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## **PESTICIDE RESIDUES IN FOOD**

### **Report of the 1973 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues**

Geneva, 26 November–5 December 1973



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1973 JOINT MEETING OF THE FAO WORKING PARTY OF EXPERTS  
ON PESTICIDE RESIDUES AND THE  
WHO EXPERT COMMITTEE ON PESTICIDE RESIDUES

Geneva, 26 November - 5 December 1973

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# PESTICIDE RESIDUES IN FOOD

## Report of the 1973 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 26 November to 5 December 1973. The Meeting was opened by Dr A. S. Pavlov, Assistant 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 21 to 24 November 1973 in Geneva in preparation for the Joint Meeting.

Dr Pavlov stressed the increasing concern over contamination of man's environment, pointing out that food is a major source of intake of chemical contaminants, particularly pesticides. The toxicological evaluation of their potential hazards is aimed at estimating acceptable daily intakes for man; these also form the basis for recommending tolerances in various food items. The recommendations will provide guidance for countries attempting to control the agricultural use of pesticides, and for the Codex Alimentarius Commission and its subsidiary body, the Codex Committee on Pesticide Residues, when recommending international tolerances. Moreover, evaluation of the hazards of pesticides will contribute towards the health protection of mankind from the pollution of the general environment by chemicals.

### 1. INTRODUCTION

The annual Joint Meeting was held in pursuance of the recommendations made in 1961, at a meeting of a WHO Expert Committee on Pesticide Residues held jointly with the FAO Panel of Experts on the Use of Pesticides in Agriculture, that studies be undertaken to evaluate possible hazards to man arising from the acceptance of residues of pesticides in foods.

The reports of previous meetings contain information on acceptable daily intakes (ADIs) established, on residue limits recommended, and on the methods of analysis suggested for the various pesticides considered. The supporting documents contain detailed monographs on these pesticides and include comments on analytical methods.

The present Joint Meeting 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 Sixth Session of the Codex Committee on Pesticide Residues held in October 1972.

During the present Joint Meeting the FAO Working Party was primarily responsible for:

- (a) reviewing data on certain pesticides and their residues;
- (b) proposing pesticide residue limits and recommending methods for their analysis.

The WHO Expert Committee was primarily responsible for:

- (a) reviewing toxicological and other relevant data on certain pesticides and their residues;
  - (b) establishing, where possible, ADIs for man for those pesticides
- Furthermore each of these groups of experts made recommendations designed to indicate, stimulate, and coordinate necessary research.

## 2. GENERAL CONSIDERATIONS

### 2.1 Principles and scope

Like its predecessors the 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, in the second and fifth reports of the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO 1958, 1961), in the report of the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives (WHO, 1967) and in reports of previous Joint Meetings (FAO/WHO 1967a, 1968a, 1969a, 1970a, 1971a, 1972a, 1973a).

The Meeting discussed a number of principles, some of which had been adopted in the past by various Meetings and felt that in relation to the substances considered at this Meeting they should be either clarified or rephrased, reaffirmed, and extended.

#### 2.1.1 *Animal feeds*

Further to the decision of the 1972 Meeting (FAO/WHO 1973a, section 2.8) to consider data and to make recommendations on residues in certain animal feeds, recommendations were made at the present Meeting for residues on crops especially grown as animal feed (e.g., alfalfa, pasture grass) and for waste from crops primarily grown for human food fed to

livestock animals (e.g., sugarbeet tops, pea and bean vines, etc.). However insufficient data were available to enable recommendations to be made with regard to residues in oilcake and compound feeds: the position concerning such products should be considered at a future meeting.

## **2.2 Considerations on certain testing procedures**

### *2.2.1 The need for long-term tests to establish acceptable daily intakes*

A number of substances that were not found to be toxic in laboratory animals in short-term tests have subsequently shown toxic effects in long-term studies. The Meeting therefore agreed that as a general rule ADIs should be established only when data showed that the possibility of a long-term toxic hazard had been substantially excluded. This will normally be the case only where data from long-term studies are available.

### *2.2.2 Data obtained by gavage administration versus feeding*

The Meeting examined the results of short-term and reproduction studies on several pesticides in which similar dosage levels of particular compounds had been administered daily to groups of experimental animals by gavage and to other groups by incorporating the compounds in the diet.

The Meeting discussed the need to expose experimental animals in a way that parallels human exposure. Species such as the rat normally feed more or less continuously during the night. When such species are used for testing substances that act only briefly and that do not accumulate or produce cumulative effects, it is to be expected that dietary administration will cause less pronounced biological effects than administration by gavage, which permits the total daily intake to enter the body in a single dose. In almost every instance administration by gavage produces higher peak levels in blood and tissue than does incorporation in the diet.

In order to facilitate the interpretation of both feeding and gavage studies, attempts should be made to determine concentrations of pesticides and their metabolites in blood and tissue.

### *2.2.3 Investigations in man*

The hazard to man from the introduction of a chemical such as a pesticide into the environment can be more reliably predicted if information from carefully planned studies in man is available. Useful information may sometimes be derived from studies on persons who are occupationally exposed to the chemical or who have been accidentally poisoned by it. In these circumstances special efforts should be made to arrange for clinical investigations, including the analysis of samples of blood and tissue from

the affected persons. Arrangements should also be made for the follow-up of exposed persons and for the collation of the data obtained. In some cases the exposed population may be large enough and sufficiently well defined to render appropriate epidemiological studies worth while. If effects that are apparently specific to man are observed, evidence obtained earlier from animal studies should be reassessed to see whether information has been overlooked or whether some different method of study might have been of greater predictive value.

Although there may be ethical and legal problems in carrying out investigations designed to establish safety or to detect toxicity in man, the use of volunteers may be justifiable when the administration of trace amounts can help in identifying metabolites. For instance, trials in man of those pesticides for which there is known to be a sensitive index of exposure (e.g., cholinesterase inhibition) might be acceptable.

#### 2.2.4 *Data obtained from the use of new methods*

The Meeting considered how the development of new methods for toxicological assessment or chemical analysis might be taken into account in relation to pesticides for which ADIs and/or residue limits had already been recommended. Recommendations are necessarily conditioned by the methods available at the time they are made. The Meeting recognized that the development of a new method might, at any time, make it desirable to review existing recommendations, whether or not they had been made on a temporary basis. A need for re-evaluation may stem from new information concerning residues or the identity of metabolites. Re-evaluation may result in either raising or lowering ADIs or residue limits.

The use of new methods may resolve anomalies and uncertainties in data on particular pesticides and thereby provide greater assurance concerning their safety, and may also provide information of value in the toxicological evaluation of other pesticides and of other environmental chemicals.

### 2.3 **Modifications and clarifications of certain terms**

#### 2.3.1 *Discontinuation of the use of the term "tentative negligible daily intake"*

At a previous Meeting (FAO/WHO 1970a) the term "tentative negligible daily intake" was adopted. Since data that are not adequate for estimating an acceptable daily intake are also not adequate for classing an intake level as negligible, the present Meeting recommended that the term be discontinued, and that the Glossary (FAO/WHO 1970a, Appendix IV) be amended accordingly.

### 2.3.2 *Temporary acceptable daily intake*

In the case of some of the pesticides previously given temporary ADIs, data required for the present Meeting were not available.

Where some of the data required were available and it was clear that an effort had been made to provide most of the data required, the Meeting agreed that it would be reasonable to extend the period of the temporary ADI. In other cases concern was expressed at the continued lack of response to requests for data and the Meeting reaffirmed the principle established in 1972 (FAO/WHO 1973a) that temporary ADIs should be withdrawn in such circumstances (see also FAO/WHO 1973a).

### 2.3.3 *“ Desirable ” studies*

In Appendix IV of the report of the 1969 Joint Meeting (FAO/WHO 1970a) terms “ further work required ” and “ further work desirable ” were defined. With regard to “ desirable ” work it was stated that results from such studies would be expected to provide additional assurance that the acceptable intakes established were adequate to protect the health of the consumer. When discussing a number of pesticides at this Meeting, it was felt that in some cases, even where the Meeting had enough toxicological data to establish acceptable daily intakes in man, further information and studies would be desirable.

Such studies may clarify points of uncertainty about a particular pesticide and also provide basic knowledge and information about methods of testing relevant to the toxicological evaluation of pesticides in general.

- Moreover, since figures expressing acceptable daily intakes stem from the evaluation of experimental studies and observations, the ADIs may be raised if data that warrant such action become available.

### 2.3.4 *Guidelines*

In the absence of ADIs the Meeting felt it necessary as an interim measure to recommend guideline levels for certain pesticides to assist regulatory authorities. The levels recommended would be those that need not be exceeded if good practices are followed. In the interest of the protection of the health of the consumer, proper toxicological evaluation of these pesticides should be carried out as soon as possible in order that tolerances and/or practical residue limits can be recommended. These guideline levels will be recorded as temporary and will be reassessed as soon as toxicological data are sufficient to establish an ADI.

## 2.4 Significance of figures for ADIs

The Meeting discussed the accuracy with which ADIs or temporary ADIs or conditional ADIs of pesticides can be estimated. The Meeting recommended that ADIs should be expressed numerically using only one significant figure. The use of more than one significant figure might be taken to imply a degree of accuracy that cannot be achieved when assessing the hazard from the many factors that influence toxicity.

## 2.5 Expression of residue limits

From time to time the Meeting had received requests to consider changing a recommended tolerance by a small amount, for example, from 3 mg/kg to 2 mg/kg, from 0.5 mg/kg to 0.7 mg/kg. Extensive data from many sources reveal that the frequency with which residue levels in food approach the tolerance level is very low. It is also important to recognize that, on statistical grounds, chemical analysis can never determine the "true" content of the residue in a given lot of a food commodity but can only provide an approximation to the true value. This is due partly to systematic errors (both human and technical) in analytical procedures and partly to the heterogeneous distribution of the residue in the lot being sampled. The "true" value would be approached only if the entire sample lot were analysed. Since this is impracticable, samples are taken for analysis and every effort is made to obtain them in such a way that they represent as closely as possible the mean value of the residue in the lot. However, if the same commercial lot is sampled and analysed by different persons or laboratories, different results will usually be obtained. In analyses of the same sample, the coefficient of variation can easily exceed 20%.

In view of these variabilities, there is little significance in recommending new, or changing old, tolerance figures in a way that would suggest a greater accuracy than that with which the original tolerances were established. It is also more logical to propose tolerances that are based on a geometrical progression (e.g., 0.1, 0.2, 0.5, 1, 2, 5, 10 mg/kg), than on an arithmetical one (e.g., 0.2, 0.3, 0.4 or 3, 5, 7, 10 mg/kg). The percentage error involved in residue analysis is not constant but decreases as the concentration of residue increases. The proposed scale is useful over the range of about 0.01 to 10 mg/kg. Concentrations below 0.01 mg/kg approach the current limits of determination of most pesticides in foods. Above 10 mg/kg the accuracy improves and figures such as 10, 15, 20, 25 mg/kg (or even closer) have greater statistical significance. Fortunately the scale encompasses the vast majority of situations that require consideration. In making

new recommendations and in revising several recommendations made previously, the present Meeting has adhered to this scale to the extent possible and permitted by the data.<sup>1</sup>

## **2.6 Residue limits for groups of foods**

The Meeting discussed the need for, and possibility of, making recommendations for residue limits for groups of foods. It was noted that some such recommendations had already been made, e.g., for "fruit", "vegetables", "leafy vegetables", and that certain principles for this practice had been established at the 1970 Meeting (FAO/WHO, 1970a, section 2.10). Some unpublished studies on the possibilities and implications of the use of "group tolerances" have been conducted in the USA. The Meeting accepted that grouping would enable a larger number of foods in commerce to be covered by the recommendations. Furthermore, provided that critical safeguards were used such recommendations could be employed without any increased risk to consumers.

In amplification of the principles set out in section 2.10 of the 1970 Report and with a view to recommending limits on a group basis, it was accepted that special efforts should be made in future to obtain and study data concerning: (1) crops generally accepted as staple food; and (2) crops generally accepted as constituting a group in their tendency to retain residues. Preferably, the crops studied should be those that are expected to show residues at levels above the mean for the group in which they fall.

These concepts should be studied at future meetings when considering data on individual pesticides and when developing general principles for future research.

It was suggested that this question be reconsidered at the 1974 Meeting. As a background, the Meeting asked that a draft text be prepared, clearly defining the commodities for which recommendations have so far been made.

## **3. SPECIFIC PROBLEMS**

### **3.1 The significance of the development of liver-cell tumours in mice**

In a previous report (FAO/WHO, 1971a) attention was drawn to the need for more information on the development of liver tumours in mice. The present Meeting considered the problem of interpreting data in respect

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<sup>1</sup> See also FAO/WHO 1971a, section 2.13; 1972a, section 2.6; and 1973a, section 2.6.

of carcinogenicity where exposure of mice to a pesticide in food is associated with evidence of increased risk of development of liver tumours. Several organochlorine pesticides increase the risk of development of nodules in the livers of mice. It is not clear what proportion of the nodules are neoplasms but there is unequivocal evidence, in the case of some of the compounds, that they increase the incidence of neoplasms that metastasize to the lungs.

A feature of many substances (e.g., phenobarbital) that increases the risk of liver tumour development in mice is that they induce microsomal drug-metabolizing enzymes and hypertrophy of the smooth endoplasmic reticulum of mouse liver cells. These biochemical and histological changes occur in the liver cells of other species but without associated tumour development. When tumours develop in the livers of mice that show these liver-cell changes, the biochemical and histological changes just referred to tend to be present in the tumour cells as well as in "normal" liver cells. Apart from this, the tumours that arise in response to exposure to chlorinated hydrocarbons are very similar in appearance and behaviour to those that arise in untreated mice. It is known that in several strains of mice liver tumours, including some that metastasize to the lungs, may arise in untreated animals and that the rate may be as high as 100%. The Meeting agreed that there is a serious lack of knowledge regarding the processes involved in the development of liver tumours by mice and that it would be unwise to classify a substance as a carcinogen solely on the basis of evidence of an increased incidence of tumours of a kind that may occur spontaneously with such a high frequency.

In general it was felt that if the exposure of mice to a pesticide was associated with an increased risk of the development of liver tumours, long-term feeding studies on at least one other species should be required. Carcinogenicity tests in two species other than the mouse would be regarded as appropriate where it was evident that man might be exposed through food to a dose level close to one that increased the incidence of liver tumour in mice.

The Meeting agreed that, although the above considerations might be useful for general guidance, it would be essential for each pesticide to be considered and assessed individually.

### **3.2 Toxicity of cholinesterase-inhibiting substances**

For animals exposed to organophosphorus compounds that inhibit cholinesterase, depression of cholinesterase activity in plasma, erythrocytes and various other tissues is usually the most sensitive measure of toxicity. However, a few organophosphorus compounds with low acute toxicity and certain carbamates produce reversible inhibition of cholinesterase. Measure-

ment of depression of cholinesterase activity in blood or tissues may then be unreliable as an indicator of potential toxicity.

The Meeting felt that because the anticholinesterase effect of certain carbamates was reversible and because many of them have only short half-lives, information on plasma concentrations and biological half-lives of such compounds was required. Such information is needed to elucidate discrepancies between signs of cholinergic stimulation and measurements of apparent *in vivo* inhibition of cholinesterase activity by such compounds as propoxur, which was considered at this Meeting.

The Meeting expressed continuing concern over the reports from Japan of ophthalmological disturbances resulting, it has been suggested, from exposure to organophosphorus pesticides (see also FAO/WHO, 1973a, section 2.3). This suggestion needs verification and its relevance to the degree of exposure to pesticide residues in food should be assessed.

### **3.3 Pharmacokinetic and enzyme kinetic studies on organophosphorus compounds**

To permit the evaluation or re-evaluation of certain organophosphorus compounds, there is a need for information from pharmacokinetic and enzyme kinetic studies, for information on the time-course of cholinesterase inhibition *in vivo*, and for studies of aliesterase inhibition and of interactions with other organophosphates. Information was also needed on the influence of exposure to enzyme-inducing agents on the response to organophosphorus compounds.

### **3.4 Testing of pesticides for mutagenicity**

The Joint Meeting discussed the need for mutagenicity tests in the evaluation of a pesticide when estimating an ADI for man. The possible mutagenic action of chemicals has already been discussed by several WHO Scientific Groups (ref. WHO 1967, WHO 1971 and WHO 1974).

For the majority of the pesticides that were evaluated or re-evaluated at the Meeting, results from one or more tests for mutagenicity were available. Most of the results were negative, but a few gave positive results in one or more microbial or isolated cell systems.

The Meeting underlined the importance of protecting the human population from exposure to mutagens in food. However, in view of the uncertainty about the extent to which most of the tests available at present are relevant for predicting the mutagenic hazard to man, the Meeting could not recommend any particular test to be required for estimating ADIs.

More weight should be attached to the results from mutagenic tests in mammals than to those from microbial or other non-mammalian systems or isolated cell systems. The significance of positive results from microbial test systems, unsupported by information from tests of other kinds, would be regarded by the Meeting as uninterpretable for the purposes of establishing an ADI.

In spite of the difficulties in interpreting the significance for human health of the results from most tests for mutagenicity, the Meeting agreed that such tests were desirable because they provided additional information on the biological activity of pesticides. The Meeting felt that tests for mutagenicity were especially desirable in certain cases, e.g., for substances that yield metabolites with stable carbonium ions or strong electrophilic reactivity.

The Meeting felt that negative results from tests for other kinds of biological activity (e.g., reproduction studies, teratogenicity studies, and tests for carcinogenicity) would give some assurance that the pesticide residue would not constitute a mutagenic hazard for man, especially when such negative results were obtained at dose levels very much higher than those to which man would be exposed.

The Meeting hoped that research now in progress would lead to the development of mutagenicity tests known to be relevant to the prediction of mutagenic potential for man.

### **3.5 Assessment of pesticides having the same or similar metabolites**

In considering the benzimidazole fungicides and the alkylthioether and benzotriazine organophosphorus insecticides, the validity of treating as a group pesticides that are structurally similar or that give rise to the same or similar metabolites was discussed.

The Meeting referred to a statement of principles for the toxicological evaluation of metabolites of pesticides (FAO/WHO, 1970a, section 2.3) and noted the need for both qualitative and quantitative data on the identity of metabolites in plants and animals, as indicated in that report.

It was recognized that the major metabolite of a pesticide might not be the most important toxicologically and that it would also be necessary to have comparative data on minor metabolites from the chemically related pesticides. It was felt that only when such information was available would it be appropriate to consider the extrapolation of toxicological data from one compound to another. On the basis of present knowledge, the only acceptable extrapolation would be when one pesticide was a quantitatively significant metabolite of another pesticide for which adequate toxicological data were available.

### 3.6 Hexachlorobenzene (HCB)

The 1969 Joint Meeting, on the basis of the results of a 13-week feeding study in rats, in which no adverse effects were detected at a daily dosage of 1.25 mg/kg, estimated a "tentative negligible daily intake" of 0-0.0006 mg/kg body-weight. The 1969 Meeting indicated that before an ADI could be established several toxicological studies would be required.

The present Meeting decided that the term "tentative negligible daily intake" should not be used (see section 2.3).

Since the 1969 Joint Meeting no further work relevant to estimating an ADI has become available. It is known, however, that several laboratories are currently engaged in research that might provide a reasonable basis for the safety evaluation of HCB, and the Meeting urged that these data should be obtained for consideration by a future Joint Meeting.

It was recognized that HCB residues in foods also arise from sources other than its proper use as a fungicide (e.g., industrial wastes from chlorination processes, and contamination of other chlorinated pesticides). Because of this, it will not be sufficient to attempt to control exposure merely by controlling the use of HCB as a fungicide. Notwithstanding the fact that residues of HCB stem less from its use as a pesticide than from other sources, the Meeting reaffirmed the recommendation made in 1969 that a suitable substitute for HCB as a seed fungicide should be sought. In addition the Meeting recommended that efforts should be made to reduce the level of HCB as an impurity in other pesticides. A specific recommendation to this effect was made in the case of quintozene.

On the assumption that there is a level of HCB below which no significant toxicological effects can be expected, it was felt possible to give some provisional guidance. A daily intake of 0.0006 mg/kg is considerably below any dosage rate *known to be harmful*, and the Meeting recommended that this value should be used as a guide for setting upper limits for residues until it was possible to establish an ADI based on the results of comprehensive toxicological studies.

The Meeting considered the further work that was required for the establishment of an ADI and its recommendations are listed in Annex 2.

## 4. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE

### 4.1 Organophosphorus insecticides

Six organophosphorus compounds were considered for the first time : azinphos-ethyl, demethon-S-methyl, oxydemeton-methyl (demeton-S-methyl sulfoxide), demeton-S-methyl sulfone, disulfoton and vamidothion.

Three organophosphorus insecticides, azinphos-methyl, thiometon and formothion, which had previously been evaluated, were also evaluated in the light of new data.

*Demeton-S-methyl and related compounds.* Demeton-S-methyl, the sulfoxide and the sulfone derivatives were assessed separately. The ADI established applies to the total intake of all three compounds. A no-effect level based on cholinesterase depression was determined by short-term feeding studies in rats and dogs and a two-year feeding test conducted with the sulfoxide. Negative results from teratogenicity tests in rabbits, mutagenicity tests in mice, and reproduction studies in rats were reassuring. As demeton-S-methyl is converted in plants and animals to the sulfoxide and sulfone, data on the sulfoxide were used to establish the ADI.

*Disulfoton.* Disulfoton had no adverse effect on reproduction and results of tests for teratogenicity, mutagenicity, and neurotoxicity were negative. Long-term studies were reported to be in progress. On the basis of short-term studies in rats and dogs, a temporary ADI was established.

*Vamidothion.* Vamidothion had no adverse effects on reproduction. The only effect found in two short-term studies was depression of cholinesterase activity. Observations were insufficient to allow an acceptable daily intake to be established.

*Azinphos-ethyl.* There were insufficient data on azinphos-ethyl to be certain that it is metabolized at the same rate and in the same way as azinphos-methyl. Data do, however, suggest that the benzotriazine moiety remains intact in both compounds. In the absence of adequate information on its metabolism and long-term toxicity the Meeting was unable to estimate an ADI.

*Azinphos-methyl.* Further information on the metabolism of azinphos-methyl and the results of a mutagenicity study have been made available. These have enabled the Meeting to confirm the ADI previously established.

*Formothion.* In the light of information gained from observations on humans exposed to dimethoate, a metabolite of formothion, an ADI was established on the basis of data from two-year feeding studies in rats and dogs.

*Thiometon.* By analogy with disulfoton, thiometon is likely to be metabolized to the sulfoxide and sulfone of the dithioate ester and to demeton-S-methyl. Experimental data to support this assumption were not yet available. On the basis of the short-term studies in two species a temporary ADI was established.

#### 4.2 Benzimidazole fungicides

Two benzimidazole fungicides, thiophanate-methyl and carbendazim, were considered for the first time. Benomyl was re-evaluated having been considered by a previous Meeting (FAO/WHO, 1973a).

*Thiophanate-methyl.* The results of short-term and long-term feeding studies in mice, rats and dogs, including tests for mutagenicity, carcinogenicity, and effects on reproduction, were evaluated and an ADI based on these considerations was established.

*Carbendazim.* The apparent occurrence of carbendazim in mammals fed thiophanate-methyl is not well documented and needs clarification. Short-term studies were evaluated but long-term toxicity studies and tests for carcinogenicity, teratogenicity, and possible effects on reproduction were regarded as necessary before an ADI could be established.

*Benomyl.* Data available for consideration by the Meeting were not sufficient to permit the establishment of an ADI.

#### 4.3 Methylcarbamate insecticides

Carbaryl was re-evaluated, it having already been considered by a previous Meeting (FAO/WHO, 1970a). Propoxur was evaluated for the first time.

*Carbaryl.* New data did not substantiate a suggestion from previous work that carbaryl interferes with pregnancy in the rhesus monkey. Additional reports of effects on reproduction and other physiological effects from gavage treatment were of concern. The Meeting felt, however, that the available data were sufficient to permit the establishment of an ADI.

*Propoxur.* Data from two-year studies in rats and dogs were evaluated. Concern was expressed over the lack of correlation between cholinesterase depression and clinical signs of poisoning (see section 3.2). Results of studies on the effect of propoxur on reproduction and on mutagenicity and teratogenicity were negative. In addition, reassurance of safety was provided by the observations that the signs of acute poisoning in man are rapidly reversible and that prolonged exposure is associated with decreasing susceptibility to the compound. An ADI was established.

#### 4.4 Miscellaneous pesticides

Bromopropylate and tetrasul were considered for the first time.

Several compounds considered at previous Joint FAO/WHO Meetings were re-evaluated at the present Meeting. An ADI was established for

captan and folpet. A temporary ADI was established for captafol, quintozene, lindane, and tricyclohexyltin hydroxide. No ADI was established for hexachlorobenzene, BHC (technical), or camphechlor.

*Bromopropylate.* An ADI was established on the basis of adequate data on metabolism and on information provided by reproduction, short-term, and long-term studies. High dosage levels of bromopropylate produce abnormalities in the liver. These may be associated with enzyme induction and the Meeting requested that the abnormality should be further studied. The finding that the mortality rate of female rats increased at high dosage levels in long-term tests was also considered to merit further investigation.

*Tetrasul.* No ADI was established for this substance because the necessary data were not available to the Meeting.

*Captan.* An ADI was established after reassessment of data on non-human primates and an examination of a study in dogs, in which it was demonstrated that captan has no teratogenic activity in these species. The Meeting felt that further studies on haematomas produced by high dosages were desirable to elucidate their role as a possible mechanism of fetal death and malformation.

*Folpet.* Data previously reported and metabolic data demonstrating the similarity of folpet to captan enabled an ADI to be estimated. Mutagenesis studies gave negative results.

*Captafol.* Although it has been shown that this fungicide is rapidly absorbed and eliminated from the body, no information has been made available on the fate of the tetrachloroethylthio moiety. The significance of the abnormalities in the kidneys and liver and in the lymphocyte-to-neutrophil ratio, previously reported, has not been elucidated. However, in the light of recent studies and of the finding that captafol is unlikely to possess teratogenic activity, the Meeting reaffirmed the temporary ADI.

*Quintozene.* The results of further metabolic studies were assessed. Teratogenicity tests have demonstrated that high dosage levels of quintozene produce various deformities in two strains of mice, while none are produced at lower dose levels in mice or at any dose level in rats. The reason for these findings should be investigated. Long-term feeding studies in rats and mice are in progress and should soon be available. The Meeting considered that sufficient information is available to extend the validity of the temporary ADI for a further two years.

*Lindane.* In a 2-year study in dogs, a no-effect level based on hepatic lesions was estimated. Tests in several species showed no effects on repro-

duction and mutagenicity tests were negative. A high level in the diet of mice produced liver enlargement and nodule formation. As long-term studies in rats did not resolve the question of carcinogenicity, the formerly established ADI was made temporary.

*Campechlor*. The Meeting did not establish an ADI and expressed concern that:

(a) not all preparations used in agriculture conform to FAO specifications;

(b) even though the toxicological tests performed during the last 20 years may have been carried out on a uniform material, conforming to FAO specifications, it is not certain that these data are applicable to campechlor from all sources ;

(c) toxicological studies, especially with regard to carcinogenesis, are inadequate in view of the current knowledge of the tumorigenic potential of chlorinated pesticides in mice.

*Hexachlorobenzene*. Data were insufficient to establish an ADI (see section 3.6).

*BHC (technical)*. There is insufficient information to permit the estimation of a no-effect level.

*Tricyclohexyltin hydroxide*. Recent studies have demonstrated that this compound has no effect on copper metabolism. While its irritant properties may account for the effects on weight gain in animals, other factors have not been investigated. The question of the previously reported pituitary and hepatic cysts has been resolved. However, the possibility that the compound might have been responsible for the induction of hepatic adenomas should be investigated and further long-term studies should be carried out. The Meeting established a temporary acceptable daily intake.

## 5. EVALUATION OF DATA FOR RESIDUE LIMITS

The Meeting reviewed and, in certain cases, amended recommendations made previously. Nine pesticides that had not been considered previously were also reviewed.

### 5.1 Information supplied by governments

The Meeting was encouraged by the information received from governments concerning compounds on the agenda. However, although the volume of this information was greater than at previous meetings, some was

not in a form that could be used to develop recommendations, since it lacked such essential details as the units in which application rates were expressed, the intervals between treatment and harvest, and the times and method of sampling. In particular, results of supervised trials were not generally provided. In many cases, the data did not reflect the approved use patterns in the particular country. It was recognized that some people preparing submissions may not have been fully aware of what was needed and that this difficulty might be avoided if the requirements were set out in greater detail.

### **5.2 Pesticides reviewed in the light of new information**

The following pesticides were reviewed in the light of information received since the previous Meeting:

azinphos-methyl, the demeton-methyl group, captafol, captan, camphechlor, carbaryl, folpet, formothion, hexachlorobenzene, lindane, BHC (technical), quintozene, tricyclohexyltin hydroxide and malathion.

Certain additions, amendments, or clarifications appear in Annex 1 to this report and in the relevant monographs (FAO/WHO, 1974b). In the case of hexachlorobenzene and BHC (technical), recommendations designed to reduce the contamination of food were made.

### **5.3 Pesticides not previously considered for establishment of tolerances or practical residue limits**

Recommendations for tolerances were made for demeton-methyl, thiometon, disulfoton, thiophanate-methyl, bromopropylate and propoxur. In the absence of an ADI it was not possible to recommend tolerances for azinphos-ethyl, benomyl, camphechlor, carbendazim or vamidothion, but guideline levels indicating the concentration of residues that could occur following approved uses of these pesticides in a variety of commodities were published for the information of regulatory and other interested authorities.

Full details of the evaluation of these compounds are contained in the monographs (FAO/WHO, 1974b) and a summary of the recommended values is provided in Annex 1.

### **5.4 Information on old compounds developed by means of new analytical procedures**

The Meeting noted that in the case of captan, captafol, folpet, vamidothion, demeton-methyl and disulfoton some of the residue data had been

based on analytical procedures that may not have been as specific, sensitive or reproducible as those available today. However, many of the data were of an adequate quality and the Meeting felt that they were valid. It was recognized that new data would be generated by the application of more sensitive techniques and it was desirable that this new information should be made available for evaluation at a future Meeting.

### **5.5 Compounds not considered**

In reviewing the compounds put forward by the Codex Committee on Pesticide Residues, it was decided that there was no evidence to suggest that residues of prometryne occur in food. This compound was therefore not evaluated by the Meeting.

Tetrasul, tetradifon, and chlorfensulfide were not reviewed either, but will be considered at the next Meeting.

## **6. FUTURE WORK**

### **6.1 General principles**

There are insufficient data on certain pesticides, including some that have been in use for many years, to permit even a temporary ADI to be estimated. It was realized, however, that sufficient toxicological information on some of these products was unlikely to be obtained. Some guidance concerning the safety of residues of such compounds would be of great value in view of the fact that their use would continue whether or not there was an ADI.

It is recommended that the principles on which guidance should be based should be discussed as a separate item by a future Joint Meeting. It would also be useful for a future Meeting to discuss means whereby adequate toxicological data could be generated to permit the establishment of ADIs.

### **6.2 Other items to be considered**

It was suggested that the following items should be considered at future Joint Meetings:

1. Consideration of the following pesticides for which the temporary ADIs and/or temporary tolerances are due to be reconsidered in 1974: dimethyldithiocarbamates (ferbam, thiram, and ziram); ethylenebis-dithiocarbamates (mancozeb, maneb, zineb); fenitrothion.

2. Evaluation of pirimiphos-methyl and fenitrothion, especially in connexion with their use as grain protectants as alternatives to malathion and volatile fumigants, to which resistant strains of insects are developing.

3. Compounds suggested by the Codex Committee on Pesticide Residues at its Seventh Session to be held in February 1974 (Priority List X). Other matters referred to the Joint Meeting by the Codex Committee on Pesticide Residues.

4. Reconsideration of tolerance recommendations for 2,4-D for which additional data on cereal grains have recently become available.

5. A number of important pesticides applied to pastures, forage crops, or plant products used as animal feedstuffs, with a view to recommending limits in animal feeds.

6. Hexachlorobenzene as a residue in food arising from uses of pesticides in agriculture.

7. Any other matters mentioned under the item "Future Work" in the reports of earlier Joint Meetings, in so far as they have not yet been dealt with and still need consideration, e.g., consideration of information on use patterns of DDT in different countries and on residues in foods as submitted by government authorities. (This is in accordance with item (e) in "Future Work" recorded on page 20 of the report of the 1972 Meeting.)

8. Pesticides consideration of which was deferred by the present Meeting:

- (a) benomyl, carbendazim and thiophanate-methyl;
- (b) tetradifon, chlorfensulfide and tetrasul.

## 7. RECOMMENDATIONS

1. In the interests of public health and agriculture and in view of the large number of pesticides that require evaluation or re-evaluation, it is desirable that further Joint Meetings should continue to be convened annually.

2. In certain instances, insufficient information was available in spite of requests made at previous meetings. The situation is particularly acute with pesticides for which only temporary ADIs have been established (see section 2.3). It is therefore recommended that an effort be made to solicit support for the required research from international organizations, govern-

ments, and interested parties, including manufacturers' associations. It is recommended that a request be forwarded to all government agencies and interested international organizations advising them of the type of information required by the Joint Meeting. This should, in particular, include information relating to toxicity and patterns of use, to residues from supervised trials, and to the fate of residues after harvesting. Information on residue levels found in food commodities moving in commerce would also be of interest.

3. The study of the relationship between intake, tolerance, and ADI should continue in the case of pesticides for which the ADIs might theoretically be exceeded. This study should be extended to additional countries and should also cover all the pesticides reviewed. It should take into consideration information now available on the disappearance of residues during storage and processing prior to consumption as outlined in the monographs. Any information on the percentage of food commodities containing residues should also be taken into account. In addition, the conclusions of these theoretical calculations should be checked by measurements of residues in total diets wherever possible.

4. In view of the potential toxicity of hexachlorobenzene and the lack of adequate toxicological data to assess its safety, WHO and FAO should promote and where necessary coordinate research needed on this seed-dressing fungicide.

5. WHO should consider investigating the significance of and inter-relationship between liver enlargement, stimulation of microsomal enzymes, and hepatoma, with respect to predicting the health hazards of certain pesticides for man.

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- FAO/WHO (1970a) *Pesticide residues in food. Report of the 1969 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Group on Pesticide Residues. FAO Agricultural Studies, No. 84 ; Wld Hlth Org. techn. Rep. Ser., No. 458*
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**RECOMMENDATIONS CONCERNING ACCEPTABLE DAILY INTAKES AND RESIDUE LIMITS  
MADE AT THE 1973 MEETING**

These recommendations are additional to, or amend, those recorded in Annex 1 of the report of the 1972 Meeting (FAO/WHO, 1973a) entitled "Index to Documentation and Summary of Recommendations Concerning Acceptable Daily Intakes, Tolerances, Practical Residue Limits, and Guideline Levels as of November 1972".

Temporary recommendations are denoted by superscripts <sup>a</sup>, <sup>b</sup>, <sup>c</sup>, <sup>d</sup>, or <sup>e</sup>, indicating that further work is to be made available not later than 30 June in the year 1974, 1975, 1976, or 1977 respectively.

Further explanatory notes are given at the end of this table (see p. 33).

Pesticides and references <sup>1</sup>	Maximum acceptable daily intake (mg/kg body weight)	Commodity	Residue limits (mg/kg)		Remarks
			Tolerances (practical limits indicated as (P))	Guideline levels <sup>2</sup>	
azinphos-ethyl		Tomatoes		1	Residues to be determined as azinphos-ethyl and its P=O analogue and expressed as azinphos-ethyl.
		Apples, pears		0.5	
		Vegetables (except potatoes and tomatoes)		0.5	
		Soybeans (dry)		0.2	
		Potatoes, cotton seed, rapé seed		0.05 *	
azinphos-methyl 1969b, 1973b	0.0025	Almond hulls	10		Where azinphos-ethyl also occurs the total residue should not exceed the levels recommended for azinphos-methyl except in the case of tomatoes, when the total should not exceed 1 mg/kg. Tolerances no longer temporary.
		Peaches	4		
		Citrus fruit	2		
		Melons	2		
		Celery	2		
		Alfalfa (green), pea vines, soybean vines	2		
		Fruit (except apricots, citrus fruit, grapes, melons, peaches)	1		
		Broccoli, Brussels sprouts	1		

			Vegetables (except broccoli, Brussels sprouts, celery)	0.5						
			Potatoes	0.2						
			Almonds (shelled nuts)	0.2						
			Raw cereals, dry soybeans, cotton seed, sunflower seed	0.2						
benomyl			Bean vines		30	Residues to be determined as the sum of benomyl and carbendazim (MBC) and calculated as MBC.				
			Cherries, citrus fruit, grapes, peaches		10					
			Apples, apricots, pears, blackberries, black currants, boysenberries, dewberries, loganberries, raspberries, strawberries, tomatoes, sugarbeet tops		5					
			Nectarines, plums, prunes, beans (lima, snap), beans (dry), celery, mangoes, barley straw, peanut hay		2					
			Bananas, mushrooms, almond hulls		1					
			Avocados, Brussels sprouts, cucumbers, melons, squash		0.5					
			Raw cereals, potatoes, sugar beets, almonds, macadamia nuts, peanuts, pecans		0.1 *					
			Meat of cattle and sheep, whole milk		0.1 *					
			bromopropylate	0.008			Apples, bananas, cherries, citrus fruit, grapes, nectarines, peaches, pears, plums, prunes, strawberries, hops (dried), tea (manufactured)	5		
							Vegetables, cottonseed	1		
Bananas (pulp), citrus fruit (pulp)	0.2									
camphechlor 1969b			Fat of meat of cattle, goats, pigs and sheep		5	Listed as toxaphene in FAO/WHO 1969b.				
			Beans (snap, dry, lima), broccoli, Brussels sprouts, cabbage, carrots, cauliflower, celery, collards, eggplants, kale, kohlrabi, lettuce, okra, onions, parsnips, peas, peppers, pimientos, pineapples, radishes, rutabagas, spinach, tomatoes, bananas (whole), nuts (shelled)		2					
			Raw cereals (barley, oats, rice; in husk), rye, sorghum, wheat		2					
			Maize (grain), peanut (groundnut), rice (polished), soybeans (dry)		0.5					
			Cottonseed oil, peanut oil (refined), rapeseed oil (refined), soybean oil (refined)		0.5					
			Milk and milk products (fat basis)		0.5					

## Annex 1 (continued)

Pesticides and references <sup>1</sup>	Maximum acceptable daily intake (mg/kg body weight)	Commodity	Residue limits (mg/kg)		Remarks		
			Tolerances (practical limits indicated as (P))	Guideline levels <sup>2</sup>			
captafol 1970b	0.05 <i>d</i>	Cranberries, leeks	8 <i>d</i>		Recommendations relate only to the parent compound. Referred to as Difolotan in FAO/WHO 1969a, page 18.		
		Apples, pears, eggplants	5 <i>d</i>				
		Pumpkins	2 <i>d</i>				
		Carrots, onions (bulb), potatoes	0.5 <i>d</i>				
		Macadamia nuts (shelled)	0.1 <i>d</i>				
captan 1970b, 1974	0.1	Apples, cherries	40				
		Pears	30				
		Apricots, blueberries, black and red currants, strawberries	20				
		Spinach	20				
		Citrus fruit, peaches, plums	15				
		Endive, rhubarb, tomatoes	15				
		Cranberries, raspberries	10				
		Green beans, cucumbers, lettuce, peppers	10				
		Raisins	5				
		carbaryl 1967b, 1968b, 1969b, 1970b, 1971b	0.01	Animal feedstuffs (green), alfalfa, bean and pea vines, clover corn forage, cowpea foliage, grasses, peanut hay, sorghum forage, soybean foliage, sugar beet tops	100		
Cherries, plums, sorghum grain	10						
Cranberries	7						
Pears	5						
Rice (rough)	3						
Root crops (beets, carrots, parsnips, radishes, rutabagas), peanuts (whole)	2						
Cowpeas, soybeans (dry)	1						
Eggs (shell-free)	0.5						
Sugarbeets, meat of cattle, goats and sheep	0.2						
carbendazim 1974b				Cherries, citrus fruit, grapes, peaches		10	

		Apples, pears, gooseberries, strawberries, lettuce, tomatoes, sugar beet tops	5
		Plums, beans (dwarf), celery, gherkins	2
		Bananas (whole), mushrooms	1
		Cucumbers, melons, bananas (pulp)	0.5
		Raw cereals, sugar beet, coffee beans (raw)	0.1 *
demeton-S-methyl, oxydemeton-methyl, and demeton-S- methyl sulfone	0.005	Currants (black and red), grapes	2
		Apples, peaches, plums	1
		Citrus fruit, pears, blackberries, gooseberries, raspberries, strawberries, lettuce, summer squash	0.5
		Raw cereals	0.2
		Beans, peas, broccoli, Brussels sprouts, cabbage, cauliflower, cantaloupes, cucumbers, eggplant, pumpkins, watermelons, winter squash, potatoes	0.2
		Cottonseed, sugar beet, turnips	0.1
		Meat and fat of cattle, pigs, sheep and poultry; milk and milk products; eggs (shell-free)	0.05 *
		Nuts (shelled)	0.05 *
		Animal feed (green)	5
		Animal feed (dry)	10
dimethoate 1971b		Strawberries	0.3
		Black currants	2.0
disulfoton	0.001 <i>c</i>	Vegetables, including beans, broccoli, Brussels sprouts, cabbage, cauliflower, lettuce, peas, potatoes, spinach, tomatoes, rice (in husk), sugar beet	0.5 <i>c</i>
		Cereals (except rice); cottonseed	0.2 <i>c</i>
		Coffee beans, peanut (kernels), pecans, soybeans (dry), pineapple	0.1 * <i>c</i>
		Forage crops (green)	5, <i>c</i>
folpet 1970b	0.1	Strawberries	20
		Lettuce	15
formothion 1970b, 1973b	0.02	Citrus fruit	0.2

The ADI refers to the sum of the compounds, demeton-S-methyl, oxydemeton-methyl, and demeton-S-methyl sulfone.

The tolerances are to apply to the sum of the three compounds determined as the sulfone and calculated as demeton-S-methyl.

From use of formothion and/or dimethoate.

Residue to be determined as disulfoton sulfone and demeton-S-sulfone and expressed as disulfoton.

Recommendations apply only to parent compound. Previous recommendations except for strawberries are confirmed and are no longer temporary.

The tolerance refers only to the parent compound. The metabolites dimethoate and omethoate arising from the use of formothion are included in the tolerances established for these compounds.

## Annex 1 (continued)

Pesticides and references <sup>1</sup>	Maximum acceptable daily intake (mg/kg body weight)	Commodity	Residue limits (mg/kg)		Remarks
			Tolerances (practical limits indicated as (P))	Guideline levels <sup>2</sup>	
hexachlorobenzene 1970b	See remarks	Milk and milk products (fat basis) Raw cereals Flour and similar milled cereal products	0.5 (P) 0.05 (P) 0.01 (P)		Intake of 0.0006 mg/kg daily is considerably below any dosage rate known to be harmful (see section 3.6). Other residue limits recommended in 1969 confirmed.
lindane 1967b, 1969b, 1972b	0.01 <sup>e</sup>	Fat of meat of cattle, pigs and sheep Apples, pears Rice (in husk) Milk and milk products (fat basis) Sugar beet (roots), sugar beet (tops) Eggs (shell-free)	2 <sup>e</sup> 1 <sup>e</sup> 0.5 <sup>e</sup> 0.1 (P) <sup>e</sup> 0.2 <sup>e</sup> 0.1 (P) <sup>e</sup>		Referred to as gamma-BHC prior to 1967. In FAO/WHO 1973a, for fat of meat etc. 2 mg/kg was erroneously listed as practical residue limit instead of as tolerance.
malathion 1967b, 1968b, 1969b, 1971b	0.02	Pulses (dried beans, lentils)	8		
propoxur	0.02	Animal feedstuffs (green) Apples, cherries, peaches, pears, plums Blackberries, gooseberries, red currants, strawberries Vegetables (except potatoes and root vegetables) Potatoes, root vegetables Rice grain (rough) Rice (hulled) Cocoa beans Meat Milk (whole)	5 3 3 3 0.5 0.5 0.1 0.05 * 0.05 * 0.05 *		Recommendations include main metabolites expressed as propoxur.
quintozene 1970b	0.001 <sup>c</sup>	Lettuce Peanuts (kernels)	3 <sup>c</sup> 2 <sup>c</sup>		

thiometon 1970b	0.005 <i>d</i>	Apples, cherries (sweet), grapes, pears, peaches, plums, strawberries, beans, lettuce, peas, peppers, tomatoes, hops (dry)	0.5 <i>d</i>	Residues are to be determined as thiometon-sulfone and expressed as thiometon.
		Carrots, potatoes, sugarbeet, raw cereals, including maize	0.05 *	
thiophanate-methyl	0.08	Celery	20 <i>b</i>	Residues to be determined as thiophanate-methyl and carbendazim (MBC) and expressed as carbendazim.
		Cherries, citrus fruit, grapes, peaches, raspberries	10 <i>b</i>	
		Apples, pears, black currants, gooseberries, strawberries, carrots, lettuce, tomatoes, sugarbeet (tops)	5 <i>b</i>	
		Plums, beans (broad, dwarf, French, runner, kidney), gherkins	2 <i>b</i>	
		Bananas (whole), mushrooms	1 <i>b</i>	
		Cucumber	0.5 <i>b</i>	
		Raw cereals, onions, sugarbeets	0.1 * <i>b</i>	
tricyclohexyltin hydroxide 1971b	0.007 <i>e</i>	Citrus fruit, tea (manufactured)	2 <i>e</i>	Expressed as the parent compound.
		Meat	0.2 (P) <i>e</i>	
		Milk and milk products (fat basis)	0.5 (P) <i>e</i>	
Vamidothion 1974b		Apples, pears	2	
		Brussels sprouts	1	
		Grapes, sugarbeets	0.5	

1. References are to FAO/WHO publications (see list of references on p. 26). Dates of publication refer to the first complete or completely revised monograph or to important mentions of the compound in a report. Where a monograph has been completely revised mention is not necessarily made of any earlier ones. Where no date is given, the compound was considered at the 1973 Joint Meeting for the first time.

2. Guideline levels are included to assist administering authorities, even though ADIs have not been established for the individual products, or temporary ADIs established at an earlier date have been withdrawn. The levels recommended are those that need not be exceeded if good practices are followed.

\* Level at or about the limit of determination.

## Annex 2

### FURTHER WORK OR INFORMATION REQUIRED (OR DESIRABLE)

If a compound has been considered at earlier meetings the requirements listed below replace those stated in earlier reports.

#### AZINPHOS-ETHYL

**Required** (before an acceptable daily intake can be estimated)

1. Long-term studies to investigate chronic toxicity and carcinogenicity.
2. Studies to identify metabolites in plants and animals.
3. Studies to investigate the toxicity of metabolites.
4. Studies to detect effects on reproduction.
5. Studies to detect teratogenic activity.

**Desirable**

1. Additional information on the nature of terminal residues in plants, animals and their products.
2. Data on disappearance of residues during storage and cooking of vegetables and fruits.

#### AZINPHOS-METHYL

**Desirable**

1. Identification and toxicity of metabolites.
2. Residue data for other crops including grapes, for which insufficient data were available to establish or amend tolerances at the 1973 Meeting.

#### BENOMYL

**Required** (before an acceptable daily intake can be estimated)

1. Full toxicological data.

**Desirable**

1. Further development of analytical methods to adapt them for regulatory purposes, especially to permit separate determination of benomyl and metabolites when present together:
2. Information on residues in food in commerce.
3. Information on the nature and level of residues in poultry and eggs following the feeding of benomyl residues in rations.

## BHC (TECHNICAL)

**Required** (before an acceptable daily intake can be established and before residue limits can be recommended)

1. Additional chronic feeding studies appropriately designed to detect carcinogenic action. The studies should be carried out on all isomers if possible, but at least on the  $\alpha$ -isomer and a typical technical mixture. A species other than the mouse would be appropriate.

2. Further comparative studies of the effects of the 4 primary isomers on reproduction, including teratogenicity.

3. The composition of BHC (technical) available and in use in various countries.

4. The uses made of these technical products, particularly the rates and frequencies of application and the identities of the crops involved.

5. The levels of the residues of the individual isomers found in plants, animals, and their products.

### **Desirable**

1. Studies to establish the extent to which one isomer may alter the action or storage of another isomer.

## BROMOPROPYLATE

### **Desirable**

1. Studies to elucidate the effects on survival rate of rats on long-term feeding.

2. Long-term studies in a second species of animal.

3. Studies on the effects of bromopropylate on the liver.

## CAMPHECHLOR

**Required** (before an acceptable daily intake can be established)

1. Adequate toxicological information on camphechlor as currently marketed, including a carcinogenicity study.

2. Comparative studies evaluating the toxicological hazard associated with polychlorinated camphene of different manufacture used in worldwide agriculture.

3. Before recommendations can be made concerning residues from the use of camphechlor, other than that conforming to FAO specifications,

information is needed on the composition, uses, and residues arising from such products.

#### **Desirable**

1. Further results of research now in progress on the chemical composition and the metabolism of individual components of camphechlor conforming to FAO specifications.

2. Information from supervised trials (in progress) designed to determine the residues likely to be found in fat of poultry and in eggs from ingestion of feed containing residues.

3. Data on residues in fat of cattle in areas where tick control requires dipping shortly before slaughter.

4. Information on the need for use on vegetables and cereals at application rates and frequencies that would require a residue limit greater than that recommended.

### CAPTAFOL

#### **Required (by 1976)**

1. Further studies to assist evaluation of histopathological changes in the kidneys and liver of rats.

2. Studies to investigate the lymphocyte-neutrophil shift noted in previous experiments.

#### **Desirable**

1. Studies to investigate the metabolism of the tetrachloroethylthio moiety of captafol.

2. Data on effects of washing, peeling, and blanching on residue levels in various crops.

3. Data on residue levels occurring in commodities moving in commerce.

4. Additional residue data and information on agricultural practices in user countries with respect to asparagus, beans, cabbage, celery, citrus fruit, coffee, grapes, lettuce, pineapple, strawberries, and tea.

### CAPTAN

#### **Desirable**

1. Investigation of the significance of haematoma formation in the fetus in relation to fetal death and malformation.

2. Information on the nature, level, and fate of residues following washing, blanching, storage, and thermal processing of treated crops.

3. Residue data obtained by the newer methods of analysis on the main commodities for which tolerances have been recommended.

4. Information on the fate of captan in the soil.

#### CARBARYL

**Required** (before a limit for residues in milk can be recommended)

1. A method suitable for regulatory purposes, for the determination of total residues of carbaryl in milk.

**Desirable**

1. Further studies to elucidate the effects of carbaryl on renal function.

2. Further studies to resolve the differences in observations of different investigators on reproductive physiology, especially with regard to neuro-endocrine and behavioural changes.

#### CARBENDAZIM

**Required** (before an acceptable daily intake can be estimated)

1. Long-term studies to investigate chronic toxicity and carcinogenicity.

2. Reproduction and teratogenicity studies.

3. Metabolism and distribution studies in several animal species.

4. Elucidation of the effect on the liver in female rats and dogs.

5. Information on the nature and level of residues in meat, milk, and eggs, after feeding animals on crops or feedstuffs treated with carbendazim.

**Desirable**

1. Further studies to define the apparent "high-level" effects on male reproductive organs.

2. Information on the possible uptake from soils into subsequent crops.

3. Information on residues in food in commerce.

#### DEMETON-S-METHYL, DEMETON-S-METHYL SULFOXIDE AND DEMETON-S-METHYL SULFONE (DEMETON-S-METHYL AND RELATED COMPOUNDS)

**Desirable**

1. Studies to elucidate fatty degeneration in liver at high doses.

2. Information on residues in animal tissues from the feeding of demeton-methyl group compounds, in the form of plant residues, to domestic animals other than cows and chickens.

#### DISULFOTON

##### **Required** (before June 1975)

1. Results of the long-term studies now in progress.
2. Kinetic studies on absorption, distribution, metabolism, and excretion in mammals.
3. Evaluation of liver damage observed in short-term studies.
4. Data on residues in meat, milk, and eggs after feeding animals on crops or feedstuffs treated with disulfoton, in order to determine residue limits in foods of animal origin.

##### **Desirable**

1. Information on residues in food moving in commerce.

#### FOLPET

##### **Desirable**

1. Investigation of the fetotoxic action of folpet.
2. Investigation of the intraperitoneal toxicity.
3. Information on the nature, level and fate of residues following washing, blanching, storage, and thermal processing of treated crops.
4. Residue data obtained by the newer methods of analysis on the main commodities for which tolerances have been recommended.
5. Information on the fate of folpet in the soil.
6. Further data on the levels of degradation products in relation to residues of the parent compound.
7. Results of metabolism studies currently planned.

#### FORMOTHION

##### **Desirable**

1. A survey of current uses of both formothion and dimethoate on crops on which either pesticide may be used with a view to making recommendations for common tolerances.
2. Additional studies to show whether residues of formothion *per se* will occur on crops, particularly olives.

## HEXACHLOROBENZENE (HCB)

### **Required** (before an acceptable daily intake can be estimated)

1. Long-term studies in suitable mammalian species to provide histologic data and biochemical data, particularly with respect to the known porphyrogenic action, and an assessment of tumorigenic potential.
2. Reproduction studies.
3. Studies of teratogenic potential.
4. Studies of pathways of metabolism and pharmacokinetics of HCB in rats and preferably in other species, including studies on tissue levels producing toxic effects.
5. Information on HCB occurring in foods moving in commerce, using analytical procedures known to recover and determine the total of any such residues that may be present.
6. Information on all possible sources of environmental contamination by HCB.
7. Information from many countries on residue levels in animal food-stuffs and compound feeds.

## LINDANE

### **Required** (before 1977)

1. A long-term carcinogenicity study.

### **Desirable**

1. The results of supervised trials currently in progress to determine residues on a variety of fruits and vegetables.
2. Information from governments on residues of lindane found in cocoa beans and cocoa products moving in commerce.
3. Further information from governments on the occurrence of lindane residues on raw grains, the effect of processing on these residues, and the fate of the residues in the various milled cereal fractions.
4. Further information and statistics on the occurrence of lindane residues in animal feedstuffs and on the uses of lindane in association with animals (such as stable treatments) with a view to a re-evaluation of the practical residue limit of 0.1 mg/kg in the fat of milk.

## PROPOXUR

### **Desirable**

1. Studies to elucidate the significance of the changes in relative liver weight in the rat.
2. Studies, including pharmacokinetic studies, to elucidate the relationships between toxicity and effects on cholinesterase levels in various species.
3. A long-term study in an animal species other than the rat.
4. Continued epidemiological studies with emphasis on cholinesterase activity.
5. Studies on behavioural responses especially with low-level exposure.
6. Results of critical studies to determine the nature and level of residues in meat (including poultry), milk, and eggs to confirm recommendations for limits in animal products.

## QUINTOZENE

### **Required (before 1975)**

1. Carcinogenicity studies in two species of animal.
2. Short-term studies to elucidate the difference in the teratogenic activity in rats and mice.
3. Studies to explain the effects on the liver and bone marrow of dogs.
4. Comparison in rats and mice of the absorption, distribution, and excretion of quintozene, its metabolites and any contaminants present in significant concentrations in the technical product.
5. Further studies on the toxicity of metabolites.
6. Studies to show the nature and levels of residues in meat, milk, and eggs following the feeding of quintozene residues in animal feeds.

## THIOMETON

### **Required (before June 1976)**

1. Long-term studies to investigate chronic toxicity in at least one species.
2. Metabolism studies in plants and animals.
3. Adequate data from supervised trials, using sensitive gas-liquid chromatography methods, on crops (including those for which temporary tolerances are recommended but excluding those at or about the limit of determination) in order that the temporary tolerances can be confirmed and additional residue limits recommended.

**Desirable**

1. Data on the rate of disappearance of residues during storage, processing, and cooking.
2. Information on the nature and level of residues in meat, milk, and eggs, following the feeding of residues of thiometon in the ration.
3. Data on the residue level in commodities moving in commerce.

**THIOPHANATE-METHYL****Required** (before temporary tolerances can be confirmed)

1. Information on the nature and fate of residues of thiophanate-methyl in meat, milk, and eggs following the feeding of thiophanate-methyl at levels likely to be found on forage and feedstuffs.

**Desirable**

1. Further studies on the metabolism of thiophanate-methyl in animals, with special reference to the occurrence of carbendazim.
2. Further studies on the effect of thiophanate-methyl on the thyroid and the testes in the rat and other species of animals.
3. Further data on residues on raspberries following good agricultural practice.
4. Further information on the need for postharvest treatment of carrots and celery.

**TRICYCLOHEXYLTIN HYDROXIDE****Required** (by 1977)

1. A long-term carcinogenicity study to elucidate the significance of the occurrence of adenomas in rats.
2. A study of the factors that lead to the diminished weight/gain in animals fed on diets containing tricyclohexyltin hydroxide.

**Desirable**

1. Further validation and study of the specific method of Kutchinski to determine its suitability as a regulatory method.
2. Additional residue data and information on use patterns for those vegetables on which the information was found inadequate at the 1973 Joint Meeting.

3. Data on the occurrence of tricyclohexyltin residues on apples and pears moving in commerce.

#### VAMIDOTHION

**Required** (before an acceptable daily intake can be established)

1. Long-term studies in at least one animal species.
2. Adequate short-term studies in several species including a non-rodent species.
3. Studies to identify metabolites and investigate their toxicity.
4. Studies on the nature and level of residues in animal products from the feeding of residues at levels occurring on food wastes.
5. Information showing the fate of residues in the major crops in countries with different meteorological and growth conditions.