milk products (on a fat basis) . . . . 0.1 *a* ● Meat (on a fat basis) . . . 2.0 *a*	

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
malathion	0.02	Fruit (excluding citrus fruit), dried fruit, nuts and raw cereals 8.0 ● Whole meal and flour from rye and wheat . . . 2.0 Citrus fruit . . . 4.0 Leafy vegetables. 6.0 Other vegetables. 3.0		
methoxychlor	0.1	None recommended		This compound v not considered further
methyl bromide	None	None recommended		See also entry u der total inorgar bromide. Con dered further b no change frc previous report
MGK 264	None	None recommended	None recommended (see 1967 Monograph, FAO/WHO, 1968 b)	
organomercurial compounds	None	None recommended	None recommended but see 1967 Monograph for comment	No objection to u of organomerc rials as seed dressings and apples up to pe fall
oxydemeton-methyl	● Withdrawn	None recommended		Tolerances consi ered but no recommendatio possible in absence of AD
oxythioquinox	None	None recommended		Considered but tolerance reco mendations possible in absence of AD
parathion	0.005	Vegetables, except carrot . . 0.7 *a* Peaches, apricots, citrus fruit . . 0.5 *a* Other fresh fruit. 1.0 *a*		
parathion-methyl	● 0.001 *c*	● Fruit, cole crops, cucurbits . . . 0.2 *c* ● Other vegetables. 1.0 *c* ● Cottonseed oil. . 0.05 *c*		
phosphamidon	0.001	● Raw cereals . . . 0.1 *c* ● Apples, pears . . 0.5 *c* ● Citrus fruit . . . 0.4 *c* ● Other fruit, cole crops . . . . . 0.2 *c* ● Root vegetables . None required ● Tomatoes, lettuce, cucumbers, water melons . 0.1 *c*		Residues to be d termined by cholinesterase inhibition tech que and results be expressed phosphamidon

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
ıeronyl ıutoxide	0.03 *c*	Raw cereals . . . 20 *c* Fruit (for canning), dried fruit and vegetables, oil seeds, tree nuts . . . . . 8.0 *c*		
·ethrins	0.04 *a*	● Raw cereals . . . 3.0 *c* ● Fruit (for canning), dried fruits, dried vegetables, oil seeds, tree nuts 1.0 *c*		No change from previous report (1967 Monograph contains correction regarding sensitivity of analytical method) Temporary tolerance to be reviewed in 1972 not 1970 as implied in 1967 report for fruit
ıphene	None	None recommended		Considered but no ADI, tolerances, or practical residue limits established or recommended

● New recommendation or modification of an earlier one.

a Temporary. Results of work required should be made available not later than 30 June 1970.

b Temporary. Results of work required should be made available not later than 30 June 1971.

c Temporary. Results of work required should be made available not later than 30 June 1972.

Explanatory Notes

1. All tolerances and practical residue limits are to apply to raw agricultural products moving in commerce unless ıtwise indicated.

2. Tolerances for fruit and vegetables should be applied as soon as practicable after harvest and, in any event, r to actual retail to the public.

3. In the case of any commodity entering international trade, tolerances are applicable at the point of entry into a ıtry, or as soon as practicable thereafter, and, in any event, before processing.

Annex 3

FURTHER WORK OR INFORMATION REQUIRED (OR DESIRABLE)

AZINPHOS-METHYL

Required before 30 June 1972

1. Information on the nature of terminal residues in plants, animals and their products.

2. Further data on residue levels in raw agricultural products moving in commerce.

3. Data on disappearance of residues during storage and household cooking of vegetables.

4. Data on the possible carry-over of residues into wine as a result of the treatment of grapes.

5. Comparative evaluation of gas-liquid chromatographic and spectrophotometric methods for the determination of azinphos-methyl and its oxygen analogue for regulatory purposes.

Desirable

1. Studies on cholinesterase inhibition of plasma and erythrocytes in man.

2. Metabolic studies in man.

3. Identification and toxicology of metabolites, especially those having the benzazimide moiety, in milk.

4. Collaborative studies to establish a referee method.

BHC (TECHNICAL GRADES)

Required (before acceptable daily intakes or tolerances can be established)

1. Information on all of the principal technical grades of BHC, expressed in terms of specific isomers, as follows :

(*a*) the chemical nature of terminal residues in plants, animals and their products

(*b*) the required rates and frequencies of application, pre-harvest intervals and the resultant residues

(*c*) residue levels in raw agricultural products moving in commerce

(*d*) the disappearance of residues during storage and processing

(*e*) residue levels in total diet studies.

2. Short- and long-term feeding studies and a reproduction study in animals on individual isomers and commonly marketed technical products.

3. Metabolic studies of isomers in animals.

4. Determination of the effects on enzyme processes, especially those involving liver microsomes (cf. lindane).

5. Study of the interaction of the isomers of BHC and residue levels in tissues.

Desirable

1. Information on the relative amounts of lindane and technical grades of benzene hexachloride used in various countries.

2. Clarification by governments of whether established tolerances are for technical grades of benzene hexachloride or for lindane (99% gamma isomer only).

3. Further information on the composition of all commercially available technical BHC products and on the amounts of these used for agricultural and veterinary purposes in the different countries of the world.

BROMIDE ION

Required before 30 June 1970

Further data on the types of cereal products to be considered and on the dosage rate, frequency and other conditions of treatment.

CARBARYL

Required before 30 June 1970

1. Further data on residue levels in whole milk.

2. Data on the required rates and frequencies of application, preharvest or withholding intervals, and the resultant residues under Australian conditions and conditions in other countries.

3. Data on the disappearance of residues during storage and processing of cocoa beans and derived products.

4. Data on the disappearance of residues during storage and processing of cereals into cereal products.

CARBON DISULFIDE

Required (before acceptable daily intakes, tolerances or negligible residue levels can be established).

Information on the level of residues that may persist in the unchanged form after processing treated food products.

CARBON TETRACHLORIDE

Required (before acceptable daily intakes, tolerances or negligible residue levels can be established)

1. Information on the level of residues that may persist in the unchanged form after processing treated food products.

2. Long-term feeding studies to be carried out on two mammalian species.

CHLOROBENZILATE

Required before 30 June 1972

1. Information on the composition of the technical product.

2. Information on the nature of terminal residues in plants, animals, and their products.

3. Data from countries other than the USA on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues.

4. Further data on the disappearance of residues in soils, in plants, and in plant products during storage and processing.

5. Data on the possible carry-over of residues into wine as a result of the treatment of grapes.

6. Further data on the occurrence of residues in milk after feeding dairy cows at normal residue levels of the compound in the feed.

7. Comparative evaluation of the different detectors used in gas chromatographic methods and of different methods of extraction for regulatory purposes.

Desirable

1. Collaborative studies to establish a referee method.

2. Metabolic studies in animals.

3. Investigation of possible testicular effects and long-term studies in species other than the rat on the incidence of neoplasms.

CHLOROPROPYLATE

Required before 30 June 1972

1. Information on the composition of the technical product.

2. Information on the nature of terminal residues in plants, animals, and their products.

3. Data on the extent of use in various countries.

4. Data from countries other than the USA and Switzerland on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues.

5. Data on residue levels in raw agricultural products moving in commerce.

6. Data on the disappearance of residues during storage and processing.

7. Data on the possible carry-over of residues into wine as a result of the treatment of grapes.

8. Comparative evaluation of the different detectors used in gas-liquid chromatographic methods and of different methods of extraction for regulatory purposes.

9. Identification of metabolites other than dichlorobenzilic acid and investigation of their toxicology.

10. Adequate reproduction studies in the rat or other species.

11. Further investigation of kidney function and excretion.

Desirable

Collaborative studies to establish a referee method.

COUMAPHOS

Required before 30 June 1972

1. Data on the required rates and frequencies of application, pre-harvest intervals and the resultant residues from countries other than the USA and Canada.

2. Short-term studies of the main metabolites, including histopathology.

3. Biochemical studies, cholinesterase inhibition studies, and haematological studies, including coagulation effects in man.

Desirable

1. Collaborative studies of the published method of analysis to evaluate its suitability as a referee method.

2. More extensive studies on the metabolite chlorferron.

3. Further information relating to the observation of lens opacities in rats.

CRUFOMATE

Required before 30 June 1972

1. Data from countries other than the USA and the United Kingdom on the use pattern and resultant residues.

2. Further data on the use pattern and resultant residues in milk from treated animals, using gas-liquid chromatographic methods.

3. Data on residues in the non-fatty portion of meat and meat products.

4. Comparative evaluation of gas-liquid chromatographic methods for regulatory purposes.

Desirable

1. Collaborative studies to establish a referee method.

2. More extensive studies on cholinesterase effects in man.

3. Studies on the metabolism in man to show that 4-*tert*-butyl-2-chlorophenol is the main metabolite in that species.

DICOFOL

Required before 30 June 1972

1. Data from countries other than the USA on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues.

2. Information on the nature of the terminal residues in plants, animals, and their products.

Desirable

1. Collaborative studies to establish a referee method.

2. Comparative metabolic studies in animals and man, including adrenal function studies after oral administration.

DIOXATHION

Required before 30 June 1972

1. Determination and identification of impurities.

2. Data on the disappearance of residues during storage and processing, including residues from impurities in the technical product.

3. Data on residue levels in raw agricultural products moving in commerce.

4. Data on residue levels in total diet studies.

Desirable

1. Estimation of the effect on aliesterase activity in dogs.

2. Long-term studies in rats.

ENDOSULFAN

Required before 30 June 1971

1. Further information on the relative amounts of endosulfan A, endosulfan B, and endosulfan sulfate on fruit and vegetables—in particular on lettuce, celery and brassicas—arising from the use of technical endosulfan in accordance with good agricultural practice.

2. Data on the disappearance of the residues during storage and processing.

3. Comparative evaluation of multidetection systems of analysis (including sample extraction techniques for agricultural produce) to select a method suitable for consideration as a referee method for residues of endosulfan A, endosulfan B, and endosulfan sulfate, determined separately.

4. Data on residue levels of endosulfan A, endosulfan B, and endosulfan sulfate in total diet studies.

Desirable

1. Clarification of the extent of use, if any, other than on fruit and vegetables.

2. Metabolic studies in man, with particular reference to storage of the original compound and metabolites.

ETHION

Required before 30 June 1972

1. Data from countries other than the USA on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues.

2. Data on residue levels in raw agricultural commodities moving in commerce.

3. Residue data in processed food, including meat, meat products and wine.

Desirable

1. Collaborative studies to establish a referee method.

2. Adequate observations of effects in man, including studies of the metabolic fate.

3. Determination of the metabolic fate in animals.

4. Long-term studies in at least two species.

5. Cholinesterase depression studies at more frequent intervals in animals.

ETHYLENE DIBROMIDE

Required (before acceptable daily intakes, tolerances or negligible residue levels can be established).

Information on the level of residues that may persist in the unchanged form after processing treated food products.

ETHYLENE OXIDE

Required (before acceptable daily intakes or tolerances can be established)

1. Additional data on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues.

2. Data on the disappearance of residues during storage and processing following bactericidal or insecticidal treatment.

3. Data on the disappearance of residues resulting from commercial fumigation treatments.

4. Identification of reaction products with food, evaluation of the effects on nutritional value, and toxicological studies on the products.

5. Determination of levels of ethylene chlorohydrin in fumigated foods.

6. Long-term studies on ethylene chlorohydrin in experimental animals.

Desirable

Data on the rate of disappearance of ethylene chlorohydrin or on the amounts excreted.

FENCHLORPHOS

Required before 30 June 1972

1. If use of the compound is to be extended to fruit and vegetables, data from several countries on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues.

2. Data from several countries other than the USA and the United Kingdom on animal use patterns and resultant residues.

3. Data on residue levels in raw agricultural products moving in commerce.

4. Data from countries other than the USA on residue levels found in total diet studies.

5. Comparative evaluation of methods of analysis for regulatory purposes.

Desirable

1. Collaborative studies to establish a referee method.

2. Estimation of effect on aliesterase activity in animals and man.

3. Determination of no-effect level with respect to cholinesterase activity in man.

4. Data on the fate of the trichlorophenol metabolite.

5. More adequate human data.

HEPTACHLOR

Required before 30 June 1970

1. Data from supervised trials on (*a*) the content of residues in soils treated for one, two and three or more years with heptachlor and (*b*) the content of residues in carrots grown in the treated soils at various intervals after cessation of treatment.

2. Data on unintentional residues in sugar beets and sugar beet pulp to indicate the maximum residue of heptachlor and heptachlor epoxide that may be fed to meat- and milk-producing animals without exceeding the currently recommended practical residue limits for these animal products.

3. Data on residues in sugar beets and sugar beet pulp from furrow seed treatment and coated seed treatment.

LINDANE

Required before 30 June 1970

1. Further information on the nature of terminal residues in plants, animals and their products.

2. Further data on the required rates and frequencies of application, pre-harvest intervals and the resultant residues.

3. Further data on residues occurring in cocoa and cocoa products.

4. Further data on residues resulting from supervised trials of bin, shiphold and other storage or conveyance treatments.

METHYL BROMIDE

Required (before acceptable daily intakes, tolerances or negligible residue levels can be established)

Information on the level of residues that may persist in the unchanged form after processing treated food products.

OXYDEMETON-METHYL

Required (before acceptable daily intake or tolerances can be established)

1. Further information on the nature and persistence of residues, especially as a result of comparative studies with the *O*-ethyl analogues.
2. Specification of the compound (or compounds) in actual agricultural use.
3. Studies to compare the metabolite fate in plants, animals and man.
4. Adequate long-term studies in two species.

Desirable

1. Further data on residue levels in raw agricultural products moving in commerce.
2. Investigation of cholinesterase inhibition in man.

OXYTHIOQUINOX

Required (before an acceptable daily intake or tolerances can be established)

1. Information on the nature of terminal residues in plants and animal products.
2. Data from countries other than the USA on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues.
3. Further data on residue levels in raw agricultural products moving in commerce.
4. Data on residue levels in total diet studies.
5. Comparative evaluation of methods of analysis for regulatory purposes.
6. Experimental studies on the metabolism responsible for liver hyperplasia in rats.
7. Biochemical studies on excretion and metabolism.
8. Two-year studies on rats at lower dosage.
9. Further information on anti-spermatogenic effects.

Desirable

1. Collaborative studies to establish a referee method.
2. Studies of metabolism in various animals including man.
3. Further studies on the cutaneous toxicity, including studies related to the question of photosensitization.

PARATHION-METHYL

Required before 30 June 1972

1. Quantitative data on the occurrence of paraoxon-methyl and other metabolites in plants and animal products.

2. Data from countries other than the Federal Republic of Germany and the USA on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues.

3. If a tolerance is required on rice, data on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues.

4. Further data on residue levels in raw agricultural products moving in commerce.

5. Data on residue levels in total diet studies.

6. Comparative evaluation of available methods for regulatory purposes.

7. Oral studies on teratogenicity and reproduction in species other than rats and mice, preferably in subhuman primates

Desirable

Collaborative studies to establish a referee method.

PHOSPHAMIDON

Required before 30 June 1972

1. Data on the required rates and frequencies of application, pre-harvest intervals, and the resultant residues from different countries.

2. Confirmatory studies of the nature and persistence of the residues in fruits and vegetables, fresh and processed.

3. Development of an analytical method that is specific for phosphamidon and its *N*-de-ethyl derivative.

Desirable

1. Biochemical and metabolic fate of phosphamidon in man following different types of exposure.

2. Reproduction studies in at least one species other than the rat.

TOXAPHENE

Required (before an acceptable daily intake or tolerances can be established)

1. Data relating to the uniformity of the technical product:

(*a*) variability in biological activity (e.g., LD_{50} variation in mammals or in insects) from batch to batch

(*b*) variability in the chemical composition as determined by gas chromatography, thin layer chromatography or other analytical methods

(*c*) variability in the starting product and in the final product from different sources

(*d*) criteria for control of the degree of chlorination.

2. Information on the chemical nature of terminal residues in plants, animals, and their products, as determined by modern analytical methods, including the possibility of formation of photo-oxidation products.

3. Further residue data from supervised trials on a variety of crops.

4. Residue data in:

(*a*) poultry, cattle, sheep and swine

(*b*) unprocessed and processed vegetable oils

(*c*) cereals, after processing into flour, bread, etc.

5. Development and comparative evaluation of methods of analysis for regulatory purposes.

6. Complete toxicological studies based upon a standardized technical product, the constituents of which have been identified.

TRICHLOROETHYLENE

Required (before an acceptable daily intake, tolerances or negligible residue levels can be established)

Information on the level of residues that may persist in the unchanged form after processing treated food products.