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PESTICIDE RESIDUES

Report of the 1967 Joint Meeting of the FAO Working Party and the WHO Expert Committee

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Monographs containing information on identity, together with evaluations, acceptable daily intakes and tolerances for pesticide residues in food are issued by FAO and WHO in a publication entitled :

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The FAO Working Party of Experts on Pesticide Residues held a meeting from 28 November to 1 December 1967 in preparation for the 1967 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. The latter meeting took place in Rome from 4 to 11 December 1967 and was opened by Dr. O.E. Fischnich, Assistant Director General, Technical Department on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization.

Dr. H. Hurtig was unanimously elected Chairman and Dr. O.G. Fitzhugh Vice-Chairman. Dr. J.M. Coon agreed to act as Rapporteur.

1. INTRODUCTION

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, 1961; WHO, 1962) recommended that studies be undertaken to evaluate the consumer hazard arising from the use of pesticides. The toxicological and other pertinent data on those pesticides known to leave residues in food, even when used in accordance with good agricultural practice, were to be examined and the conclusions made known.

Since then the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues met in 1963 and 1965 and issued reports (FAO, 1963; WHO, 1964; FAO/WHO, 1965a) and supporting documents (FAO/WHO, 1965 b and c).

The reports of these joint meetings, which were concerned primarily with the recommendation of acceptable daily intakes, were then considered by the FAO Working Party of Experts on Pesticide Residues with a view to recommending tolerances and appropriate methods of analysis for certain pesticides used on cereals (FAO, 1966).

To facilitate the recommendation of acceptable daily intakes, tolerances and methods of analysis for additional pesticides, the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues met jointly in 1966. In the report of this meeting (FAO/WHO, 1967a) they recommended acceptable daily intakes and tolerances for a number of pesticides. The supporting document (FAO/WHO, 1967b) contains detailed monographs on the pesticides which were considered and includes recommended analytical methods.

As will be seen from the above discussion, therefore, three different designations have been used to refer to the FAO group of experts concerned with pesticide residues :

FAO Panel of Experts in the Use of Pesticides in Agriculture (FAO, 1961)

FAO Committee on Pesticides in Agriculture (FAO, 1963; FAO/WHO, 1965a)

FAO Working Party of Experts on Pesticide Residues (FAO/WHO, 1967a)

The present meeting of the FAO Working Party and the WHO Expert Committee on Pesticide Residues was convened to consider a further number of pesticides, together with requests of both a general and specific nature which were made at the Second Session of the Codex Committee on Pesticide Residues held in The Hague in September of 1967 (FAO/WHO, 1967c).

The FAO Working Party of Experts on Pesticide Residues undertook :

(a) to survey and collect residue data;

(b) to propose pesticide residue tolerances;

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

The WHO Expert Committee on Pesticide Residues 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 undertook to make recommendations designed to initiate, stimulate and co-ordinate necessary research.

2. GENERAL CONSIDERATIONS

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, 1963; 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). It was agreed to endorse these principles and 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 of establishing temporary acceptable daily intakes and temporary tolerances, and certain of the concepts were accepted and, in part, adopted.

The report of the Second Meeting of the FAO/WHO Codex Committee on Pesticide Residues (FAO/WHO, 1967c) was received and special note was taken of the various requests addressed to this Joint Meeting.

2.1 Glossary

Partly in response to a request from the Codex Committee on Pesticide Residues and in the interests of facilitating the use of this report and the associated monographs (FAO/WHO, 1968), a review of terms used in previous reports was made. Terms now in current use have been carefully studied and, where necessary, redefined and explained in the glossary included with this report as Appendix I. Those terms which appear to be obsolete have not been included. The Joint Meeting wishes to emphasize that the definitions which have been agreed are solely for convenience in clarifying the present report and the accompanying monographs which are specifically concerned with the hazards to consumers arising from the use of pesticides in the production and protection of food.

2.2. Index to Previous Summaries on Specific Compounds

The list of compounds with which this meeting was primarily concerned was the Priority II List prepared at the First Session of the FAO/WHO Codex Committee on Pesticide Residues and was subsequently slightly modified by the deletion of the compound endrin, at the Second Session. Additionally, certain compounds on the Priority I List, which had previously been considered at the 1966 Joint Meeting, were referred back to this Joint Meeting for reconsideration from a variety of standpoints. These compounds include aldrin, carbaryl, DDT, dieldrin and organomercurials. Finally, any other compounds on the Priority I List, for which additional data had become available, were also considered.

While only a few of the compounds reviewed at this meeting have been previously considered from an agricultural standpoint (the penultimate group of compounds plus dichlorvos), all of them, except mancozeb and N-(2-ethylhexyl) bicyclo(2,2,1)hept-5-ene 2,3-dicarboximide [N-(2-ethylhexyl)-5-norbornene 2,3-dicarboximide, N-octylbicycloheptene dicarboximide, also known and hereafter referred to as MGK 264], have been considered from the toxicological standpoint at some time in the past. Therefore, to avoid unnecessary re-publication of toxicological, chemical, physical and agricultural data, many of the monographs associated with this report and appearing in the volume entitled "1967 Evaluations of Some Pesticide Residues in Food", (FAO/WHO, 1968) only contain data to supplement that appearing in earlier monographs on the particular compounds. An index to previously published documentation on each compound has been prepared and appears in this report as Appendix II.

Specific questions relating to individual compounds, which are dealt with more fully in the monographs (FAO/WHO, 1968) are mentioned below under the headings "Evaluation for Acceptable Daily Intakes" and "Evaluation for Tolerances" respectively.

2.3. Summary of Acceptable Daily Intakes and Tolerances

For the convenience of the reader, and to avoid unnecessary referral to the detailed monographs on the various compounds considered at this meeting, a table of acceptable daily intakes and recommendations for tolerances and practical residue limits has been prepared and is attached as Appendix III. This table includes all compounds which have been considered at the First and Second Joint Meetings of the FAO Working Party and the WHO Expert Committee on Pesticide Residues. In this connection, it should be noted that there was an error in the table included in the report of the previous meeting (FAO/WHO, 1967a) with respect to a tolerance of 8 ppm for malathion on cereal products. This entry has been omitted from Appendix III.

2.4. Methods of Estimating Tolerances

The meeting studied a paper by the Netherlands delegation to the Second Session of the Codex Committee on Pesticide Residues on methods of estimating food consumption for arriving at recommendations for residue tolerances (CCPR, 1967). The meeting concluded that the figures for the ninth decile of consumption, obtained from consumer intake studies undertaken in the U.S.A. (USDA, 1957), for which the details were fully available at the time of the meeting, should be used on this occasion. However, as it would be desirable to use more realistic figures, the meeting requested the Director-General of FAO to ask Member Governments to furnish data on national food consumption patterns. The meeting also recommended that the information so obtained, together with any that may be available from other sources, should be summarized for consideration at the next Joint Meeting.

To keep the number of tolerances for a specific pesticide to a minimum, broad classes of food were considered as units except in special cases where the pesticide residue in or on the various food within a class varied substantially.

In many instances tolerances are not required for all food within a class. In these cases only an appropriate fraction of the applicable ninth decile consumption figures have been used. It should be pointed out that the use of different food consumption patterns might reflect additional safety factors in the range of one order of magnitude or less, whereas two other considerations enter into the calculation of theoretical daily intakes; (a) that all food in the class will bear residues up to the maximum of the tolerance, (b) that all food in the class will bear residues. Both of these factors represent additional safety factors of several orders of magnitude.

The meeting agreed that initial proposals for tolerances should be made on the basis of residues that result when pesticides are used in accordance with good agricultural practice. Furthermore, such proposals should be accepted as tolerances if the estimated per capita daily intake of the pesticide residue, calculated theoretically from the proposed tolerances and the appropriate food consumption data, did not exceed the acceptable daily intake. Alternatively, such proposals might be accepted where total diet or other residue intake studies, including data on the effects of cooking or any other processing which may be necessary before consumption, are available and are sufficient to show that there is no risk of the acceptable daily intake being exceeded. In those cases where the initial theoretical calculation gives a figure higher than the acceptable daily intake, and therefore per se does not provide the complete assurance required, any recommendation for tolerances is made on a temporary basis. Any tolerance recommendations for compounds for which there are temporary acceptable daily intake figures are also made on a temporary basis. In considering this matter, the meeting noted Appendix III of the report of the Second Session of the Codex Committee on Pesticide Residues (FAO/WHO, 1967c).

For each temporary tolerance a final date has been specified for the submission of the information required for the review of the recommendation. The periods of time that have been proposed have been provided to enable necessary experimental or other work to be conducted and for the results to be furnished to FAO and WHO by the stated dates. The temporary tolerances will be reviewed by the joint meeting and further recommendations will be made in the light of any new information received. It should be emphasized that studies into the amounts of pesticide residues at the consumer level, including the examination of both subjective and objective samples and including total diet studies, are particularly valuable to determine whether acceptable daily intakes are being approached or exceeded.

2.5. Sampling for Estimation of Pesticide Residue Levels

The validity of any chemical analysis is highly dependent upon the adequacy of the sample. Great care must be exercised in obtaining a representative sample from the lot of food material and then that sample must be reduced to a small sample in a representative fashion. Usually, when sampling for pesticide residue analyses, it is necessary to take a larger sample than for some other types of food analyses because often the distribution of pesticide chemicals is not uniform. For general reference on this subject matter see Lykken (1963), Lykken et al (1957) and Sutherland (1965).

The meeting noted that the International Organization for Standardization (ISO) had been requested by the Third Session of the Codex Alimentarius Commission to elaborate methods of sampling for food and food products; and that arrangements had subsequently been made (ISO, 1967) for ISO Technical Committee 34 to do this. Whilst recognizing that sampling for pesticide residue analysis was a very specialized aspect of food sampling, it was agreed that FAO should establish the scope of the ISO considerations in order that work in this field should not be needlessly duplicated.

2.6. Analytical Difficulties in Total Diet Studies

Total diet studies represent one of the most difficult exercises which may be presented to the residue analyst since the clean-up difficulties normally associated with meat samples, for example, can be added to those associated with vegetables or cereals. At the same time some residues which may occur in fruit samples, for example, may never normally be encountered in meat or dairy products so that when all samples are mixed together, these residues are diluted and thus call for methods of analysis which are more sensitive than would otherwise be required. This is of particular importance where the methods at present available have already to be used at or near to their limit of sensitivity. However, the particular difficulty can be avoided by dividing food samples into suitable groups and analysing these separately. Even when this is done, however, it is not always easy to devise a simple extraction and clean-up technique which is applicable quantitatively to a wide range of different foods and to a wide range of different pesticides and their breakdown products. This is especially true of residues of organophosphorus compounds; whilst methods are available for residues of many of the parent thio-compounds, this is not always true of some of the many possible oxidative breakdown products. Indeed, there is in some cases a problem of the actual identity of the terminal residues themselves.

At present, it is not possible to devise a procedure which will enable residues of a wide range of types such as organochlorine, organophosphorus, organomercury, dithiocarbamate and carbamate pesticides to be identified and measured in a single system of extraction, clean-up and analysis.

2.7. Significance of Interactions of Pesticides

The Joint Meeting reviewed the subject of toxicological interactions between pesticides and between pesticides and other chemicals with the purpose of determining whether any such interactions might constitute a consumer hazard. It was seen that numerous toxicological interactions can occur between pesticides of the same class, between those of different classes, and between pesticides and drugs.

Detailed consideration was given to interactions between various groups of agents in which pesticides are one or both of the interactants. These groups included organophosphorus with organophosphorus insecticides; organochlorine with organophosphorus insecticides and drugs; organophosphorus insecticides with drugs, etc; organochlorine with organochlorine insecticides. A summary of the deliberations on this subject appears in Appendix IV to this report.

The Joint Meeting agreed that at the present levels of pesticide residue intake, the effects that pesticides can have on enzyme systems that metabolize other pesticides or drugs do not appear to present hazards to the consumer and that, with the continuation of the present criteria for a maximum no-effect level, there should be no need to alter any ADI or tolerance on this account. It was also agreed that, with the present levels of consumption as indicated by current total diet surveys, there is no need for concern about the possible additive or potentiative effects of an intake of more than one pesticide of the same group or of different groups.

2.8. The Interpretation of Negligible Residues

The meeting noted the request of the Codex Committee on Pesticides Residues and agreed that the term could only be used to denote that small but known amounts of residues of specified compounds are toxicologically insignificant. (See Glossary - Appendix I). No figure for a negligible residue was assigned to any pesticide at this meeting.

2.9. Further Work or Information

In each monograph an attempt has been made to indicate what further information would assist in making a complete assessment of the possible consumer hazard. When the meeting recommended acceptable daily intakes or tolerances on only a 'temporary' basis, due to insufficiency of information on any particular question, the nature of such additional information has been indicated and has been described as 'required' because it is considered to be essential before acceptable daily intakes or tolerances can be recommended or confirmed. In other cases the information is stated to be 'desired'.

2.10. Compounds for Consideration at Future Meetings

To allow for the orderly study of the large number of pesticides used in the production and protection of food, the meeting previously agreed to request the Codex Committee on Pesticide Residues to provide priority lists of compounds. Two such lists were prepared at the First Session of the Codex Committee on Pesticide Residues (FAO/WHO, 1966) and these compounds have been considered at the First and Second Joint Meetings of the FAO Working Party and WHO Expert Committee on Pesticide Residues in November of 1966 and December of 1967, respectively. Three additional lists were prepared at the Second Session of the Codex Committee on Pesticide Residues and all five lists have been included as Appendix X in the report of that meeting. (FAO/WHO, 1967c).

The meeting reviewed the compounds in these lists and noted that compounds in Priorities I and II had already been considered. It was decided to consider at the 1968 Joint Meeting methyl parathion, technical BHC, toxaphene and demeton methyl as well as the compounds in Priority III, together with such other compounds as may be found to be necessary in the light of intervening developments. The meeting noted the increase in the production and use of fenitrothion and proposes to include an evaluation of the residues of this compound at the Joint Meeting in either 1969 or 1970.

the various recommendations are given in greater detail in the respective monographs contained in the publication entitled "1967 Evaluations of Some Pesticide Residues in Food" (FAO/WHO, 1968).

The meeting noted with concern that although requests had been made in past reports for further toxicological data with which to evaluate the toxicological significance of certain pesticide residues, very few of these data had been provided. The responsible authorities were urged to make every effort to provide the facilities and to encourage research workers to carry out the necessary experiments, in order that required information may be furnished not later than the dates given in Appendix III.

4. EVALUATIONS FOR TOLERANCES

The meeting reviewed data on the residues and methods of analysis of carbon disulphide, carbon tetrachloride, chlordane, demeton, diazinon, dichlorvos, dimethoate, endosulfan, ethylene dichloride, hydrogen phosphide, MGK 264, parathion and the dithiocarbamate fungicides. The recommendations for tolerances and practical residue limits for the compounds discussed at the 1966 meeting were also reviewed and in some instances amended. The results of these reviews are summarized in Appendix III.

The dithiocarbamates can be divided into the dimethyldithiocarbamates and the ethylenebisdithiocarbamates. In the former group, ferbam, thiram and ziram, and, in the latter, maneb, nabam and zineb were reviewed in 1965 (FAO/WHO, 1965b). The report suggested that further information was required to determine metabolites occurring in the plant and to evaluate their toxicity. With the latter group it was particularly recommended that the chemical nature of the residues in or on the plant should be ascertained with subsequent evaluation of the toxicity of the plant residues.

Members of the latter group currently in commercial use include metiram (a variation of zineb) and mancozeb (a complex of zinc and maneb) while nabam is mostly used as the zinc salt. No information on the above requests had been received since

1965 except for a progress report on work concerned with the plant and animal metabolism of mancozeb. When this work has been completed it will be possible to review this compound together with any others for which the requested information has been provided.

Because of incomplete toxicological or residue data, the meeting was unable to recommend tolerances for carbon disulphide, carbon tetrachloride, demeton, endosulfan, ethylene dichloride and MGK 264. Specific deficiencies in information have been indicated in the pertinent monographs (FAO/WHO, 1968).

Temporary tolerances were recommended for diazinon, dichlorvos, dimethoate and parathion and temporary tolerances and practical residue limits were recommended for chlordane.

In the case of aldrin and dieldrin in the light of new data, particularly from dietary intake studies, it was agreed to recommend certain temporary tolerances for the combined total residue of the two compounds. Additionally, practical residue limits for whole milk were increased and practical residue limits for cereal grains and for milk products were added. Temporary tolerances were also made for vegetables, fresh fruit and rice.

Recent data on the disappearance of carbaryl residues enabled the meeting to recommend higher residue tolerances for many foods. With heptachlor, which includes residues of heptachlor epoxide, the recommended practical residue limits have been amended. In accordance with recommendations of the International Organization for Standardization, the name 'gamma BHC' has been replaced by 'lindane' because the product under consideration is the commercially purified product rather than the 100% gamma isomer. Furthermore, the temporary tolerance on milk products on a fat basis has been changed to a practical residue limit.

As stated elsewhere in this report, cereal products should not have been included with raw cereals in the recommendations for a tolerance of 8 ppm of malathion in the previous report and this error has now been remedied.

3. EVALUATIONS FOR ACCEPTABLE DAILY INTAKES

A number of organochlorine pesticides were considered by the meeting. It was informed of the recent finding that the residues from aldrin and dieldrin contained a photoisomerization product of dieldrin which was more acutely toxic to several species than dieldrin and for which insufficient toxicity studies had been reported. It was also informed that studies with dieldrin were in progress on mice which indicated a possible tumorigenic effect. As the latter experiments were not completed and so could not be examined by the meeting, it was decided to postpone further consideration of aldrin and dieldrin until that work was available and in the meantime to adhere to the toxicological evaluation published in the last report.

Since the last report further details on the long-term toxicity of DDT in mice had become available (Kemény and Tarján, 1966; Tarján, 1967 unpublished report submitted to WHO). Although these studies are not yet complete, the results cannot be ignored. Therefore, taking into account the difficulties of extrapolating the results to man, the meeting recommended that the Director-General of WHO invite the appropriate international agency to take steps to re-evaluate the potential hazard of this chemical in the light of the new data. If further experiments are considered necessary, the meeting urged that these should be given a high priority by those laboratories carrying out such work; but pending the full assessment of the significance of the findings, the meeting did not consider that an alteration in the acceptable daily intake for DDT would be justified at the present time. By way of clarification, however, the meeting decided that the acceptable daily intake for this compound should apply to DDT, DDE and DDD or any combination of the three.

The organochlorine pesticides have been extensively used, have proved efficacious and have lower acute toxicities than many other pesticides. However, they pose many problems including possible tumorigenic effects mentioned above. In addition, even at relatively low doses, they have effects on liver enzyme systems.

The toxicological significance of these effects and of the associated morphological changes are difficult to evaluate and the meeting endorsed the recommendation of the previous meeting for further studies on this subject.

The meeting reconsidered the organomercury compounds (including phenyl mercuryacetate) discussed in previous reports and was unable to alter its previous decision. Though it would not take objection to those agricultural uses which do not increase the level of mercury in food, it felt that any such use of compounds that did should be strongly discouraged. More information is required on the "background" level of mercury in different parts of the world as well as epidemiological observations on people living in areas with a higher "background" of mercury.

The dithiocarbamate pesticides were considered in two groups, the dimethyldithiocarbamates and the ethylenebisdithiocarbamates (See Section 4 of this report). The consideration of both groups, however, was severely hampered by lack of knowledge of the exact chemical nature and toxicity of the residues on the crop. Much more work is required on these questions. As some of the original compounds might persist in the final residues, however, the meeting felt it worthwhile to establish separate temporary acceptable daily intakes (0 - 0.025 mg/kg body weight) for each of the two groups of the parent compounds, except for nabam. (See Appendix III).

Further work on the human response to dimethoate had become available since the last year, which enabled the meeting to increase the acceptable daily intake to 0 - 0.02 mg/kg body weight. An acceptable daily intake also was proposed for chlordane (0 - 0.001 mg/kg body weight).

The meeting reconsidered ethylene dichloride, carbon tetrachloride, carbaryl, demeton, diazinon, dichlorvos, parathion, diphenyl, heptachlor, hydrogen phosphide, lindane, malathion, oxydemeton-methyl (previously referred to as demeton-S-methyl sulfoxide), piperonyl butoxide and pyrethrins, and, despite the availability of additional data in some cases, reaffirmed the decisions expressed in previous reports. No acceptable daily intakes were recommended for endosulfan or MGK 264. Reasons for

To avoid confusion in the interpretation of those recommendations which relate to the presence of inorganic bromide in foods after treatment with methyl bromide or ethylene dibromide, a new entry has been included in the table in Appendix III on "bromide ion resulting from the use of ethylene dibromide and methyl bromide". The meeting noted that the Codex Committee on Pesticide Residues at its second session (FAO/WHO, 1967c) had expressed its recommendations to governments for raw grain as "inorganic bromide, determined and expressed as total bromide from all sources"; but as the suggested tolerance was appreciably greater than the amount of inorganic bromide normally present in raw cereals from sources other than fumigation, in this case, the change in the manner of expressing the tolerance did not appear to be important. The meeting made no recommendations for tolerances for either unchanged methyl bromide or unchanged ethylene dibromide.

Although no acceptable daily intake figure for organo-mercurials could be recommended, the meeting was of the opinion that the use of organomercurial seed dressings and of organomercurial sprays on apples up to the time of petal fall, will not result in residues in excess of the background levels of mercury.

Data are now available to show that some processed foods when fumigated with aluminum phosphide, on condition that no aluminum phosphide or its unreacted residues are brought into direct contact with the food during the fumigation process will, at the time of marketing, have residues only slightly above or close to the limit of sensitivity of the analytical methods currently used (0.01 - 0.001 ppm, depending on the equipment and experience in the particular laboratory). Therefore, while no acceptable daily intake figure is necessary, tolerances for residues of hydrogen phosphide have been recommended for certain products before cooking.

There are no changes in the information concerning diphenyl, piperonyl butoxide and pyrethrins contained in the previous report, except that a correction has been made concerning the limit of sensitivity needed for the analysis of residues of the last substance.

5. RECOMMENDATIONS

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 pesticides already evaluated in the light of additional residue and toxicological information and also to consider the pesticides not yet dealt with by the joint meetings. It is desirable that these meetings should be held annually.

2. The organochlorine insecticides have been proved to be very effective and they have been used extensively with very beneficial effects. Their acute toxicities are much lower than those of many other pesticides. However, some of them have been shown to be persistent in the animal and human body. In addition, even at relatively low doses they have effects on the liver. The toxicological significance of the stimulation of the activity of liver enzymes and of the associated morphological changes is difficult to evaluate. The meeting has reaffirmed the recommendation for further studies on the subject made in the report of its last meeting (FAO/WHO, 1967).

3. For some of the organochlorine insecticides which may occur as residues in food, notably dieldrin, their ability to produce hepatomas in laboratory animals has been suggested by some experiments. It is strongly recommended that WHO should promote action aimed at the collection and discussion of the relevant scientific information and the evaluation of its significance for man.

4. It is recommended that the Director-General of WHO should invite the appropriate international agency to take steps to re-evaluate the recent work on the chronic toxicity of DDT in mice. If further experiments are considered necessary the meeting urged that these should be given a high priority by those laboratories carrying out such work.

5. In the course of its work, and as indicated in the pertinent monographs, the meeting frequently encountered gaps in information required for the evaluation of tolerances. The Director-General of FAO is requested to ask Member Governments to undertake survey or other work and to make the results available for consideration

at future meetings. In particular further information is needed on :-

(i) Food consumption patterns in member countries (See Section 2.4)

(ii) The results of analyses of subjective and/or objective sampling, including total diet studies in member countries. (See Section 2.4).

6. REFERENCES

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APPENDIX I

GLOSSARY

The definitions hereunder were adopted by the meeting for use in the report and the associated monographs (FAO/WHO, 1968).

PESTICIDE RESIDUE

A pesticide residue is a residue in or on a food of any chemicals used for the control of pests and the term includes derivatives of such chemicals. The amounts are expressed in parts by weight of the chemical and/or derivative per million parts by weight of the food (ppm).

Explanatory note

In interpreting this definition it is proposed to include the consideration of any substance which may, at a given time, be known to be derived from the product and which may be held to influence the toxicology of the residue. Residues from unknown sources (i.e. background residues) will be considered as well as those from known uses of the chemical in question. The term pesticide will be held to include any constituent of a pesticide used for the control of pests during the production, transport, marketing or processing of food or which may be administered to animals for the control of insects or arachnids in or on their bodies; it will not apply to antibiotics or other chemicals administered to animals for other purposes, such as to stimulate their growth or to modify their reproductive behaviour, or to fertilizers or, at least for the present, to other substances, other than herbicides, used to influence the rate of growth of plants.

NEGLIGIBLE RESIDUE

A negligible residue is an amount of a pesticide residue that is regarded as toxicologically insignificant.

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UNINTENTIONAL RESIDUE

An unintentional residue is one which occurs in a food as a result of circumstances not designed to protect the food against pest attack.

Explanatory note

For this purpose the range of pesticide uses is as indicated under 'pesticide residue'. The food should be specified in each case and the term includes products such as milk and meat from treated animals. Furthermore, the residue may be acquired at any stage in the growing, harvesting, distribution, marketing or processing of the food. The unintentional residue also includes a residue of a chemical which occurs in nature as part of the environment but which cannot be distinguished from residues due to the use of pesticides. Residues sometimes described as 'incidental', 'accidental' or 'background' residues are included within this term.

PRACTICAL RESIDUE LIMIT

The practical residue limit is the maximum unintentional residue (see definition) allowed in a specified food.

Explanatory note

A practical residue limit is the level of pesticide residue above which a regulatory action may be taken. It applies to a specific commodity and pesticide for which no tolerance has been established. Observation of a residue level above the 'limit' may be presumptive evidence of violation of good agricultural practice; values below the 'limit' are presumed to result from incidental effects, including possibly isolated effects, from other approved use of the pesticide.

ACCEPTABLE DAILY INTAKE

The acceptable daily intake of a chemical is the daily intake which, during an entire lifetime, appears to be without appreciable risk on the basis of all the known facts at the time. It is expressed in milligrams of the chemical per

APPENDIX I (Cont'd)

kilogram of body weight (mg/kg).

Explanatory note

For this purpose 'without appreciable risk' is taken to mean the practical certainty that injury will not result even after a lifetime of exposure. Furthermore, for a pesticide residue, the acceptable daily intake is intended to give a guide to the maximum amount that can be taken daily in the food 'without appreciable risk' to the consumer. Accordingly, the figure is derived as far as possible from feeding studies in animals and/or in man. The studies are usually conducted with the pesticide chemical itself. However, if the residues of a pesticide are known to consist of more than one chemical which may influence the toxicology of the residue (see definition of 'pesticide residue'), information on the toxicology of the respective residual chemicals and, where appropriate, their respective acceptable daily intakes has to be taken into account when assessing the risks. Acceptable daily intakes are always subject to revision at any time in the light of new information.

TEMPORARY ACCEPTABLE DAILY INTAKE

A temporary acceptable daily intake is one which is recommended for a limited period.

Explanatory note

A specified period is provided to enable additional biochemical, toxicological or other data to be obtained, as may be required for establishing an ADI. (See 'Further Work Required'). In such cases any recommendation will normally involve the application of a safety factor, the size of which will be dependent upon the nature of the toxicity of the compound, but which will be larger than that normally used in estimating acceptable daily intakes. In all cases the position will be reviewed not later than the first meeting following the specified date.

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TOLERANCE

A tolerance is the maximum concentration of pesticide residue that is permitted in or on food at a specified stage in the harvesting, storage, transport, marketing or preparation of the food, up to the final point of consumption, and the concentration is expressed in parts by weight of the pesticide residue per million parts by weight of the food (ppm).

TEMPORARY TOLERANCE

A temporary tolerance is one that is valid for a limited time which is specified in each case.

Explanatory note

Such tolerance recommendations are made when they are derived from Temporary Acceptable Daily Intakes or from figures for commodities at some stage prior to the point of consumption as food and when, in the absence of adequate information on losses of residue during storage, handling or preparation, calculations based on such figures using appropriate food consumption data reveal a theoretical possibility that the acceptable daily intake could be exceeded. In cases of this kind, to obtain assurance that acceptable daily intakes are not likely to be exceeded in practice, and before proceeding to recommend temporary tolerances, the meeting considers information on the actual occurrence of residues in food as offered to the consumer. This information includes the results from subjective sampling and/or from objective sampling, including total diet studies, in various countries and particularly in places where pesticides are most widely used. In all cases the position will be reviewed not later than the first meeting following the specified date.

GOOD AGRICULTURAL PRACTICE

Good agricultural practice is the recommended usage of a pesticide which is necessary and essential for the control of a pest under all practical conditions

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bearing in mind any toxicological hazards involved.

Explanatory note

The 'recommended usage' complies with the procedures, including the formulation, dosage rates, frequency of application and pre-harvest intervals recommended by appropriately trained specialists; it is the usage that has been registered, approved or otherwise accepted for the purpose by the relevant official department and which is normally included on the label. Such recommended methods of application should be based on supervised trials and other experimental work and should take into account such variations in climate, in crop husbandry and in incidence of pests as may occur under practical conditions from time to time in the various places in which the pesticide may be used. For this purpose good agricultural practice shall be held to include practice in the control of pests during the storage, transport, marketing and processing of foods.

TOTAL DIET STUDIES

A total diet study is one designed to show the pattern of pesticide residue intake by a person consuming a typical diet.

Explanatory note

To make total diet studies random samples of food are usually purchased in representative population centres in the country, or district, concerned and weighed out in the proportions in which they are consumed in the total diet. The weighed portions are then washed, cooked or otherwise prepared in the normal way for table presentation and then mixed to give a number of predetermined food group samples comprising, for example, cereals, green vegetables, root crops, fruits and preserves, fats, meats and milk. These groups are chosen with the intention of minimizing the subsequent analytical problems; they also serve to identify the areas of the diet which contribute most to total residue present. The foods are purchased and prepared under

APPENDIX I (Cont'd)

expert supervision with the requirements of the studies in mind; but otherwise they resemble as far as possible the normal character of the total diet. Water and beverages are included.

Each food group sample, prepared as above, is analysed for various residues. This may involve several different analyses for each group. The exact analytical procedure may vary from group to group. In addition, from experience, it may become possible to omit certain analyses for some groups. Thus, the different groups will not necessarily be subject to exactly the same analytical procedure. Similar studies have also been described as 'market basket studies'.

SUBJECTIVE SAMPLE

A subjective sample is one taken after a known, or a suspected, use of a pesticide on a crop.

Explanatory note

Subjective samples include those taken during the early stages of the introduction of a pesticide into practical application when it is desirable to ascertain the residues occurring after known methods of application in the field, as well as those taken in circumstances where there are reasons to suspect that good agricultural practices have not been properly followed. Such samples may relate to crops from specific sites or from districts, or from countries where particular pesticides are known, or suspected, to have been used. Subjective sampling, rather than total diet studies, is sometimes used to assess the actual dangers to consumers, particularly where the sampling and analytical facilities are limited: it enables the facilities to be concentrated on those categories of food intake considered to offer the greatest risks. Subjective sampling also enables certain of the analytical difficulties encountered in total diet studies to be avoided.

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OBJECTIVE SAMPLE

An objective sample is a random or impartial sample.

Explanatory note

The samples taken during total diet intake studies fall into this category.

FURTHER WORK REQUIRED

Further work required is work which must be done and properly reported before acceptable daily intakes and/or tolerances can be recommended or confirmed.

Explanatory note

In certain instances although acceptable daily intakes have been established, further work has been considered to be essential to remove doubts about the toxicological significance of some experimental observations, and it has therefore been "required". Results of the further work required should be made available not later than the specific date mentioned, after which the compound will be re-evaluated. The re-evaluation may be done at an earlier meeting should relevant information become available.

FURTHER WORK DESIRABLE

Further work desirable is work which, when properly reported, would be expected to provide additional assurance that recommended acceptable daily intakes and/or tolerances are adequate for the protection of the health of the consumer.

Definitions of the terms FOOD FACTOR, PERMISSIBLE LEVEL and ACCEPTABLE CONSUMER LEVEL have not been included because they are regarded as obsolete.

APPENDIX II

INDEX TO MOST RECENTLY PUBLISHED PRIOR DOCUMENTATION ON SPECIFIC COMPOUNDS

COMPOUND	FAO/WHO PUBLICATION AND YEAR	COMPOUND	FAO/WHO PUBLICATION AND YEAR
Acrylonitrile	1965c	Ethylene dibromide	1967b
Aldrin	1967b	Ethylene dichloride	1965c
Allethrin	1965b	Ethylene oxide	1965c
Azinphos-methyl	1965b	Ferbam	1965b
BHC	1965b	Heptachlor	1967b
Captan	1965b	Hydrogen cyanide	1965c
Carbaryl	1967b	Lead arsenate	1965b
Carbon disulfide	1965c	Lindane	1967b
Carbon tetrachloride	1965c	Malathion	1967b
Chlorbenside	1965b	Maneb	1965b
Chlordane	1965b	Methoxychlor	1965b
Chlorfenson	1965b	Methyl bromide	1967b
Chlorobenzilate	1965b	Methyl parathion	1965b
Chloropicrin	1965c	Mevinphos	1965b
Chloropropham	1965b	Nabam	1965b
Chlorthion	1965b	Oxydemeton-methyl *	1965b
DDT	1967b	Parathion	1965b
Demeton	1965b	Phenylmercuric acetate **	1967b
Diazinon	1967b	Phosphamidon	1967b
Dichlorvos	1967b	Phosphine ***	1967b
Dieldrin	1967b	Piperonyl butoxide	1967b
Dimethoate	1967b	Propham	1965b
Dimethrin	1965b	Pyrethrins	1967b
Diphenyl	1967b	Thiram	1965b
DNOC	1965b	Triphenyltin compounds	1965b
Endosulfan	1965b	Zineb	1965b
Endrin	1965b	Ziram	1965b

* previously referred to as "demeton-S-methyl sulfoxide"
** plus other organo mercurials
*** also referred to as "hydrogen phosphide"

FAO/WHO. Evaluation of the Toxicity of Pesticide Residues in Food. FAO Mtg.
1965b Rep. No. PL/1965/10/1; WHO/Food Add./27.65. 194 p.

FAO/WHO. Evaluation of the Hazards to Consumers Resulting from the Use of
1965c Fumigants in the Protection of Food. FAO Mtg. Rep. No. PL/1965/10/2; WHO/Food Add./28.65. 71 p.

FAO/WHO. Evaluation of Some Pesticide Residues in Food. FAO Mtg. Rep. No.
1967b PL:CP/15; WHO/Food Add./67.32. 237 p.

APPENDIX III

SUMMARY OF RECOMMENDED ACCEPTABLE DAILY INTAKES, TOLERANCES, TEMPORARY TOLERANCES AND PRACTICAL RESIDUE LIMITS

[See "1967 Evaluation of Some Pesticide Residues in Food" (FAO/WHO, 1968) for further details]

(Figures are for raw agricultural products moving in commerce except where otherwise indicated)

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
aldrin	0.0001	See dieldrin		Combined total aldrin + dieldrin
bromide ion (total resulting from the use of ethylene dibromide and methyl bromide)	1.0	Dried eggs, spices, herbs 400*		No change from previous report
		Cereals 50		
		Dried figs 250*		
		Avocados 75*		
		Dried raisins, dates .. 100*		
		Dried peaches 50*		
		Dried prunes 20*		
		Other dried fruits 30*		
		Citrus, strawberries .. 30*		
		Other fresh fruit 20*		

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
carbaryl	0.02	Tree fruits including citrus, small fruits and berries, leaf veg. and brassica, olives, nuts, cucurbits, melons .... 10* Other veg., poultry, cotton seed .... 5* Rice 2.5*		Residue largely in the skin of poultry, other meat animals show no residue.
carbon disulphide	None recommended	None recommended		
carbon tetrachloride	None recommended	None recommended		
chlordane	0.001	Large root crops, leafy stalk vegetables..... 0.3* Small root crops, (except carrots), cucurbits, pineapple. 0.2* Sugar beets, whole pods of pod vegetables, berries, tomatoes and related garden crops, sweetcorn and popcorn 0.1*	Cereals 0.1*	Measured as alpha plus gamma chlordane Tolerances are for residues resulting from soil treatment only.

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
DDT	0.01	Apples, pears, peaches, apricots, small fruits, except strawberries, all vegetables except root veg. fat of meat, fish and poultry .... 7.0* Strawberries, root vegetables .... 1.0* Cherries, plums, citrus, tropical fruits 3.5*	Milk......... 0.005* Milk products (on fat basis)..... 0.2*	For DDT, DDD or DDE or any combination of the three
demeton	0.0025	None recommended		
diazinon	0.002	Peaches, citrus and cole crops .... 0.7* Other fruits and veg. and meat (on fat basis) 0.5*		
dichlorvos	0.004	Cereals .... 2.0* Cereal products and fresh vegetables ..... 0.3* Canned and frozen veg., fruit other than citrus 0.1*		Content of dichlor-acetaldehyde (DCA) to be reported where possible

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
dieldrin	0.0001	Vegetables and fresh fruit (other than citrus) ....0.1*** Citrus, rice 0.05***	Cereal grains ....0.02*** Whole milk ..0.005*** Milk products (fat basis) ...0.125*** Meat (fat basis) 0.2***	Combined total aldrin and dieldrin
dimethoate	0.02	Tree fruits and veg excluding tomatoes and peppers............ 2.0* Tomatoes and peppers............ 1.0*		Residues to be reported as dimethoate plus the oxygen analogue
diphenyl	0.125	Citrus............... 110		No change from previous report
dithiocarbamates, dimethyl (ferbam, thiram and ziram)	0.025**	None recommended		Acceptable daily intake applies to parent compounds and to their sum if more than one is present.

Compound	Maximum acceptable daily intake (mg/kg) body-weight	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
dithiocarbamates, ethylene bis - mancozeb, maneb and zineb (including zineb derived from nabam plus zinc sulfate)	0.025**	None recommended		Acceptable daily intake applies to parent compounds and to their sum if more than one is present.
endosulfan	None recommended	None recommended		Residues should be measured and reported as total of endosulfan A and B, and endosulfan sulphate
ethylene dibromide	None recommended	None recommended		See entry under total bromide ion
ethylene dichloride	None recommended	None recommended		

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
heptachlor (and heptachlor epoxide)	0.0005	Root veg. other than potatoes, cole crops, head lettuce spinach, other leafy veg...............0.1*	Whole milk ...0.005* Milk products (on fat basis) .....0.125* Meat (on fat basis) 0.2* Cereals ..... 0.02* Veg. 0.05*	Practical residue limit changed from previous report
hydrogen phosphide	Not necessary	Cereal products (only items to be cooked) dried vegetables and spices............. 0.01 Raw cereals 0.1		See report for restrictions
lindane	0.0125	Cereals .... 0.5* Vegetables, small fruits 3.0*	Whole milk ...0.004* Milk products (on fat basis) .....0.1* Meat (on fat basis) 0.7*	Tolerances for milk products in previous report changed to practical residue limit

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
malathion	0.02	Fruit (excluding citrus), dried fruits, nuts and cereals ....8.0 Citrus ....4.0 Leafy vegetables ....6.0 Other vegetables 3.0		Cereal products deleted. Otherwise unchanged from previous report
methyl bromide	None recommended	None recommended		See entry under total bromide ion
MGK 264 N-(2-ethylhexyl) bicyclo(2,2,1) hept-5-ene 2,3-dicarboximide	None recommended	None recommended	None recommended (see monograph)	
organocercurial compounds	None recommended	None recommended	None recommended (see monograph)	No objection to use of organocercurial seed dressings and on apples up to petal fall.
oxydemeton methyl	0.0025	Not considered at 1967 meeting		

Compound	Maximum acceptable daily intake (mg/kg body-weight)	Tolerances (ppm)	Practical residue limits (ppm)	Remarks
parathion	0.005	Vegetables, except carrots ....0.7* Peaches, apricots, citrus ....0.5* Other fresh fruits 1.0*		
piperonyl butoxide	0.03***	Cereals ....20*** Fruit (for canning) dried fruit and vegetables, oil seeds, tree nuts 8.0***		No change from previous report
pyrethrins	0.04*	Cereals .... 3.0* Fruit (for canning) dried fruit and vegetables, oil seeds, tree nuts 1.0*		No change from previous report. (Monograph contains correction regarding sensitivity of analytical method)

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

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

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

APPENDIX IV

SIGNIFICANCE OF INTERACTIONS OF PESTICIDES

Numerous instances have been observed in which one pesticide may influence the metabolism and toxicity of another pesticide administered simultaneously or subsequently in experimental animals. Most studies of such pesticide interactions have been carried out on a relatively short term basis, involving single or only a few daily doses of one agent accompanied or followed at various intervals by a single dose of another. Thus little is yet known of the significance of the interactions discovered in this way in relation to the safety of chronic exposure to low levels of pesticides in the environment. However, since it is known that relatively low non-toxic doses of some pesticides, given acutely or subacutely, do produce biological changes in the body that can affect the fate and actions of other chemical substances, such interactions should be examined or further investigated to ascertain whether they might occur at hitherto accepted chronic exposure levels.

Some of the mechanisms involved in interactions between pesticides may also play a role in interactions between pesticides and drugs, or between pesticides and other environmental chemicals. Since drugs are taken into the body in amounts expected to exert definite effects, it might be thought there would be greater likelihood of significant interactions between drugs in the body and low environmental levels of pesticides than between two or more pesticides at such low levels. However, there appears to be no indication of any hazard in this regard as a result of the present levels of pesticides in any part of our environment.

Following is a short summary of the more important types of toxicologic interactions that have been seen to occur between the major groups of agents.

1. Organophosphorus insecticides versus organophosphorus insecticides

A number of pairs of organophosphorus insecticides have been observed to show potentiative toxicologic interactions when administered together in acute toxicity tests in animals (Frawley et al., 1957 a, b; DuBois, 1958, 1961; Rosenberg and

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Coon, 1958). Most pairs of this class of insecticides, however, show only additive or less than additive toxicity. There is thus far no evidence that any of the pairs of these agents that show potentiative interactions in acute toxicity tests exhibit this type of interaction when consumed in the diet at or near existing tolerance levels (DuBois, 1961). This has been confirmed also in man (Moeller and Rider, 1962). It thus appears from existing knowledge that the simultaneous presence in food of residues of two organophosphorus insecticides should not be considered a hazard to public health.

It has been observed, however, that some of the aliesterases are more sensitive than are the cholinesterases to inhibition by certain organophosphorus insecticides (Frawley, 1965). Furthermore, those organophosphates that are more active as aliesterase inhibitors than as cholinesterase inhibitors appear to be the most effective in potentiating the toxicity of other organophosphates (DuBois, 1967). Also, the aliesterases participate in the detoxication of many of the organophosphates and probably other chemicals to which man may be exposed. For these reasons it is suggested that consideration be given to the use of no-effect levels for aliesterase inhibition, rather than no-effect levels for cholinesterase inhibition, as the basis for estimating the daily acceptable intakes of those organophosphorus insecticides to which the aliesterase systems are more sensitive than are the cholinesterases.

2. Organochlorine insecticides versus organophosphorus insecticides and drugs

Much information about toxicologic interactions in which pesticides play a role has been reviewed by Conney (1967).

With small single doses (Triolo and Coon, 1966) or at low levels in the diet (Kinoshita et al., 1966), some of the organochlorine insecticides protect animals against the toxicity of many of the organophosphorus insecticides or increase the activity of enzymes that are responsible for detoxifying organophosphates and

APPENDIX IV (Cont'd)

numerous drugs. For example, a single dose of 1 mg/kg of aldrin reduces the toxicity of parathion in mice, and 1 ppm of DDT in the diet of rats increases the activity of enzyme systems that metabolize EPN and several drugs. This type of enzyme increase, which appears to be a characteristic effect of most, if not all, organochlorine insecticides, is considered by many to be a physiological adaptation, not a toxic effect. The protective action of the organochlorine compounds against the toxicity of the organophosphates is potentially a beneficial type of interaction, and it may be concluded that there is no reason to suspect any hazard in the simultaneous presence of these two classes of insecticides as residues in foods.

The ability of organochlorine compounds to enhance the metabolism of various drugs (Welch and Harrison, 1966; Cucinell et al., 1965) might be expected to shorten or distort the expected beneficial effects of the drugs when prescribed for therapeutic purposes. This could be considered a potentially adverse effect of this class of insecticides. However, in the relatively steady state that exists with respect to the levels of these substances in the environment sudden changes in drug metabolism and interference with schedules of drug therapy would not be anticipated.

3. Organophosphorus insecticides versus drugs and other substances

Conney et al (1967) have reviewed succinctly the effects of pesticides on drug metabolism.

The organophosphorus insecticides are primarily enzyme inhibitors, thus affecting the cholinesterases, the aliesterases that metabolize some drugs and organophosphates, and the microsomal enzymes that oxidize barbiturates, hydroxylate testosterone, deoxycorticosterone, and other steroids, and epoxidize aldrin and heptachlor. Through some of these inhibitory effects on enzymes this class of insecticides can delay the rate of detoxication and increase the toxicity of other pesticides or of drugs and other chemicals. Toxicity studies of this nature, however, have been almost exclusively acute or subacute, with little attempt to estimate no-effect levels of intake for any extended period of time. Though some of the results reported show that the organophosphorus insecticides can interact toxicologically with drugs or other chemical substances, further investigations are needed to show any potential hazard to health in this regard as a consequence of the presence of these insecticides as residues in foods.

4. Organochlorine versus organochlorine insecticides

In a series of recent reports (Street and Blau, 1966; Street et al, 1966; Street and Chadwick, 1967) the effects of various organochlorine insecticides on the storage, excretion and metabolism of others have been described. For example, as little as 5 ppm of DDT in the diet of rats reduced the fat storage of dieldrin fed concurrently. Methoxychlor had a similar effect. Also DDT depressed the storage of heptachlor epoxide when heptachlor was fed and hastened the depletion of dieldrin previously stored in the fat. The effect of DDT on dieldrin storage was also seen in swine and sheep, but not in chickens. Evidence was presented that DDT increases the activity of enzymes that metabolize dieldrin.

Acute toxicity tests with many paired combinations of organochlorine insecticides (Keplinger and Deichmann, 1967) showed that some pairs had additive, some less than additive, and some greater than additive toxic effects. Toxicity testing by this technique, however, is considered to have little relevance to the question of toxicological interactions between these insecticides when consumed at practical residue levels over a long period of time.

The above reported observations provide no basis for any special concern regarding toxicological interactions between organochlorine insecticides as they might appear together as residues in foods. Many of the results reported show less than additive effects when two or more of these compounds enter the body simultaneously.

APPENDIX IV (Cont'd)

5. Miscellaneous

Fitzhugh (1965) fed rats for 2 years with combinations of pesticides (DDT, aldrin, pyrethrin, piperonyl butoxide, malathion, 2,4D) and flavoring substances (allyl heptylate, anethole, amyl butyrate, cinnamic aldehyde, citral, ethyl methylphenylglycidate) at levels up to 50 and 400 times the estimated use levels of the pesticides and flavors respectively. No adverse effects were seen in the rats receiving up to 50 and 100 times the respective use levels of these two groups of agents. It was concluded that no hazard to health would result from the combined intake of these substances at presently estimated use levels.

Piperonyl butoxide and other pesticide synergists inhibit numerous enzymatic mechanisms that detoxify or activate various pesticides (Wong and Terriere, 1965; Nakatsugawa and Dahm, 1967). When given subcutaneously at relatively high dose levels to new-born mice piperonyl butoxide markedly increased the acute toxicity of the freons, benzo(a)pyrene and griseofulvin. A similar combined treatment of new-born mice with piperonyl butoxide and freons synergistically increased the incidence of hepatomas after one year (Epstein et al., 1967a; Epstein et al., 1967b).

In view of the known effects of piperonyl butoxide and related pesticide synergists on enzyme systems that function in activation and detoxication processes, and in view of the little that is known about the toxicologic interactions in which these compounds may participate in mammals, further exploration should be made into their interactions with pesticides and other chemicals to which man may be exposed.

APPENDIX IV (Cont'd)

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