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[1] **T = Toxicology**
R = Residue and analytical aspects
*** = First evaluation**

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1991 JOINT MEETING OF THE FAO PANEL OF EXPERTS ON PESTICIDE RESIDUES IN FOOD AND THE ENVIRONMENT AND THE WHO EXPERT GROUP ON PESTICIDE RESIDUES

Geneva, 16-25 September 1991

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ABBREVIATIONS WHICH MAY BE USED IN THIS REPORT

(n.b.: chemical elements and pesticides are not included in this list)

AChE	acetylcholinesterase
ADI	acceptable daily intake
ai	active ingredient
approx.	approximate
at. wt.	atomic weight
b.p.	boiling point
bw	body weight
c	centi - (x 10^{-2})
°C	degree Celsius (centigrade)
CCPR	Codex Committee on Pesticide Residues
ChE	cholinesterase
cm	centimetre
CNS	central nervous system
cu	cubic
cv	coefficient of variation
DFG	Deutsche Forschungsgemeinschaft
DL	racemic (optical configuration, a mixture of dextro- and laevo-; preceding a chemical name)
EC	emulsion concentrate
EMDI	estimated maximum daily intake
EPA	Environmental Protection Agency
ERL	extraneous residue limit
F_1	filial generation, first
F_2	filial generation, second
f.p.	freezing point
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
g	gram
ìg	microgram
GAP	good agricultural practice
GC-MS	gas chromatography - mass spectrometry
G.I.	gastro-intestinal
GL	guideline level
GLC	gas-liquid chromatography
GPC	gel-permeation chromatography
h	hour(s)
ha	hectare
Hb	haemoglobin
hl	hectolitre

HPLC	high-performance liquid chromatography
IBT	Industrial Bio-Test Laboratories
i.d.	internal diameter
i.m.	intramuscular
i.p.	intraperitoneal
IPCS	International Programme on Chemical Safety
IR	infrared
IRDC	International Research and Development Corporation (Mattawan, Michigan, USA)
i.v.	intravenous
JMPR	Joint FAO/WHO Meeting on Pesticide Residues (Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues)
k	kilo- (x 10^3)
kg	kilogram
l	litre
LC	liquid chromatography
LC_{50}	lethal concentration, 50%
LD_{50}	lethal dose, median
LOAEL	lowest observed adverse effect level
LSC	liquid scintillation counting or counter
m	metre
mg	milligram
µm	micrometre (micron)
min	minute(s)
ml	millilitre
MLD	minimum lethal dose
mm	millimetre
M	molar
mo	month(s)
m.p.	melting point
MRL	Maximum Residue Limit (This term replaces "tolerance")
MTD	maximum tolerated dose
n	normal (defining isomeric configuration)
NCI	National Cancer Institute (United States)
NMR	nuclear magnetic resonance
no.	number
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NTE	neuropathy target esterase
o	ortho (indicating position in a chemical name)
OP	organophosphorus pesticide
p	para (indicating position in a chemical name)
PHI	pre-harvest interval

ppm parts per million (Used only with reference to the concentration of a pesticide in an experimental diet. In all other contexts the terms mg/kg or mg/1 are used).

PT prothrombin time
PTT partial thromboplastin time

RBC red blood cell

s.c. subcutaneous
SD standard deviation
SE standard error
sp./spp. species (only after a generic name)
sp gr specific gravity
sq square

t tonne (metric ton)
TADI Temporary Acceptable Daily Intake
tert tertiary (in a chemical name)
TLC thin-layer chromatography
TMDI theoretical maximum daily intake
TMRL Temporary Maximum Residue Limit
TPTA triphenyltin acetate
TPTH triphenyltin hydroxide
UDMH 1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine)
USEPA United States Environmental Protection Agency
USFDA United States Food and Drug Administration
UV ultraviolet

v/v volume ratio (volume per volume)

WHO World Health Organization
wk week
WP wettable powder
wt weight
wt/vol weight per volume
w/w weight per weight

yr year

< less than
≤ less than or equal to
> greater than
≥ greater than or equal to

PESTICIDE RESIDUES IN FOOD

REPORT OF THE 1991 JOINT FAO/WHO MEETING OF EXPERTS

1. INTRODUCTION

A Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues (JMPR) was held in Geneva, Switzerland, from 16 to 25 September 1991. The Meeting was opened by Dr N.P. Napalkov, Assistant Director-General, WHO, on behalf of the Directors-General of FAO and WHO. Both the FAO Panel of Experts and the WHO Expert Group had met in preparatory sessions on 12-13 September.

The Meeting was held in pursuance of recommendations made by previous Meetings and accepted by the governing bodies of FAO and WHO that studies should be undertaken jointly by experts to evaluate possible hazards to man arising from the occurrence of residues of pesticides in foods. The reports of previous Joint Meetings (see references, Section 7) contain information on acceptable daily intakes (ADIs), maximum residue limits (MRLs) and general principles for evaluation of the various pesticides considered. The supporting documents (Residues and Toxicological Evaluations) contain detailed monographs on these pesticides and include comments on analytical methods. The present Meeting was convened to consider a further number of pesticides together with items of a general or a specific nature. These include items for clarification of recommendations made at previous Meetings or for reconsideration of previous evaluations in the light of findings of subsequent research or other developments.

During the Meeting the FAO Panel of Experts was responsible for reviewing pesticide use patterns (good agricultural practices), data on the chemistry and composition of pesticides and methods of analysis for pesticide residues and for estimating the maximum residue levels that might occur as a result of the use of the pesticides according to good agricultural practices. The WHO Expert Group was responsible for reviewing toxicological and related data and for estimating, where possible, ADIs for humans of the pesticides. The recommendations of the Joint Meeting, including further research and information, are proposed for use by Member Governments of the respective agencies and other interested parties.

The Meeting noted with sadness the death of Ms E. Arnold, Health Protection Branch, Canada, who had made valuable contributions at several Joint Meetings as a WHO Temporary Adviser.

2. GENERAL CONSIDERATIONS

2.1 MODIFICATIONS TO THE AGENDA

Owing to lack of data, butocarboxim was not reviewed toxicologically. Several compounds could not be evaluated for residues because information and/or time was insufficient.

2.2 DIETARY INTAKE OF PESTICIDE RESIDUES

Following the methods described in *Guidelines for Predicting Dietary Intake of Pesticide Residues*[i] (WHO, 1989). Theoretical Maximum Daily Intake (TMDI) and, where applicable, Estimated Maximum Daily Intake (EMDI) calculations have been made for this Meeting by the International Programme on Chemical Safety (IPCS). See Annex III.

2.3 USE OF MONITORING DATA IN ESTIMATES OF DIETARY INTAKE

The Meeting was pleased to receive results of the GEMS Joint FAO/UNEP/WHO Food Contamination Monitoring Programme, summary of 1986-1988 monitoring data (WHO/HPP/FOS/91.4).

The residue data on foods, and in particular the data on intakes of pesticides for various diets, are a valuable source of information for old compounds.

The CCPR has initiated a re-evaluation process for old compounds, which requires the re-examination of old and new residue information from supervised trials in the light of current GAP. The GEMS results provide a more balanced picture of what residues are being detected in food than theoretical intake calculations based on MRLs, and permit better estimates of actual intakes.

The value of GEMS would be further enhanced if countries were to report <u>all</u> the relevant data including null results i.e. results for compounds which are determined by the screening methods employed but which are not detected above the validated limit of determination. Food contamination monitoring reports which do not include the null results should clearly state that they are not included.

The Meeting <u>recommended</u> that results of food monitoring surveys suitable for intake estimates be reported in full. These reports should include null results and the relevant limits of determination.

2.4 CONCLUSIONS AND RECOMMENDATIONS OF THE MEETING

In its consideration of data submitted to the JMPR, the

WHO Expert Group on Pesticide Residues and the FAO Panel of Experts on Food and the Environment reviews the data and other relevant information summarized in the monographs on individual pesticides. The interpretations and conclusions of the Meeting are contained in the report and derived from the monographs. The report contains the conclusions and recommendations of the Meeting as a whole rather than those of any group, organization or individual. This continues the Meeting's longstanding practice and provides for its independence and impartiality.

2.5 DRAFT FAO GUIDE ON THE EVALUATION OF PESTICIDE RESIDUE DATA AND THE ESTIMATION OF MAXIMUM RESIDUE LEVELS IN FOOD AND FEED.

The Meeting welcomed the availability of the first draft of the FAO Guide. The aim of the Guide is to clarify the approach taken by the FAO Panel of Experts on Pesticide Residues in Food and the Environment in estimating maximum residue levels, and to ensure consistency in its evaluations.

The FAO Panel considered the first draft and provided general comments to the authors with respect to the focus of the paper and its organization and suggested some additional topics. Some topics were further considered and recommendations made at the current Meeting (Section 2). The Panel also suggested that existing Codex/FAO Guidelines on specific subjects be clearly referenced with the text of the Guide, providing insight as to how the Panel interprets this information. The Panel emphasized the importance of using representative examples as a means of elucidating the evaluation process.

The Meeting supported the proposal that the revised Guide should be circulated to members of the Codex Committee on Pesticide Residues (CCPR) for comment and discussion at the 24th Session of the CCPR in April 1992. The Meeting looked forward to the opportunity to review a further draft in time for the 1992 JMPR.

2.6 PURITY AND SPECIFICATIONS OF PESTICIDES EVALUATED BY THE JMPR AND REGISTRATION AUTHORITIES

The assessment of pesticides by the JMPR should be of help to FAO and WHO Member States in the safety assessment of pesticides and their residues. However, two major problems are encountered when some Member States attempt to use these assessments: (1) the JMPR assesses active ingredients and not formulations, which are controlled at the national level, and (2) relationships between the purity and specifications of the active ingredients that were tested and evaluated by the JMPR and technical materials of commerce are often unknown.

The Joint Meeting evaluates toxicological studies on test materials that in most cases correspond to active ingredients that are sold by the company(ies) that provided the data. However, this is often not known with certainty. More data on purity and specifications should be provided to the Joint Meeting to enable this connection to be established unequivocally.

The purity and specifications of active ingredients that regulatory authorities are asked to approve may or may not correspond to those that were tested and summarized in the JMPR monographs. For this reason, registration authorities should carefully consider the extent of similarity between any active ingredient being considered for registration and the technical material assessed by the Joint Meeting. To be able to make this determination, registration authorities should seek information on manufacturing impurities in pesticide products, as emphasized in Sections 6.2.2 and 6.2.3 of the FAO International Code of Conduct on the Distribution and Use of Pesticides. The safety of other components of formulations should, of course, also be considered when registering pesticides.

Adequate information should be provided to registration authorities so that better comparisons can be made between the active ingredients which have been evaluated by the JMPR and those they may be considering.

2.7 COMMODITY DESCRIPTIONS IN SUPERVISED TRIALS

The Meeting supported recommendation 2 from the Report of the *ad hoc* Working Group on Acceptances, presented at the Twenty-third Session of the CCPR (1991):

> That member countries and basic manufacturers provide all relevant data on pesticide residues and toxicology to the JMPR, as are provided to national registration authorities, in the appropriate format and within the time frames specified by the JMPR.

The implementation of this recommendation would be further assisted if commodity descriptions in supervised trials and processing studies agreed with those in the Codex Classification of Foods and Animal Feeds.

Examples of commodity descriptions whose exact Codex equivalents are not immediately apparent are:

> pollard, ears of corn, corn stover, bibb lettuce, grits, soapstock, meal.

The Meeting recognized that it would not be practical to rewrite studies already provided to national governments to meet this need. The purpose would be served if a table were

appended to such studies showing commodity descriptions used in the studies and the exact Codex commodity equivalent. If no Codex commodity equivalent exists a brief description would suffice.

Further, if the portion of the commodity analysed differed from that given in the Guide, a full description should be provided.

2.8 INTERPRETATION OF A RESIDUE ANALYSIS FOR COMPARISON WITH AN MRL

The Meeting considered recommendation 7 from the Report of the *ad hoc* Working Group on Acceptances presented at the Twenty-third Session of the CCPR (ALINORM 91/24A, para 43):

> That the JMPR be requested to provide guidance as to the appropriate interpretation of Codex MRLs, either as strict limits, or with the allowance of a further margin when considering the analysis of samples for enforcement purposes.

By definition an MRL is a limit not to be exceeded. The onus of proof requires the regulatory authority to establish, with a high degree of assurance, that the residue in the lot being examined exceeds the MRL. To this end, it must be recognized that MRLs depend on estimates made from supervised trial residue data, which contain sampling and analytical variation and errors.

Errors in sampling for enforcement are dealt with by assuming that a sample taken according to Codex protocols is representative of the lot being examined (see *Guide to Codex Recommendations Concerning Pesticide Residues, Part 5*). It should be recognized however that sampling errors may frequently exceed analytical errors.

For the comparison of an analytical result with the MRL it is the accuracy, rather than the precision, which is most important. Errors in, and the interpretation of, analytical results with respect to regulatory limits have been previously reviewed[ii].

A summary of answers to a questionnaire sent out by the Working Group on Methods of Analysis in 1987 was reported at the Twentieth Session of the CCPR (1988). The question: 'what are considered acceptable values for reproducibility (deviations between laboratories)?' produced the information summarized in Table 1.

Table 1. Reproducibility of representative residue methods at different concentrations (data from responses to CCPR questionnaire).

Concentration, mg/kg	Coefficient of variation, %	
	Mean	Range
0.01	77	20-200
0.1	45	10-100
1	22	5-50

The figures in Table 1 are typical of the range of errors routinely encountered (using accepted analytical methods) in analyses for pesticide residues at the concentrations indicated.

In view of the variability inherent in an analytical method, a decision is needed on what analytical results are required to be sure that the residue concentration in the sampled product exceeds the MRL.

One approach is to assume a normal distribution of the data and pose the question: if the true concentration in the sample is equal to the MRL, what is the probability that the analytical result will be x or greater?

The normal distribution provides the following relationships:

$p = 0.05 \qquad x = MRL + 1.6449 \times SD$
$p = 0.01 \qquad x = MRL + 2.3264 \times SD$
$p = 0.001 \qquad x = MRL + 3.0902 \times SD$

SD is the standard deviation for an analytical result at the MRL.

The analytical result necessary to prove, with the specified degree of assurance (p = 0.95, 0.99 or 0.999), that the sample fails to comply with the MRL can then be calculated and some examples are given in Table 2. These calculations show that if an analytical method with a coefficient of variation (CV) of 22 % is used to obtain an analytical result of 1.4 mg/kg there is still a 5 % chance that the actual residue in the laboratory sample is less than or equal to the MRL of 1 mg/kg.

There are situations where the percentage CV for the analytical method is better or worse than those quoted in Table 1. For a correct interpretation of the data it is necessary to know the reproducibility of the analytical method for the specific pesticide/commodity combination under consideration.

Table 2. An example of analytical results needed to demonstrate that a sample fails to meet the MRL, based on the reproducibility data in Table 1.

MRL, mg/kg	CV%, anal. method (Table 1)	Analytical results, mg/kg		
		p = 0.95	p = 0.99	p = 0.999
0.01	77	0.023	0.028	0.034
0.1	45	0.17	0.20	0.24
1	22	1.4	1.5	1.7

Recommendations:

The Meeting recognised that there is uncertainty or error in any analytical result. Proof that a sample fails to comply with the MRL must take into account this error as well as the degree of assurance required (p = 0.95, 0.99 or 0.999).

The Meeting recommended that analytical chemists conducting regulatory residue analyses report their analytical accuracy (reproducibility) and ensure that regulatory agencies are aware of the variability inherent in the residue data when interpreting results.

The Meeting reaffirmed that an MRL is a level not to be exceeded, recognizing that the approach used to determine when an MRL is exceeded is the prerogative of national regulatory authorities. The Meeting supports any efforts to delineate and harmonize national approaches to the interpretation of residue data which may facilitate the acceptance of Codex MRLs by member countries.

2.9 SUMMARY OF GOOD AGRICULTURAL PRACTICES (GAP) FOR PESTICIDE USES

The Meeting considered Recommendation 1 from the Report of the *ad hoc* Working Group on Acceptances presented at the 23rd Session of the Codex Committee on Pesticide Residues (ALINORM 91/24A, para 43):

> That member countries and manufacturers provide up-to-date information on national Good Agricultural Practices (GAP) to the JMPR in the format to be prescribed in the (FAO) Guidelines under development.

The Meeting discussed a proposal for standardized reporting of summaries of good agricultural practices. This proposal reflected similar documents developed in the JMPR over many years. The tabled draft format is presently under

consideration by the EEC member states. It was developed principally for applications on agricultural and horticultural crops.

The Meeting discussed the proposed format and recommended, after some revision to accommodate JMPR needs and experience, that it be used whenever possible in submissions to the JMPR. A copy of the revised format is attached in Annex IV to this report and will be included in the FAO Guide.

It was recognized that for reporting special GAP data such as post-harvest treatments, seed dressing and animal treatments other formats might be more appropriate. It was proposed that these be developed as part of the FAO Guide.

It should be noted that these GAP summaries are intended as an aid to the evaluation of submitted data and are to be submitted in addition to "certified" labels.

2.10 SUBMISSION OF RESIDUE DATA SUMMARIES FROM SUPERVISED TRIALS

The Meeting considered Recommendation 2 from the Report of the Ad Hoc Working Group on Acceptances presented at the Twenty-third Session of the Codex Committee on Pesticide Residues (ALINORM 91/24A, para 43):

> That member countries and basic manufacturers provide all relevant data on pesticide residues and toxicology to the JMPR, as are provided to national registration authorities, in the appropriate format and within the time frames specified by the JMPR.

The Meeting discussed a proposal for standardized reporting of residue data summaries from field trials. This proposal reflected similar documents developed by the JMPR over many years. The tabled draft format is presently under consideration by the EEC member states. It was developed mainly for agricultural and horticultural crops.

The Meeting discussed the proposed format and recommended, after some revision to accommodate JMPR needs and experience, that it be adopted and used whenever possible in submissions to the JMPR. A copy of the revised format is attached as Annex V to this report and will be included in the draft FAO Guide.

It was recognized that more than one format will be required to summarize adequately the residue data arising from such different uses as post-harvest treatments, seed dressing and animal treatments. It was proposed that these be developed as part of the FAO Guide.

It should be noted that these summaries are to aid in the evaluation of submitted data and are to be provided in addition to detailed reports of the residue trials.

2.11 REPORT OF THE FAO/WHO CONFERENCE ON FOOD STANDARDS, CHEMICALS IN FOOD AND FOOD TRADE (March 1991) and REPORT OF THE *AD HOC* WORKING GROUP ON ACCEPTANCES (April 1991)

The Meeting considered those recommendations contained in the Reports of the *ad hoc* Working Group on Acceptances (CCPR 1991, Alinorm 91/24A, para 42-45) and the FAO/WHO Conference on Food Standards, Chemicals in Food and Food Trade which were directed towards the JMPR. Most of the Food Conference recommendations were adopted by the Nineteenth Session of the Codex Alimentarius Commission (CAC) in July 1991 (summarized in ALINORM 91/10). It was noted that these recommendations were largely derived from initiatives undertaken by the Codex Committee on Pesticide Residues (CCPR) at a pre-meeting Workshop in April 1990. The Meeting considered the recommendations of the Joint FAO/WHO Conference on Food Standards, Chemicals in Food, and Food Trade especially important because they brought issues of importance to the JMPR to the attention of high-level national regulatory officials. The Meeting considered it significant in that it is these officials who have the greatest influence on national programs in food safety which affect the work of the JMPR (and CCPR).

The Meeting supported those recommendations which encouraged greater participation on the part of Member Countries and basic manufacturers, particularly those regarding the provision of information on current GAP and residue and toxicology data. It was anticipated that the recently published *Principles for the Toxicological Assessment of Pesticide Residues in Food* (WHO, 1990)[iii] and the draft FAO *Guide on the Evaluation of Pesticide Residue Data and the Estimation of Maximum Residue Levels in Food and Feed* (see section 2.5) would increase the transparency of the JMPR evaluation process and ensure consistency in risk assessment. In addition, the consultations associated with the development of the FAO Guide would provide an opportunity for interested parties to develop further insight into the evaluation procedures of the JMPR.

Responses to specific recommendations, most of which will be included in the draft FAO Guide, are included in Sections 2 and 3 of this Report.

Recommendations directed to the JMPR.

1. JMPR and the CCPR should make every effort to inform countries about the basis for evaluation, so as to increase the transparency of the process and to take

steps to resolve differences in approach which might arise, between CCPR and JMPR and national authorities. **(Food Conference)**

The JMPR is devoting considerable effort to improving presentations in reports and monographs to explain the basis for its recommendations.

The Meeting is also co-operating in the preparation of the FAO *Guide on the Evaluation of Pesticide Residue Data and the Estimation of Maximum Residue Levels in Food and Feed*. This Guide will detail the evaluation procedure which has been and/or will be used by the FAO Panel of Experts on Pesticide Residues in Food and the Environment. Governments and other organizations will have an opportunity to comment on drafts of the Guide through participation in the CCPR. These actions will significantly enhance the transparency of the evaluation process.

A similar document detailing evaluation procedures used by the WHO Expert Group on Pesticide Residues was recently published (WHO, 1990[2]).

2. That all Codex Committees, as well as JECFA and JMPR, continue to base their evaluations on suitable scientific principles and ensure necessary consistency in their risk assessment determinations. **(Food Conference)**

The JMPR supports this request and will continue to follow these principles.

3. That the JMPR be requested to provide guidance as to the appropriate interpretation of Codex MRLs, either as strict limits, or with the allowance of a further margin when considering the analysis of samples for enforcement purposes. **(Recommendation 7, 1991 CCPR)**

The JMPR has responded in Section 2.8.

Recommendations relevant to the activities of the JMPR

1. JMPR should be provided with complete and timely toxicology and residue data. This should include specific GAP information reflecting nationally approved uses. **(Food Conference)**

The Meeting strongly supports this recommendation. The JMPR has repeatedly requested this information and has provided guidance in its reports on what is desired. The major responsibility for this lies with governments

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[2] **WHO, 1990. Principles for the Toxicological Assessment of Pesticide Residues in Food, Geneva, World Health Organization (WHO Environmental Health Criteria, No. 104).**

and industry.

2. GAP information provided to the JMPR should be under constant review and reflect effects on the environment to the degree that this is possible. **(Food Conference)**

The Meeting supports this recommendation, and anticipates that as older compounds are re-evaluated this will become a critical factor.

Although the JMPR already reviews data on certain aspects of the fate of pesticides in the environment (for example fate in soil, water and potential for residues in subsequent crops), consideration of any expanded role in reviewing effects on the environment will be limited by available resources.

3. FAO should consider the manner in which assistance could be given to developing countries for the purpose of generating GAP data. **(Food Conference)**

The JMPR endorses this recommendation, although its implementation is outside the purview of the JMPR.

4. That the Codex Alimentarius Commission (CAC) review the Codex standards, from the standpoint of their <u>current</u> relevance and sound scientific basis, in view of the new international status which they would have under GATT proposals in the area of sanitary and phytosanitary regulations and measures, under the Uruguay Round of Multilateral Trade Negotiations. **(Food Conference)**

The Meeting supports this recommendation to the extent that JMPR evaluations contribute to CAC efforts to comply with it. The JMPR presently considers new information in the context of current standards when such information is made available. The Meeting also noted with interest Codex proposals for the periodic review of old chemicals, their ADIs and MRLs. The Meeting supports this effort, while also recognizing the potential resource implications.

5. That FAO consider ways (e.g., consultant or circular letter) of determining the procedures followed by national governments in establishing Good Agricultural Practices (GAP) with a particular view to the role of efficacy evaluation (accepted in principle by FAO).**(Recommendation 5, 1991 CCPR)**

The Meeting noted the letter of the Working Group on Acceptances (circulated to member countries on August 31, 1991) which requested information on how GAP is determined by national governments. The paper which will be produced as a result of this inquiry will also be of interest to the JMPR.

6. That WHO seek to develop internationally agreed principles for the risk assessment of residues of substances (including pesticides) that have been shown to be carcinogenic in animal studies. That this be the first toxicological end-point considered and that IPCS continue this work in other areas of toxicology, e.g. teratology, neurotoxicity, etc. **(Recommendation 10, 1991 CCPR)**

The Meeting questioned the appropriateness of the first end-point chosen, carcinogenicity, because of the contention surrounding the risk assessment of substances that have been shown to be carcinogenic in animal studies. A more productive approach might be to gain experience by harmonizing the principles of risk assessment for toxicological end-points about which less controversy exists. The documents on methods that have been published or are in preparation by the International Programme on Chemical Safety (IPCS) series could provide a useful starting point. The Meeting observed that pesticide residues in food occurred with variable frequency and usually at very low concentrations. Total dietary exposure to pesticide residues should be assessed from appropriate dietary estimates and not by comparison with legal residue limits. The Meeting considered that these features needed to be considered in the development of any risk assessment for pesticide residues.

The Meeting was informed that the International Programme on Chemical Safety (IPCS) is developing an appropriate response to this proposal.

7. That scientific data submitted to the JMPR for evaluation be required to comply with appropriate Good Laboratory Practice (GLP) procedures recognizing that these increased requirements would not generally be applied retrospectively. **(Recommendation 11, 1991 CCPR)**

The Meeting expects that studies should normally comply with recognized GLP codes and should always be performed in the spirit of good scientific practice. As noted in *WHO Environmental Health Criteria (EHC 104)*[3], compliance with GLP codes can ensure that the quality of unpublished studies is acceptable. However, the Meeting also noted that certain information, such as studies reported in the published literature, may be valuable in the evaluation of a compound despite the lack of formal compliance with GLP.

2.12 WORK-LOAD OF THE JMPR

[3] **WHO, 1990. Principles for the Toxicological Assessment of Pesticide Residues in Food, Geneva, World Health Organization (WHO Environmental Health Criteria, No. 104).**

The Meeting drew attention to the increased work-load in 1991. In particular, the re-evaluation process for old compounds has introduced an additional area of work. Re-evaluation of an old compound is usually more time-consuming than evaluation of a new compound because data on toxicology and residues have been produced over many years by different methods, perhaps with different residue definitions, and considerable changes to GAP.

Some older toxicological studies for several compounds considered at the present Meeting were inadequate by contemporary standards; deficiencies included inadequate animal numbers, limited study description, poor data presentation and lack of information on purity of the test material. In some cases detailed study reports were not available.

Recent Meetings have devoted considerable additional effort to describing and explaining their interpretations and recommendations so as to increase the clarity of their reports.

Residue re-evaluations of some compounds scheduled for 1991 had to be postponed to 1992 because they could not be dealt with in the available time.

If the JMPR is to respond adequately to the increasing work-load, additional resources will be required.

3. SPECIFIC PROBLEMS

3.1 INCREASED INCIDENCE OF HEPATIC TUMOURS IN MICE.

During the Meeting, among the effects noted with several compounds (e.g. buprofezin, fentin and hexythiazox) were the induction of hepatocellular adenomas and/or carcinomas in mice. These lesions were generally induced at high doses and often in only one sex. The problems with these types of lesions, as well as the enhancement of other spontaneously occurring tumours in rodents, have been commented upon by earlier Joint Meetings (1977, 1983 and 1984).

The 1983 JMPR Meeting stated "The enhancement of these common spontaneous lesions must therefore be taken to be an indication of possible carcinogenicity, which must be resolved by further experiments" (Section 2.4). Since this statement was made, many studies have demonstrated that compounds of this type may act as tumour promoters in various *in vivo* or *in vitro* tests. This effect may be mediated through various mechanisms, most of them still not known. However, the data base in this field is rapidly growing. The present Meeting endorsed the statement of the 1983 JMPR and recommended that further studies (*in vivo* and *in vitro*) into the mechanisms of these effects be pursued on compounds associated with the induction of hepatic and other tumours. Proposed mechanisms of action cannot be considered in the evaluations unless they are well supported by experimental data.

3.2 CHOLINERGIC TOXICITY AND SAFETY FACTORS

On several occasions the JMPR has made recommendations on the end-points to be used to assess the cholinergic toxicity of organophosphorus and carbamate pesticides, based on the Meeting's understanding of their mechanisms of toxicity. In particular the 1982 JMPR indicated the limitations of using the inhibition of plasma cholinesterases and the value of using the inhibition of erythrocyte acetylcholinesterase as an indicator of toxicity. The 1988 JMPR recognized the value of brain acetylcholinesterase inhibition to establish NOAELs.

The overall assessment of the toxicity of organophosphorus and carbamate pesticides is likely to be more accurate in those cases where toxicity is due solely to acetylcholinesterase inhibition. The toxic consequences of acetylcholinesterase inhibition are the same irrespective of the dosing regime which causes such inhibition, i.e. single or repeated dosing. Consequently when the end-points for NOAEL estimation are cholinesterase inhibition and cholinergic toxicity, then the potential toxicity of a given compound might be assessed from dose-response curves. Assessment of the slopes of such curves would provide a more accurate basis than present procedures for the allocation of safety factors

applied to NOAELs from appropriate studies.

Most cholinesterase inhibitors have relatively steep dose-response relationships. The use of conventional 100-fold safety factors for the inhibition of brain acetylcholinesterase in animal studies may therefore be viewed as conservative in that the margin of safety is greater than this factor implies. The selection of safety factors for cholinesterase inhibitors should be further explored.

3.3 FAT-SOLUBLE PESTICIDES

The expression of MRLs for fat-soluble pesticides in meat, animal fat and edible offal was discussed at the Twenty-third Session (1991) of the CCPR (ALINORM 91/24A, paras 299-301). The discussions had arisen from the report of the *ad hoc* Working Group on Methods of Analysis, and were referred to the JMPR for consideration.

The physical property chosen by the JMPR to represent solubility in fat is the octanol-water partition coefficient, usually reported as log P_{OW}. The Meeting examined those compounds with MRLs in animal commodities and their P_{OW}s where they were immediately available (54 compounds).

The Meeting found that a compound had been designated as fat-soluble when log P_{OW} exceeded 4 (with 3 exceptions) and not so designated when log P_{OW} was less than 3 (2 exceptions). Between log P_{OW} 3 and 4, interpretations varied.

Compounds with log P_{OW} exceeding 4, but which are not designated fat-soluble;

Phorate (Codex Classification No. 112) (literature log P_{OW}s of 3.83 and 4.26), phosalone (060) (literature log P_{OW}s 4.30 and 4.38) and cyhexatin (067) (literature log P_{OW} 5.39, calculated).

MRLs for phosalone in sheep fat and sheep meat are 0.5 and 0.05 (at or about the limit of determination) mg/kg respectively, which suggests that phosalone could be designated fat-soluble.

Compounds with log P_{OW} less than 3, but which are designated fat-soluble;

Methidathion (051) (literature log P_{OW}, 2.42) and phosmet (103) (literature log P_{OW}s 2.83 and 2.78).

Separate MRLs for methidathion in animal meats and fats have been established at 0.02* mg/kg, while the MRL for milk specifies analysis of the fat portion.

The Meeting noted that there were also anomalies between designation as fat-soluble and the MRL expression in meat for fensulfothion (038), isofenphos (131) and pirimiphos-methyl

(086).

The Meeting further noted that there were errors in estimates of log P_{OW}, with differences of 1 unit for the same compound being reported. Different approaches to the development of these data often give different results. Interpretations must recognize these differences[iv].

The variable composition of some residues, e.g. where the residue is defined as a mixture of parent and metabolites, presents a problem since the fat-solubilities of the metabolites may be different from that of the parent compound. Information on the log P_{OW} of each individual metabolite is often not available. The relative concentrations within the mixture are also subject to change, and as a result the tendency of the mixture to partition into fat will also change. Phorate, phosmet, cyhexatin and phosalone residues are defined as a mixture of parent compound and metabolites.

A further factor which may influence designation as a fat-soluble residue is the nature of the available residue data from supervised trials. Data are frequently reported only on a fat basis or only on a whole commodity basis.

Recommendations:

The Meeting <u>recommended</u> that the octanol-water partition coefficient should be the prime indicator of fat-solubility, supplemented by inferences which may be drawn from the distribution of residues between muscle and fat tissues, when the residue consists of a single compound.

In cases where the residue is defined as a mixture of the parent compound and metabolites, information on the log P_{OW} of the individual compounds should be considered if available.

The Meeting recognized that many compounds which are neither clearly fat-soluble nor clearly water-soluble required special consideration.

In general, when log P_{OW} exceeds 4 the compound would be designated fat-soluble and when log P_{OW} is less than 3 it would not be so designated.

The Meeting also recommended that the data supporting the apparently anomalous cases identified above should be examined at a future Meeting so that they might be resolved.

4. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE FOR HUMANS AND MAXIMUM RESIDUE LIMITS

Explanation

This section contains brief comments on, and where appropriate estimated acceptable daily intakes for humans (ADIs), for the compounds considered by the present Meeting. The ADIs, together with recommendations for maximum residue limits (MRLs), appear also in Annex I. The information provides a summary of the material that will appear in the evaluations, including details of further work or information considered necessary or desirable by the Meeting. The requirements for further work or information are additional to those mentioned in earlier reports that have not been previously satisfied. Attention is drawn to the terminology used by the WHO Expert Group to describe such information and to the definitions of the terms "Required" and "Desirable", as used by the FAO Panel, given in Section 2.5 of the 1986 report.

Compounds evaluated for the first time are identified by their chemical names, according to IUPAC nomenclature, as well as by their common names. Standard common names of the International Organization for Standardization (ISO) are used wherever possible. Each compound is followed by its Codex Classification Number in parenthesis.

4.1 AMITRAZ (122)

RESIDUE AND ANALYTICAL ASPECTS

At the 23rd (1991) Session of the CCPR, some delegations opposed the current expression of the residue of amitraz in terms of the metabolite N-(2,4-dimethylphenyl)-N'-methylformamidine. Expression in terms of the parent compound was preferred. The JMPR was requested to consider the question (ALINORM 92/24A, para. 156).

Definition of the residue as the "sum of amitraz and N-(2,4-dimethylphenyl)-N'-methylformamidine) calculated as N-(2,4-dimethylphenyl)-N'-methylformamidine" is consistent with the recommendations of the 1979 JMPR and with the FAO Guidelines on Pesticide Residue Trials. Most of the residues resulting from supervised trials, on which the existing MRLs are based, were expressed in this way.

The metabolite is more toxic than amitraz. It is usually the main identified component of the residue and is often virtually the only component of any toxicological significance.

The molecular weight of amitraz is 1.8 times that of N-(2,4-dimethylphenyl)-N'-methylformamidine), so the existing MRLs of 0.01, 0.05, 0.2 and 0.5 mg/kg would have to be increased to 0.02, 0.1, 0.5 and 1 mg/kg respectively if the residue were expressed as amitraz, although this would not affect the level of the residue or the relation between a determined residue and the MRL.

The Meeting noted that all the maximum residue levels estimated by the JMPR had already been adopted as Codex MRLs under the present definition of the residue.

The Meeting recommended that the definition of the residue should not be changed at present, but suggested that the CCPR should ascertain the definition used in national legislations with the aim of securing international harmonization.

4.2 AZINPHOS-METHYL (002)

TOXICOLOGY

Azinphos-methyl was evaluated for acceptable daily intake by previous Joint Meetings in 1963, 1965, 1968 and 1973. An ADI of 0 - 0.0025 mg/kg bw was allocated in 1965. Since the previous evaluations additional information has become available which was evaluated by the present Meeting.

The toxicokinetics of azinphos-methyl have been investigated following oral administration in rats. It does not accumulate in body tissues.

In a 52-week study in dogs, using dietary concentrations of 0, 5, 25 or 125 ppm the NOAEL was 25 ppm (equal to 0.74 mg/kg bw/day), based on reduced body-weight gain and inhibition of acetylcholinesterase activity in brain at 125 ppm.

Long-term/carcinogenicity studies in rats at dietary concentrations of 0, 5, 15, or 45 ppm and in mice at 0, 5, 20 or 40 ppm showed that azinphos-methyl has no carcinogenic potential in either species. These results clarified earlier equivocal findings in rats in an NCI bioassay. The NOAEL in rats was 15 ppm (equal to 0.86 mg/kg bw/day), based on effects on brain acetylcholinesterase at 45 ppm. In mice the NOAEL was 5 ppm (equal to 0.88 mg/kg bw/day), based on inhibition of cholinesterase in plasma, erythrocytes and brain at 20 ppm.

In a two-generation reproduction study in rats at dietary concentrations of 0, 5, 15 or 45 ppm, fertility and pup viability during lactation were adversely affected, equivocally at 15 ppm and markedly at 45 ppm. The NOAEL was

5 ppm, equal to 0.48 mg/kg bw/day. Teratology studies in rats, mice and rabbits did not indicate teratogenic effects at doses up to 2, 5 and 6 mg/kg bw/day respectively.

The data from genotoxicity studies with azinphos-methyl were conflicting. However, *in vivo* studies were negative, the positive data being confined to some *in vitro* studies. After reviewing the available information it was concluded that it is unlikely that azinphos-methyl is genotoxic to humans.

Acute delayed neurotoxicity tests in hens with azinphos-methyl gave negative results.

The 1973 JMPR reported that daily doses up to and around 0.3 mg/kg bw/day for 30 days in human volunteers had no effect on plasma or erythrocyte cholinesterase activity. New data were not available from occupational exposure or human volunteer studies with azinphos-methyl. A review of the available literature and reports of human poisoning with azinphos-methyl revealed no information relevant to the estimation of the ADI.

Since the critical toxicological end-point was not acetylcholinesterase inhibition, the human data were not appropriate for estimation of the ADI, which was based on the NOAEL in the rat multigeneration study in rats using a 100-fold safety factor.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 5 ppm (equal to 0.88 mg/kg bw/day)
Rat: 15 ppm (equal to 0.86 mg/kg bw/day) in a long-term/carcinogenicity study
5 ppm (equal to 0.48 mg/kg bw/day) in a multigeneration study
Dog: 25 ppm (equal to 0.74 mg/kg bw/day)
Human: 0.3 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.005 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Further observations in humans

RESIDUE AND ANALYTICAL ASPECTS

Azinphos-methyl was re-evaluated in response to a

proposal of the Ad Hoc Working Group on Priorities of the CCPR (ALINORM 89/24A, Appendix V).

The compound was first evaluated by the 1963 JMPR. Residue data were reviewed by the JMPR in 1968, 1972 and 1974 and several maximum residue levels were estimated. Since 1974 the use pattern has changed in many countries and expanded.

Extensive and very detailed information on current GAP in the use of azinphos-methyl in several countries around the world was received by the Meeting together with comprehensive data on the fate of azinphos-methyl in plants, domestic animals and the environment (soil, soil/water suspensions, water, air and UV light), and on its leaching properties in soil.

Extensive data were available from supervised residue trials, carried out according to current GAP. The trials were mainly in the USA, with some results of trials in Canada, Germany, Portugal, Mexico and South Africa.

The highly divergent GAP in various countries is striking, especially with respect to recommended dosage rates and PHIs for the same crop and against the same or similar insect pests.

It is obvious that countries whose GAP includes high dosage rates combined with relatively short PHIs dominate the residue picture with regard to the estimation of maximum residue levels which would be applicable to world-wide trade in the commodity concerned.

Citrus fruits. The CXL of 2 mg/kg was based on maximum residue levels estimated in 1970 from supervised residue trials according to GAP which was quite different from the current GAP. The Meeting therefore recommended withdrawal of the existing CXL. The data from supervised residue trials provided to the present Meeting are from trials which were not in accordance with current GAP, so no maximum residue levels could be estimated for this commodity.

Pome fruit (apples and pears). It was concluded that azinphos-methyl used according to GAP in the country in which most of the trials were carried out, involving a PHI of 7 days, would give rise to residues up to 2 mg/kg.

Apricot. The 1968 JMPR estimated a maximum residue level of 4 mg/kg, based on a small number of trials. This level was criticized for many years in the CCPR, and after consulting governments according to the Codex step procedure, the 1977 CCPR proposed an MRL of 2 mg/kg. The Meeting recommends withdrawal of the original estimate of 4 mg/kg, but the new data are too limited for a new estimate.

Cherries (sweet and sour). In a series of trials on sweet cherries, only one residue (of 1.44 mg/kg) exceeded 1 mg/kg. In all other trials the residue ranged between 0.11 and 0.93 mg/kg, while the residues in sour cherries ranged from <0.02 to 0.60 mg/kg. A maximum residue level of 2 mg/kg

was estimated for the whole group.

Peaches; Nectarines. Trials on peaches at dosage rates up to 2.24 kg ai/ha (highest dosage rate in the country concerned) and a recommended PHI of 14 days gave rise to residue levels up to 2 mg/kg. The Meeting proposed amendment of the existing CXL of 4 mg/kg and estimated maximum residue levels for both commodities of 2 mg/kg.

Plums Since the high application rate of 2.24 kg ai/ha is included in the GAP of the country in which a large series of trials was carried out, a maximum residue level of 2 mg/kg was estimated, based upon a PHI of 14 days.

Blueberry. The range of residue levels found in a series of trials was very wide, between 0.11 and 4.63 mg/kg. A maximum residue level of 5 mg/kg, after observing the recommended PHI of 7 days, was estimated.

Cranberry. At the registered PHI of 21 days and the maximum dosage rate of 1.12 kg ai/ha, all residues were well below 0.1 mg/kg, which was estimated as a maximum residue level.

Currant, Black. The available residue data were too limited to estimate a maximum residue level.

Grapes. The additional residue data were insufficient to propose amendment of the existing CXL of 4 mg/kg.

Strawberry. The available data were too limited to estimate a maximum residue level.

Onion, Dry and Green. The number of trials was too limited to estimate a maximum residue level.

Broccoli. Results of the additional trials are consistent with the existing CXL of 1 mg/kg.

Cucumber; Melons, except Watermelon; Watermelon. After observing the recommended PHI of 1 day for cucumber and 7 days for the other commodities the residues were below 0.2 mg/kg.

Tomatoes; Peppers, sweet. With the exception of one trial on tomatoes, which was not according to current GAP, all residue levels were below 1 mg/kg.

Artichoke. Since no residue data were available after observing the registered PHI (30 days) no maximum residue level could be estimated.

Soya bean; Potato; Cotton seed. The additional residue data were consistent with the existing CXLs; no changes need to be proposed.

Since azinphos-methyl is no longer registered for use on

Brussels sprouts, celery or sunflower seeds, the CXLs for these commodities should be withdrawn. The existing CXLs for Fruits (except as otherwise listed) and Vegetables (except as otherwise listed) should be withdrawn or replaced by the maximum residue levels listed in Annex I.

The Meeting was unable to make recommendations for the commodities listed below, either because GAP information was inadequate, or because available residue data from supervised trials were not suitable in terms of current GAP.

FS 0140	Apricot	FI 0341	Kiwifruit
FC 0001	Citrus fruits	VS 0624	Celery
		AL 0528	Pea vines (green)
FB 0269	Grapes	AL 1625	Soya bean forage (green)

FURTHER WORK OR INFORMATION

Required (by 1993)

Residue data from supervised trials according to GAP on commodities for which information on GAP for azinphos-methyl exists, but no or insufficient data from supervised trials were available, e.g. apricot, black currants, citrus fruits, strawberries, kiwifruit, bulb and spring onions.

Desirable

Residue data from countries other than the USA on blueberries, cherries (sweet and sour), and grapes.

4.3 AZOCYCLOTIN (129)

TOXICOLOGY

Azocyclotin was last evaluated by the JMPR in 1989. The ADI was estimated to be 0-0.003 mg/kg bw by the 1981 Meeting.

Because azocyclotin is metabolized rapidly to cyhexatin, concern had existed that adverse reproductive effects seen with cyhexatin could also be caused by azocyclotin. In 1989, the Meeting evaluated several teratogenicity studies conducted with azocyclotin and determined a NOAEL of 1 mg/kg bw/day (the highest dose tested) for teratogenicity in rabbits. Maternal toxicity occurred at this level.

The present Meeting reviewed data on cyhexatin which has resulted in a reduction in the ADI for cyhexatin from 0-0.008 to 0-0.001 mg/kg bw. The new ADI was based on a NOAEL determined from a multigeneration study in rats. The Meeting therefore decided that since azocyclotin is converted rapidly to cyhexatin the ADI for azocyclotin should be reduced from 0-0.003 mg/kg bw to 0-0.001 mg/kg bw.

RESIDUE AND ANALYTICAL ASPECTS

Azocyclotin is registered on a wide range of fruits and vegetables in many countries. The current application rates in some countries are up to three times those reported by the 1979 JMPR.

The registered uses of azocyclotin in many countries include many more crops than those for which maximum residue levels were estimated by the JMPR.

The results of recent supervised trials carried out in accordance with the current use patterns were considered, together with relevant data reported in previous evaluations. The data available for evaluation, however, do not cover the range of commodities on which the compound may be used.

The Meeting also considered the request of the 1988 CCPR (ALINORM 89/24, para 131) to combine the limits for cyhexatin and azocyclotin into a single list as had previously been done in similar situations (e.g. carbendazim / benomyl / thiophanate-methyl). The meeting agreed to accede to this request but noted that the cyhexatin / azocyclotin situation differed from that of the benomyl group in several respects. Firstly, in the case of azocyclotin, the residues can include the parent compound in addition to the metabolites. For this reason, separate residue definitions are proposed for azocyclotin and cyhexatin residues, both of which are expressed as cyhexatin. In the recommendations, the compound whose use results in the estimated maximum residue is indicated. Secondly, cyhexatin is chosen as an indicator compound for the organotin metabolites of azocyclotin, since the residues of dicyclohexyltin oxide and cyclohexylstannoic acid are generally less than 30% of those of tricyclohexyltin hydroxide (cyhexatin) which is the major residue. Thirdly, the indicator concept is particularly suitable for newer analytical procedures which determine the individual components of the residues separately. The residue situation described below provides support for this approach.

The residue data show that azocyclotin is degraded rapidly to tricyclohexyltin hydroxide (cyhexatin), which is the major detectable residue on all commodities one week or more after application. The concentration of dicyclohexyltin oxide varied from non-detectable up to about 30% of the tricyclohexyltin hydroxide (22 - 25 % of the total residue), reaching the maximum concentration between 20 and 40 days after application. Cyclohexylstannoic acid was present in negligible amounts (less than 10% of the total) in all the samples (1979 and 1989 Evaluations).

In apples dicycloheyltin oxide amounted to about 30% of the cyhexatin residue 30 to 45 days after application. The trials carried out with 500 SC formulations gave rise to somewhat higher residues than those observed after treatments

with WP formulations. Taking into account the increased dosage rates in current GAP, residues up to 5 mg/kg can be expected.

In grapes after 28 days, tricyclohexyltin hydroxide ranged from 0.05 to 0.11 mg/kg, while dicycloheyltin oxide was below the limit of determination. The must and wine produced from treated grapes did not contain any detectable residues.

In oranges dicyclohexyltin oxide amounted to about 30% of the total residue, which is in accordance with the residue composition found after treatment with cyhexatin (1973 evaluation). Taking into account the peel/pulp ratio of 1/3, the residue in the whole fruit will be unlikely to exceed 0.5 mg/kg. There was no information on residues in other citrus commodities.

In peaches and nectarines the proportion of dicyclohexyltin oxide amounted to a maximum of 30% of the total residue. The Meeting considered the residue data available for peaches and nectarines together and concluded that the residues would not exceed 1 mg/kg if GAP were followed.

In strawberries the estimated maximum residue level of 0.5 mg/kg resulting from the current use of cyhexatin covers the limit of 0.1 mg/kg (at or about the limit of determination) recommended originally by the 1979 JMPR.

Dicyclohexyltin oxide amounted to about 17 to 33% of the total residue in beans 6 weeks after application, while the content of monocyclohexyltin oxide was below 10% (1979 evaluation).

The results of supervised trials reflecting the current use patterns of azocyclotin enabled the Meeting to estimate maximum residue levels for several commodites. In making recommendations the Meeting also took into account the residues resulting from the use of cyhexatin.

In view of the specific the GLC method which measures azocyclotin, tricyclohexyltin hydroxide, dicycloheyltin oxide and cyclohexylstannoic acid separately (Weber, 1988), and the HPLC and GLC residue analytical methods developed recently for the determination of cyhexatin (see the evaluation of cyhexatin), the Meeting concluded that the residue definition should be changed to be appropriate to current analytical methods.

The re-definition of the residue does not affect the limits recommended by previous Meetings, which also included dicyclohexyltin oxide.

Definition of the azocyclotin residue: sum of azocyclotin and cyhexatin expressed as cyhexatin.

Definition of the cyhexatin residue: cyhexatin.

FURTHER WORK OR INFORMATION

Desirable

Residue data from supervised trials on additional crops carried out in accordance with current GAP.

4.4 BENTAZONE (172)

3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide

Bentazone was considered for the first time by the present Meeting. It is used as a post-emergence herbicide for the control of broad-leaved weeds and Cyperaceae in several crops, including dicotyledonous (broad-leaved) crops, e.g. Phaseolus beans, broad beans, soya beans, peas, potatoes, peanuts. The main uses are on cereal grains, including maize and rice. It is also used as a herbicide in non-edible agricultural crops such as grass seed cultures, fibre flax (linseed) and on sports fields, lawns and pastures (on the latter with no grazing for a week or more).

Bentazone has a contact action on the leaves and to a lesser extent an action via the soil. The active ingredient is mainly absorbed by the green parts of the plant, where it acts as a photosynthesis inhibitor.

TOXICOLOGY

After oral administration bentazone is rapidly absorbed, mainly via the stomach, and rapidly excreted, largely unchanged, in the urine. Only 1-2% appeared in faeces over the first 96 hours. Two metabolites have been identified in animals, 6-hydroxy- and 8-hydroxy-bentazone, at very low levels. Residues in plants, which are present at very low levels, comprise mainly 6-hydroxy metabolite. Absorption and excretion in rats and in rabbits were not affected by sex, dose level, or repeated dosing.

Bentazone has a relatively low acute toxicity in rats, guinea-pigs and rabbits. WHO has classified bentazone as slightly hazardous.

There were two short-term studies in rats. The first indicated a NOAEL of 400 ppm, equal to 25.3 and 28.9 mg/kg bw/day for males and females respectively, using dietary concentrations of 0, 400, 1200, or 3600 ppm for 13 weeks. The primary toxic effects observed were changes in serum electrophoretic patterns and, at higher doses, increased prothrombin time (PT), increased partial thromboplastin time (PTT) and decreased body-weight gain. In the second study,

using dietary concentrations of 0, 70, 200, 800 or 1600 ppm, 800 ppm (equivalent to 40 mg/kg bw/day) was accepted as a NOAEL, the changes in testicular histopathology noted at 200 and 1600 ppm being non-dose-related in incidence and occurring in very few animals. Further, no signs of testicular effects occurred in rats even in the long-term studies at doses up to 4000 ppm. The limiting toxicological effects were decreased body-weight gain.

A 90-day study in dogs, using dietary concentrations of 0, 100, 300, 1000 or 3000 ppm, indicated a NOAEL of 300 ppm, equal to 12 mg/kg bw/day, based on sedation at 1000 ppm,, and a maturational arrest in the testes (polynuclear spermatocytes and empty epididymal tubules) in one animal at 1000 ppm and in one animal at 3000 ppm. A later study, lasting one year and using dietary concentrations of 0, 100, 400 or 1600 ppm, indicated a NOAEL of 400 ppm, equal to 13 mg/kg bw/day. At 1600 ppm, various clinical signs were observed in males, and increased PT and PTT were observed in both sexes. At 1600 ppm two dogs showed reduced spermiogenesis.

Three teratology studies in rats failed to demonstrate teratogenic potential, as did two teratology studies in rabbits. The NOAELs in the rat studies were 100 mg/kg bw/day for maternal and embryo/fetotoxicity in the first study (dose levels of 0, 40, 100 or 250 mg/kg bw/day) the next dose causing decreased maternal food intake and reduced pup weight; 2000 ppm (equal to 162 mg/kg bw/day) in the second study (dietary concentrations of 0, 2000, 4000 or 8000 ppm) and 200 mg/kg bw/day (the highest dose) in the third study (dose levels 0, 22, 67 or 200 mg/kg bw/day). In rabbits the NOAELs were 150 mg/kg bw/day (dose levels 0, 75, 150 or 375 mg/kg bw/day) and 50 mg/kg bw/day (dose levels of 0, 50, 100 or 150 mg/kg bw/day) in two different studies. In these studies abortion and vaginal haemorrhage were the limiting factors.

Two multigeneration studies in rats were provided. In the first, using dietary concentrations of 0, 20, 60 or 180 ppm, no effects were observed at the highest dietary level of 180 ppm, equal to 14 mg/kg bw/day. The second study indicated a NOAEL of 200 ppm, equal to 15 mg/kg bw/day, the higher dietary concentrations (800 and 3200 ppm) resulting in reduced pup weights and reduced maternal weights during lactation.

Three long-term/carcinogenicity studies in mice were reviewed. Two of these studies were unacceptable by present day standards. The third study (dietary concentrations of 0, 100, 400 or 2000 ppm) indicated a NOAEL of 100 ppm, equal to 12 mg/kg bw/day, based on increases in prothrombin time and changes in the male pituitary weight. The majority view of the three pathological reviews of hepatocellular neoplasia was accepted, i.e. that there was no evidence of tumour induction.

Two long-term/carcinogenicity studies in rats were reviewed. One of these was unacceptable by present standards. The second study (using dietary concentrations of 0, 200, 800

or 4000 ppm) indicated a NOAEL of 200 ppm (equal to 9 and 12 mg/kg bw/day for males and females respectively) based upon changes in urine volume and colour, PTT in males and clinical chemical parameters occurring at 800 ppm. The occurrence of cataracts noted in this study was determined not to be related to compound administration.

After reviewing the available *in vitro* and *in vivo* genotoxicity data, it was concluded that there was no evidence of genotoxicity.

The ADI was determined using a 100-fold safety factor applied to the long-term study in rats. The ADI was supported by NOAELs in mice and dogs. The 3-month study in dogs, even though it indicated a lower NOAEL, was not used since the number of animals (3/sex/dose) was low.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 100 ppm equal to 12 mg/kg bw/day (both sexes)
Rat: 200 ppm equal to 9 (males) or 11 (females) mg/kg bw/day
Dog: 400 ppm equivalent to 10 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.1 mg/kg bw.

Studies which will provide information valuable in the continued evaluation of the compound

1. Further observations in humans.

2. 90-day feeding study in rats of 6-hydroxy-bentazone.

3. Genotoxicity tests on 6-hydroxy-bentazone.

RESIDUE AND ANALYTICAL ASPECTS

Bentazone is authorized or registered for use in several countries around the world. Detailed information was provided on GAP for bentazone and on the national MRLs currently valid in these countries.

Bentazone is marketed in several formulations (SL, EC and to a lesser extent WP) either with one active ingredient, bentazone or its sodium salt, or as a mixture with other herbicides.

Extensive data were provided on residues from supervised trials (about 128 reports) carried out in 16 countries around the world.

Extensive data were also provided on the fate and metabolism of bentazone in plants, animals, soil and soil/water suspensions. There is some evidence that the residue degradation in these substrates follows broadly similar pathways, but with quantitative differences in the occurrence of transient intermediate metabolites. Bentazone is hydroxylated in the aromatic ring and the heterocyclic ring is opened by hydrolysis. In plants two derivatives hydroxylated at the 6 and 8 position of the aromatic ring are found besides the unchanged parent compound. In particular, 6-hydroxy-bentazone is a major part of the residue during degradation.

Hydrolysis of conjugated metabolites in plants gives 2-amino-N-isopropylbenzamide (AIBA), and smaller amounts of N-(isopropylsulphamoyl)anthranilic acid (NISAA) and anthranilic acid (AA).

In animal tissues, milk and eggs, the 6- and 8-hydroxy derivatives are not found in measurable amounts. Besides the parent compound residues consist of small amounts of AIBA and AA. NISAA, if present, is at low levels.

Bentazone and its metabolite 2-amino-N-isopropylbenzamide (the only degradation product detected in soil) are readily leached in light sandy soils.

Specific methods of analysis involving GLC with sulphur-specific flame photometric detection are available for estimating residues of bentazone and 6- and 8-hydroxy-bentazone in plants, which may be suitable for regulatory purposes. The limit of determination for the parent compound and both hydroxy derivatives is about 0.02 mg/kg. No suitable multi-residue method is available for either bentazone or its hydroxy derivatives.

Specific GLC methods are also available for the determination of bentazone and AIBA in animal products (meat, milk and eggs). The limits of determination of both bentazone and AIBA are 0.02 mg/kg in milk and 0.05 mg/kg in animal tissues and eggs.

On the basis of data from supervised residue trials and the available information on GAP the maximum residue levels reported in Annex I were estimated.

Definition of the residue: Plant material: sum of bentazone, 6-hydroxy-bentazone and 8-hydroxy-bentazone, expressed as bentazone. Animal material: sum of bentazone and 2-amino-N-isopropylbenzamide, expressed as bentazone.

4.5 BIORESMETHRIN (093)

TOXICOLOGY

Bioresmethrin is a synthetic pyrethroid insecticide. It is the (+)-*trans* isomer of resmethrin which itself contains a minimum of 30% bioresmethrin.

The Joint Meeting evaluated the available toxicological data in 1976, at which time the data were insufficient for the allocation of an ADI.

Bioresmethrin was absorbed and distributed rapidly following oral administration, and was quickly metabolized by oxidation and hydrolysis at various sites in the molecule. Complete elimination of bioresmethrin occurred slowly. The enterohepatic circulation system was involved in the elimination. There is no indication that isomerization of bioresmethrin to the (+)-*cis* isomer occurs.

In general, bioresmethrin has low acute toxicity after oral administration. In mammals, the *cis* isomers are generally more toxic than the corresponding *trans* isomers. Some metabolites of bioresmethrin are more toxic than the parent compound.

Short-term studies in rats show that bioresmethrin fed at 1000 ppm caused a slight increase in liver weight and a reduction in thymus weight in rats. In a 90-day feeding study in rats, at dietary concentrations of 0, 400, 1200 or 8000 ppm, bioresmethrin at 1200 ppm or above induced an increase in liver weight and fatty liver which was accompanied by changes in blood enzyme levels (serum alkaline phosphatase and aspartate aminotransferase) indicative of liver injury. In a 90-day gavage study in dogs, bioresmethrin at 250 mg/kg bw/day or above reduced the erythrocyte count, haemoglobin content, and packed cell volume.

A carcinogenicity study in mice with resmethrin (containing at least 30% bioresmethrin) at dietary concentrations of 250, 500 and 1000 ppm for 85 weeks did not demonstrate a carcinogenic effect. However, resmethrin decreased survival rate in both male and female mice at 1000 ppm and adrenal weights were significantly increased in males at 500 and 1000 ppm. The NOAEL for resmethrin was 250 ppm, which was equal to 38 mg/kg bw/day for resmethrin and 11 mg/kg bw/day for bioresmethrin.

In a long-term carcinogenicity study in rats at dietary concentrations of 0, 50, 250 or 1250 ppm for 104 weeks, bioresmethrin did not produce an increase in the tumour incidence. However, it induced an increase in alkaline phosphatase in males at 250 and 1250 ppm and a decrease in cholesterol levels in males at 1250 ppm. Bioresmethrin caused

an increase in the incidence of non-neoplastic liver changes, including pallor and hypertrophy of hepatocytes in males at 250 ppm and in males and females at 1250 ppm. Based upon these findings, the NOAEL for chronic toxicity was 50 ppm, equal to 3.0 mg/kg bw/day.

In a two-generation reproduction study in rats, at dietary concentrations of 0, 80, 250, 750 or 2250 ppm, bioresmethrin did not affect reproductive performance at dietary concentrations of 250 ppm or less, although reproduction was adversely affected at 750 and 2250 ppm. Based on a decrease in parental body weight and hepatotoxicity observed at 250 ppm, the NOAEL for this study was 80 ppm, equivalent to 4 mg/kg/day.

Studies on the developmental toxicity of bioresmethrin in rats and rabbits failed to elicit effects at doses up to 200 and 240 mg/kg bw/day respectively.

After reviewing all available *in vitro* and *in vivo* short-term assays with bioresmethrin, the Meeting concluded that there was no evidence of genotoxicity.

The ADI was based upon the long-term/carcinogenicity study in rats utilizing a safety factor of 100.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Rat: 50 ppm in the diet, equal to 3.0 mg/kg bw/day
Dog: 80 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Bioresmethrin was evaluated in 1975 and 1976 and guideline levels were estimated for cereal commodities.

Bioresmethrin, with piperonyl butoxide as synergist, is used in Australia as a grain protectant. It is registered for use on stored cereal grain at 0.5 or 1 g ai/t for storage periods up to 3 months and 3 to 6 months respectively.

In Spain bioresmethrin is used in glasshouses for the control of pests on vegetables and strawberries. Other

countries which have registrations for glasshouse uses include Bulgaria, Czechoslovakia, France, Greece, Hungary, Romania, Saudi Arabia and the USSR. Bioresmethrin is also used as an insecticide in public and domestic health.

In a supervised trial in Australia in 1986 wheat (548 t) was treated with bioresmethrin at a nominal 1 g ai/t and held in commercial storage. Samples were withdrawn and milled in a Buhler laboratory mill at intervals during the storage. The residue distribution was typical of a grain protectant, more concentrated in the bran fraction (up to 4.9 mg/kg) and depleted in the flour. Residues in wholemeal bread ranged from not detected (<0.1 mg/kg) to 0.3 mg/kg, while residues in white bread were not detectable (<0.1 mg/kg).

In 1989 a supervised trial in Australia involved commercial treatment and storage of wheat (500 t lots treated with bioresmethrin at nominal rates of 1.2 and 2.0 g ai/t). Wheat (50 t lots) was milled in two commercial flour mills after 8 and 12 weeks storage, and was also sent (in 4 t lots) to a pilot mill for milling and cooking studies.

Milling produced flour with bioresmethrin residue levels usually 1/4 to half of those in the wheat, bran with residues about four times those in the wheat, and germ with residues two to 2 1/2 times those in the wheat. Residues in wholemeal were similar to those in the wheat.

In the commercial milling trials residue levels in flour ranged from 1/8 to 4/5 of those in the wheat. The uncertainty in these ratios includes the analytical error, and from the analyses by two laboratories on split samples it is clear that results were not always in good agreement. The majority of the flour samples contained less than 0.5 mg/kg bioresmethrin, but a flour sample containing 0.8 mg/kg was produced from wheat containing 1 mg/kg bioresmethrin in the commercial mill. The Meeting concluded that an MRL of 1 mg/kg for flour was needed.

Bioresmethrin residues in bread (wholemeal, white, steamed, flat) and noodles (yellow, white), were at similar levels to those in wholemeal and flour.

Methods of residue analysis used hexane or methanol for extraction. Milled commodities and bread required more clean-up than did wheat. Clean-up was effected by solvent partition and column chromatography. Analysis was on a reversed phase HPLC column with UV detection. Another method used capillary GLC with flame-ionisation detection, but appeared less satisfactory than HPLC.

In the milling trials samples were split and sent to two laboratories for analysis. Agreement on the results for the milled commodities was not as good as for wheat itself.

The Meeting was aware of national MRLs for cereal

grains, wheat bran and wheat germ in Australia, and for strawberry and vegetables in Spain.

The Meeting recommended withdrawal of the MRL for cooked cereal products including bread because the CCPR had decided that MRLs for such processed foods would not normally be established (ALINORM 91/24A, para 337).

Definition of the residue: bioresmethrin

FURTHER WORK OR INFORMATION

Desirable

A published regulatory analytical method suitable for monitoring bioresmethrin residues in cereals and cereal commodities, preferably a multi-residue method.

4.6 BITERTANOL (144)

RESIDUE AND ANALYTICAL ASPECTS

At the 22nd and 23rd Sessions of the CCPR the JMPR was requested to re-evaluate the data on residues of bitertanol in stone fruits and to estimate separate maximum residue levels for each species. Residue data from supervised trials on stone fruits were submitted to the 1988 JMPR, and a maximum residue level of 1 mg/kg for stone fruits was estimated to replace the TMRL.

Bitertanol is registered for use on stone fruits in many countries. Supervised trials according to GAP were carried out in Germany, France, Israel and South Africa on apricots, cherries, peaches, nectarines and plums during the years 1977-1989. On the basis of the data available from supervised trials and information on current GAP, the Meeting estimated a maximum residue level of 1 mg/kg for apricots, peaches and nectarines, and supported the current CXLs for cherries and plums.

The Meeting reviewed current processing studies on cherries and plums which resulted in residues below 0.5 mg/kg in juice, preserves and jam.

The 1988 and 1989 Meetings required an enforcement method for the determination of bitertanol residues in animal products. The present Meeting reviewed a newly developed GLC method. Preliminary clean-up by gel permeation chromatography is followed by HPLC as a final clean-up step. Bitertanol is derivatized with trifluoroacetic anhydride and the derivative determined by GLC with a nitrogen-phosphorus thermionic detector. The limit of determination is 0.05, 0.02 and 0.001

mg/kg for tissues, eggs and milk respectively. It may be possible to adopt the method for the determination of total residues of bitertanol in animal products.

FURTHER WORK OR INFORMATION

Desirable

Additional residue data on plant commodities likely to be used as animal feed, so that maximum residue levels in animal products can be estimated.

4.7 BUPROFEZIN (173)

2-tert-butylimino-3-isopropyl-5-phenyl-1,3,5-thiadiazinan-4-one

Buprofezin was considered for the first time by the present Meeting. It is an insect growth regulator used for the control of several species of Homoptera. It is formulated in several ways and is registered in many countries for use on a number of crops, primarily on citrus and vegetables for the control of white flies, leaf hoppers and scale.

TOXICOLOGY

The toxicokinetics and metabolism of buprofezin have been studied in rats. It is rapidly absorbed and excreted after oral administration. After oral administration of ^{14}C-buprofezin, radioactivity was widely distributed in the tissues. After 48 hours, 91-93% of the administered radioactivity had been eliminated, 70-80% via faeces and 22-25% via urine. Up to 38% had been excreted in the bile after 24 hours. Buprofezin is metabolized by hydroxylation of the phenyl ring and oxidation of sulphur.

The acute oral toxicity of buprofezin was low in mice, rats, hamsters and rabbits. WHO has classified buprofezin as "unlikely to present an acute hazard in normal use".

In a 90-day study in rats, buprofezin was administered at dietary concentrations of 0, 40, 200, 1000 or 5000 ppm. The NOAEL was 40 ppm, equal to 3.4 mg/kg bw/day for males and 4.1 mg/kg bw/day for females. At higher concentrations an increase in organ weights and histological changes were noted in the liver and thyroid.

In a 13-week study in dogs, buprofezin was administered orally in gelatin capsules at doses of 0, 2, 10, 50 or 300 mg/kg bw/day. The NOAEL was 10 mg/kg bw/day. Raised plasma alkaline phosphatase activity and elevated liver weights were

seen at both higher doses.

In a two-year study in dogs buprofezin was administered orally in gelatin capsules at doses of 0, 2, 20 or 200 mg/kg bw/day. The NOAEL was 2 mg/kg bw/day. Increased liver weight (associated with enlargement of centrilobular hepatocytes and bile duct hyperplasia) was seen at higher doses.

Teratogenic studies in rats at doses of buprofezin of 0, 50, 200 or 800 mg/kg bw/day and in rabbits at 0, 10, 50 or 250 mg/kg bw/day gave no indication of teratogenic potential. The NOAEL for maternal toxicity in both species was 50 mg/kg bw/day.

Two reproduction studies were performed in rats with buprofezin at dietary concentrations of 0, 10, 100 or 1000 ppm. The first of these was a two-generation study in which no clear NOAEL could be identified for possible adverse effects upon pup-weight gain; consistent treatment-related effects were observed only at 1000 ppm in both litters of each generation. No effects were noted in the F_2 generation that were not also present in the F_1 generation. The second study was a single-generation study in which there were two matings. The only effects attributable to treatment were reproducible reductions in pup-weight gain at 1000 ppm. The NOAEL in this study was 100 ppm, equal to 6.4 mg/kg bw/day and 8.9 mg/kg bw/day for males and females respectively.

In a long-term/carcinogenicity study in mice at dietary concentrations of 0, 20, 200, 2000 or 5000 ppm the NOAEL was 20 ppm, equal to 1.82 and 1.89 mg/kg bw/day for males and females respectively. Absolute liver weight was increased at 200 ppm and above. The incidence of hepatocellular adenoma was increased in females at 5000 ppm. There was an increased overall incidence of lung adenoma and carcinoma in males dosed at 200 and 5000 ppm, but not at 1000 ppm. However, the incidences were within the historical control range for the strain used.

In rats fed dietary concentrations of 0, 5, 20, 200 or 2000 ppm buprofezin for 24 months, the NOAEL was 20 ppm equal to 0.9 and 1.1 mg/kg bw/day for males and females respectively. The absolute thyroid weight and incidence of hypertrophy and hyperplasia of the epithelial cells in thyroid increased at 200 ppm and above. The incidence of hepatic hyperplastic nodules was slightly increased in rats at 2000 ppm. The Meeting concluded that there was no convincing evidence of carcinogenicity in rodents.

After reviewing the available *in vitro* and *in vivo* genotoxicity assays, the Meeting concluded that there was no evidence of genotoxicity.

An ADI, which was based on the NOAEL in the 2-year study in rats using a safety factor of 100, was allocated.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 20 ppm equal to 1.82 mg/kg bw/day
Rat: 20 ppm equal to 0.9 mg/kg bw/day
Dog: 2 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Information on the fate of buprofezin was provided for animals, plants, soil and water. In the case of animals, metabolism studies were provided only for rats and chickens. The fate of residues in rats is described in the Toxicology Evaluations.

In the case of chickens approximately 93% of the radioactivity from a single dose was excreted within 96 hours, the major identified excretory products after 24 hours being p-hydroxy-buprofezin (11.6% of excreted radioactivity); buprofezin (3.6% of excreted radioactivity); p-acetamidophenol (1.6%); 1-(4-hydroxyphenyl)-3-isopropylurea (0.8%) and three additional identified compounds, none exceeding 0.2%.

Because buprofezin is used extensively on citrus fruit and tomatoes and because products therefrom can be major ruminant feed items on which residues occur, ruminant metabolism studies are needed before it can be concluded that the fate of residues in animals is understood. Since no information has been received on major uses on commodities which are poultry feed items, poultry feeding studies or additional poultry metabolism studies are not critical at present, but will become important if that situation changes.

Although the Meeting could not conclude that the fate of residues in domesticated animals is adequately understood, available information suggests that phenyl ring hydroxylation, oxidation of the sulphur, and cleavage of the thiadiazinane ring are major routes of metabolism.

In geoponic [soil] and hydroponic-grown rice plants

radioactivity was shown to be taken up through the roots and translocated throughout the plants from water fortified with [phenyl-U-^{14}C]buprofezin. Buprofezin was the major residue identified in ethyl acetate extracts, decreasing from 16.4% of the plant radioactivity after 7 days to 0.75% after 119 days at harvest. The next most abundant residue was p-hydroxy-buprofezin at 4.38% after 7 days and 0.64% after 119 days. 1-(tert-butyl)-3-isopropyl-5-phenylbiuret and 1-isopropyl-3-phenylurea were also identified at less than 1% each. The latter constituted a more or less constant proportion of the total radioactivity from 4 to 119 days at about 0.5%.

In glasshouse-grown tomato plants spray-treated with [phenyl-U-^{14}C]buprofezin, radioactivity in the fruit declined slightly over seven days, but was not identified. It was not established to what extent residues in the fruit resulted from contact of the spray with the fruit or the foliage, although the fact that radioactivity in the fruit declined slightly, rather than increased, over 7 days suggests minimal translocation from plant to fruit from the 4 applications. When fruits were topically treated with an ethanolic solution of [phenyl-U-^{14}C]buprofezin directly by syringe, radioactivity in the fruit declined in a similar fashion. It was found to consist of over 90% unchanged buprofezin. Radioactivity was primarily in or on the peel with up to 13% penetrating into the pulp and none detected in the seed. Washing with water removed about 5-10% of the fruit radioactivity over the 7-day test period and washing with ethanol removed more.

While this experiment provides important insight into the nature of the residue in tomatoes under laboratory conditions from buprofezin applied topically to fruit in ethanolic solution, it does not clearly show whether residues are absorbed through the foliage and translocated to the fruit under practical conditions and if so whether the same metabolic profile would be found. However, it has been shown (see next para) that buprofezin is taken up through the roots of hydroponically grown tomato plants and translocated throughout the plant. Although the fruits from the latter study were not analyzed, buprofezin was again the major identified residue in the plants, but most of the residue (80% of the extractable or 92% of the total plant radioactivity) was not identified. The Meeting concluded that buprofezin metabolism in tomatoes is reasonably understood, taking into account the metabolism in tomato plants shown in hydroponic studies.

Studies of the fate of buprofezin resulting from hydroponic uptake by rice, grass, tomatoes, soya beans and Chinese cabbage plant confirm root uptake and translocation of buprofezin-related residues. Unchanged buprofezin was the major identified extractable residue in all of these plants, ranging from 9.6% in tomatoes to 52.9% in Chinese cabbage. Buprofezin sulphoxide was generally the

predominant identified metabolite, followed in order by 1-tert-butyl-3-isopropyl-5-phenylbiuret, 1-isopropyl-3-phenylurea and p-hydroxy-buprofezin. The major exception was rice plant, in which the latter was the major identified metabolite. Unidentified material accounted for approximately 45% of the extracted residues in all of these plants except tomato, in which it amounted to approximately 80%.

Generally total radioactivity was significantly greater in the roots than in the rest of the plants, with fewer metabolites identified. This will be of special interest for future uses that may be planned on root crops. No information was provided on residues in rice grain, tomato fruit, or soya beans (pods or seeds) in this study.

Available hydroponic metabolism studies demonstrate similarities among plants, but also significant differences, especially quantitative but to some extent qualitative. This indicates the need for separate metabolism studies on commodities representing the major uses, including more information on metabolism in plants grown geoponically.

In soils buprofezin was found to be the major residue, followed by 1-isopropyl-3-phenylurea. The residue tends to bind to the top layers with low mobility relative to the reference compound atrazine. Only low levels of applied radioactivity (less than 0.5%) were found in leachates. Soil microorganisms play a significant role in buprofezin degradation.

Formation of the thiobiuret, i.e. 1-tert-butyl-3-isopropyl-5-phenyl-2-thiobiuret, (compound O), reported at up to 47% of the residue in acidic aqueous media under dark conditions and at lower levels in distilled water under natural sunlight, was not reported in metabolism studies provided to the Meeting, which was informed that radiograms from these studies "did not show evidence" of this compound.

Formanilide was the major product formed during photodegradation.

Analytical methods are available for the determination of buprofezin or its p-hydroxy metabolite in several crops, soil and water. They are based on acetone or methanol extraction, clean-up by organic solvent/aqueous partitioning and/or column chromatography and analysis by GLC with thermionic detection. The analytical method used for most of the non-Japanese trials was the "PPRAM 82" method which was provided too late for review and will be reviewed at a future Meeting. Validation is needed for fruiting vegetables.

Supervised trials data were available for cucumbers, green beans, oranges, tomatoes and tamarillos (tree tomatoes). Buprofezin *per se* was the residue determined,

except in two cases where the p-hydroxy-buprofezin was also determined (tomatoes in Japanese trials and tamarillos in a New Zealand trial), with no residues of the metabolite reported above the limit of determination. No analytical methods or trials data were available for buprofezin sulphoxide, generally the most abundant metabolite found in plant metabolism studies. Also, except in one country, the cucumber and tomato trials were in glasshouses, which parallels the emphasis given to hydroponics in the studies on the fate of residues. Small plot sizes (generally 5-15 m^2) generally reflected the indoor uses. Even in the limited outdoor trials the plots were small. With limited outdoor data, no firm conclusion could be drawn comparing indoor to outdoor residues, although they appear to be of the same order. In most of the reported GAP, there does not appear to be any restriction to indoor uses.

In the case of cucumbers the maximum residue reflecting the GAP of the countries in which the trials were conducted was 0.13 mg/kg, but this value was from only 0.6 times the maximum permitted application rate. It was 0.57 mg/kg from twice the allowed rate. Residues were up to 0.21 mg/kg at a 3-day PHI in a country with only pending GAP but at application rates comparable to those in the GAP of countries nearby.

Data from supervised trials on green beans in one country suggest that 0.1 mg/kg might not be exceeded from that country's indoor GAP. However, because data were limited and because information on the analytical method, sample handling and storage conditions was not provided, the Meeting concluded that a limit for green beans could not be recommended.

In the case of tomatoes, maximum residues reflecting the GAP of the countries in which the trials were conducted were 0.41 mg/kg and were slow to decline during 14 days from the day of application. Residue levels were roughly proportional to application rates.

Supervised trials data on oranges were available from four countries, but only in one (Japan) did the trials accurately reflect the cited GAP (application rate and PHI). Maximum residues in the whole fruit reflecting this GAP were approximately 0.3 mg/kg. In all trials residues in the flesh were not more than 0.07 mg/kg and were about one third to one eighth of those in the whole fruit. In the peel they were about two to three times those in the whole fruit. Important details were not provided for some of the trials.

In a single trial (summary data) at 1 and 2 times the GAP rates on tamarillos, neither buprofezin nor its p-hydroxy metabolite was detected (limits of detection 0.01 and 0.02 mg/kg respectively) after a 28-day PHI which represented GAP. The Meeting concluded that sufficient data and detail had not been provided to support an MRL for

buprofezin on tamarillos.

Feeding buprofezin to cows at levels equivalent to 20 ppm in the total diet produced no residues of buprofezin *per se* (<0.01 mg/kg) in muscle, kidney, liver or milk and ≤0.02 mg/kg in fat. Given that 20 mg/kg is 40 times the maximum level estimated for feed items (raw commodities) to date, and that even the processed products of these commodities are fed as only a portion of the diet, it might be tentatively concluded that residues of buprofezin *per se* are unlikely to be detected in the milk and tissues of cows. However, this conclusion may have to be reconsidered if processing studies show significant residue concentration in relevant commodities. Furthermore, additional studies on the fate of the compound in animals could identify residues of metabolites in addition to buprofezin at levels which might be of concern. If this should happen, feeding trials in which the additional residues are also determined may be required.

There was no decrease in residues in apples, peaches or courgettes after storage at -20 °C for approximately 1 year. A reduction of approximately 13% was observed for kiwifruit.

FURTHER WORK OR INFORMATION

Required (by 1994)

1. Information on the fate of buprofezin in citrus fruits.

2. A ruminant metabolism study.

3. Proof or confirmation of the identity of 1-tert-butyl-3-isopropyl-5-phenyl-2-thiobiuret reported to be formed during the aqueous hydrolysis of buprofezin (Tsuchyia, 1983 and 1985). If confirmed, samples from any additional metabolism studies (or reserve samples from previous ones) should be analysed for this compound and/or it should be determined in reserve or future field trial samples if present at significant levels.

4. Validations of the Plant Protection Division Analytical Method (PPRAM 82).

5. Additional data from outdoor supervised trials on cucumbers and tomatoes, if outdoor uses are confirmed to be GAP, reflecting the GAP of relevant countries and including methods of application other than by knapsack if they are GAP. Larger plot sizes than 5 to 15 m^2 are desirable. Information should include the analytical methods used, validation thereof and sample chromatograms (see 8 below).

6. Additional supervised trials data on oranges reflecting GAP (see 8 below), including the final report on the Brazilian trials (Nihon Nohyaku, 1990) and information on GAP relevant to any data provided. Complete trial details should be provided, including the methods used, validations thereof and sample chromatograms.

7. Information on the fate of buprofezin in commodities during storage and processing (e.g. tomato processing into pulp, juice, ketchup or puree) and the Brazilian citrus pulp data cited.

8. In reserve and/or future field trial samples, in addition to 6 above, analyses for buprofezin sulphoxide, 1-tert-butyl-3-isopropyl-5-phenylbiuret and p-hydroxy-buprofezin, together with sample chromatograms and validated analytical methods.

Desirable

1. A poultry metabolism study. If uses on major poultry feed items become GAP this study, and possibly also poultry feeding trials, will be required rather than desirable.

2. Reference (Nishizawa and Uchita, 1982) cited in the text (page 18) of the company 'Summary of Residues in Food and Their Evaluation', but not located in the submission nor in references included with the summary.

3. Further confirmation of limits of determination as defined by Codex for the analytical methods provided, especially values for untreated validation control samples and fully labelled sample chromatograms (Goto, 1982; Nihon Nohyaku, 1980; Nihon Nohyaku, 1981).

4. Information on residues of buprofezin in foods in commerce or at consumption.

4.8 CADUSAFOS (174)

S,S-di-sec-butyl O-ethyl phosphorodithioate

Cadusafos was considered for the first time by the present Meeting. It is effective for controlling attacks by nematodes and soil-borne insects on bananas, citrus, maize, potatoes and sugar cane. It is formulated for soil application as granules, an emulsifiable concentrate and a microemulsion.

TOXICOLOGY

Following oral administration to rats cadusafos was absorbed and eliminated mainly via the urine (50-70%), but also via expired air (10-15%) and faeces (5-10%). Extensive metabolism proceeds by hydrolysis and oxidation.

Cadusafos has a marked acute oral toxicity with typical signs of cholinesterase inhibition in the rats and mice tested.

In a 90-day study in rats at dietary concentrations of 0.1, 0.5, 1, 5 or 800 ppm, a NOAEL of 1 ppm (equal to 0.07 mg/kg bw/day) was determined, with 5 ppm causing inhibition in plasma and erythrocyte cholinesterase.

In short-term studies in dogs cadusafos was administered by capsule at dose levels 0, 0.01, 0.03, 0.09 or 0.1 mg/kg bw/day for 91 days or 0.0002, 0.001, 0.005 or 0.02 mg/kg bw/day for 1 year. No adverse toxicological effects were observed. The NOAEL for dogs, based on these studies, was 0.1 mg/kg bw/day.

In a 2-year long-term/carcinogenicity study in mice using dietary concentrations of cadusafos of 0, 0.1, 0.5, 1 or 5 ppm, a NOAEL of 0.5 ppm, equal to 0.089 mg/kg bw/day, was determined, based on the occurrence of renal necrotizing arteritis at 1 ppm. There was no evidence of carcinogenicity.

In a 2-year long-term/carcinogenicity study in rats at dietary concentrations of 0, 0.1, 0.5, 1 or 5 ppm, a NOAEL of 1 ppm, equal to 0.05 and 0.06 mg/kg bw/day for males and females, respectively, was established. At 5 ppm, erythrocyte acetylcholinesterase was inhibited without a corresponding inhibition of brain acetylcholinesterase. However, clinical signs of toxicity were observed in females at 5 ppm. There was no evidence of carcinogenicity.

In a multi-generation study in rats at dietary concentrations of 0, 0.1, 0.5 or 5 ppm, a NOAEL of 0.5 ppm, equal to 0.03 mg/kg bw/day, was determined. At 5 ppm, reduction in body-weight gain and inhibition of cholinesterase in plasma and erythrocytes were noted in the F_1 generation. There were no adverse effects on reproduction.

An oral teratogenicity study in rats at dose levels of 0, 2, 6 or 18 mg/kg bw/day indicated dose-related maternal toxicity including clinical signs such as tremors, and red oral discharge at 6 and 18 mg/kg bw/day. Embryo/fetotoxicity at 18 mg/kg bw/day was indicated by a decrease in fetal body-weight gain. There were no teratogenic effects. The NOAEL was 2 mg/kg bw/day. A teratogenicity study in rabbits at dose levels of 0, 0.1, 0.3 or 0.9 mg/kg bw/day showed maternal toxicity and embryotoxic effects at dose levels of 0.3 and 0.9 mg/kg

bw/day respectively.

After reviewing the *in vitro* genotoxicity data it was concluded that, on the basis of the limited data available, there was no evidence of genotoxicity. A positive response was limited to a cell transformation assay with BALB/3T3 mouse embryo cells after activation.

The ADI was based upon the results of the reproduction study in rats, using a 100-fold safety factor.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 0.5 ppm, equal to 0.089 mg/kg bw/day
Rat: 1 ppm, equivalent to 0.05 mg/kg bw/day (2-year study)
0.5 ppm, equal to 0.03 mg/kg bw/day (reproduction study)
Dog: 0.1 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.0003 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Residue data from supervised trials on bananas and potatoes were supplied to the Meeting.

Cadusafos granules were soil-applied at the base of banana plants at rates of 2-20 g ai/plant in a series of residue trials in nine countries. No residues were detected in banana pulp (< 0.005 mg/kg), even with exaggerated use rates. Residues on banana skin were generally not detected (< 0.005 mg/kg) except from some exaggerated use rates.

Cadusafos granules were soil-applied at the time of sowing potatoes in three countries. Data from Spanish trials suggest that a maximum residue of 0.02 mg/kg would be expected in potatoes from cadusafos use according to GAP.

The major metabolic reaction of cadusafos involves cleavage of the P-S bond to release 2-butyl mercaptan, which is then either oxidized or S-methylated. Oxidation produces sulphonic acids while S-methylation leads to sulphones. The

metabolic fate is similar in plants (maize, bananas) and mammals (rats).

The estimated half-life for the aerobic degradation of cadusafos in a silt loam soil was 14 days. The highest concentration of its major metabolite, methyl sec-butyl sulphone, was detected on day 14. Anaerobic degradation in the same soil was slower, the half-life being 55 days. The same metabolites were formed.

Cadusafos was classed as having low mobility in all soils except sands where it was classed as mobile or of intermediate mobility. It was less mobile than carbofuran and atrazine and more mobile than ethion.

In field studies, cadusafos was also classed as of low mobility. The estimated half-lives for disappearance from the top 0-15 cm were in the range 30 to 170 days. Cadusafos levels in the 0-15 cm sample were always higher than levels further down the profile.

Cadusafos was not degraded photolytically, and was stable in stored analytical samples of crop matrices held in a freezer at -18 °C for 14-15 months.

Methods of analysis used GLC (with a phosphorus-sensitive detector) after extraction from the sample and a column chromatography clean-up. Limits of determination from 0.005 to 0.2 mg/kg were achieved with satisfactory recoveries. Soils were the most difficult samples, with the highest limit of determination.

MRLs for cadusafos on bananas have not yet been established at the national level. Mexico and Spain have established MRLs on potatoes of 0.05 and 0.03 mg/kg respectively.

On the basis of the data on residues from supervised trials the Meeting concluded that the residue levels listed in Annex I are suitable for establishing MRLs. The limits refer to cadusafos.

FURTHER WORK OR INFORMATION

Desirable

1. Information on the fate of cadusafos during the cooking and processing of potatoes.

2. A published method of residue analysis suitable for regulatory purposes. Ideally residues of cadusafos should be able to be monitored in a multi-residue method.

4.9 CARBOFURAN (096)

RESIDUE AND ANALYTICAL ASPECTS

In response to a request of the 1991 CCPR (ALINORM 91/24A, paras. 129, 185) that the definitions of the residues of carbosulfan and its metabolite carbofuran should be harmonized, the Meeting recommended that separate limits should be established for carbosulfan and carbofuran, with the latter to accommodate residues resulting from the use of carbofuran or carbosulfan. The current temporary limit of 2 mg/kg for carbosulfan in citrus fruits includes carbosulfan, carbofuran, 3-hydroxy-carbofuran and 3-keto-carbofuran. The Meeting has recommended (see 4.10) that the definition of the carbosulfan residue should be changed to "carbosulfan" with no revision of the limit until additional data are reviewed. It also estimated a separate temporary maximum residue level for carbofuran in citrus fruits to accommodate the use of carbosulfan. There was previously no recommendation for carbofuran in citrus.

Data from the 1984 monograph and the 1991 carbosulfan submission were reviewed in order to estimate the maximum residue level for carbofuran in citrus from the use of carbosulfan. Maximum levels of the sum of carbofuran and 3-hydroxy-carbofuran in the 1991 carbosulfan submission were 0.25 mg/kg on a whole fruit basis (at 60 to 120 days) and in the 1984 monograph 1.7 mg/kg at 28 days. The Meeting estimated a maximum residue level of 2 mg/kg.

4.10 CARBOSULFAN (145)

RESIDUE AND ANALYTICAL ASPECTS

Carbosulfan was first reviewed by the 1984 JMPR which recommended a temporary limit for citrus fruits and listed several requirements for further work before additional maximum levels could be estimated or temporary estimates confirmed. Of these, only residue data on citrus fruits and information on GAP were provided in time for evaluation. Additional information on citrus and other fruits and vegetables was received too late for evaluation and will be reviewed at a future Meeting.

The Meeting also considered requests from the CCPR to harmonize the definitions of the residues of carbosulfan and its pesticide metabolite carbofuran, and to consider whether or not conjugated residues and/or residues of keto-carbosulfan should be included in carbosulfan limits (ALINORM 91/24A, paras. 129, 185).

The Meeting concluded that the 2 mg/kg limit for carbosulfan in citrus fruits should remain temporary and not be revised (except for the definition of the residue, see below) pending a future review of the additional residue and GAP information and a more complete response to the 1984 requests for required and desirable information.

On consideration of the 1990 CCPR question on whether conjugated residues should be included in the residue expression for carbosulfan, the Meeting agreed that enforcement of GAP does not require inclusion of conjugated residues in the residue expression. This would tend to complicate enforcement unnecessarily. The Meeting observed that in most cases (including trials on citrus) analytical methods used to produce both the residue data evaluated in 1984 and the new data included an acid hydrolysis step to accommodate conjugated 3-hydroxy-carbofuran residues. Hydrolysis must be done on a sub-sample since acidic conditions decompose carbosulfan. Conjugated 3-hydroxy-carbofuran was, therefore, included in the previously proposed limit for citrus (and in the data on most other commodities) although it is not specified in the residue definition. Except for 3-hydroxy-carbofuran and occasionally carbofuran or keto-carbofuran at extended PHIs, the carbamate residues appear to be mostly unconjugated. The Meeting agreed that methods which determine conjugated 3-hydroxy-carbofuran residues should continue to be used for data development and for determining 3-hydroxy-carbofuran.

The Meeting also concluded that it would be unnecessary to include conjugated 3-hydroxy-carbofuran in the definition of the carbofuran residue. Most carbofuran MRLs recommended by the 1976 JMPR were based on analytical methods which also included the hydrolysis step to determine 3-hydroxycarbofuran. It was not stated whether this was also true of the additional data reviewed by the 1979 JMPR, but it is probably a reasonable assumption that it was.

The Meeting also considered whether keto-carbofuran should be retained in the definition of the carbosulfan residue. Keto-carbosulfan was included by the 1984 JMPR because it is a significant carbamate residue in citrus fruit (as much as 20% of total carbamate residues) and occurs at higher levels than carbosulfan, which is included in the definition. Citrus is the commodity in which residues of keto-carbofuran derived from carbosulfan tend to be highest among the commodities for which information is available.

The Meeting agreed that inclusion of the keto-carbofuran metabolite in the definition of the carbosulfan residue is not necessary for the enforcement of GAP. It also agreed that it should still be determined, together with carbofuran and 3-hydroxy-carbofuran, during the analysis of samples from supervised residue trials on carbosulfan.

In order to harmonize the residue definitions for

carbosulfan and carbofuran and to accommodate practical enforcement considerations, the Meeting recommended that residues of carbosulfan should be defined as carbosulfan, and residues of carbofuran should be defined as the sum of carbofuran and 3-hydroxy-carbofuran to accommodate resides resulting from the use of carbofuran or carbosulfan. The Meeting recommended that lists of carbofuran limits should clearly indicate whether each limit is based on data derived from the use of carbosulfan, carbofuran or both. The JMPR has previously followed this approach in similar situations.

FURTHER WORK OR INFORMATION

Required (by 1993)

From the 1984 JMPR:

1. Information on nationally registered, approved or recommended good agricultural practices. This should include approved formulations, application rates (ai/ha), number and types of applications and intervals between them, interval from last application to harvest and any other information for the Meeting to determine whether residue field trials data reflect approved uses. Emphasis should be given to uses in countries where the trials were conducted or those in close proximity.

2. Metabolism studies on a root crop after uptake from both foliar and soil treatment.

3. Identification of residues found in ruminant tissues and milk.

4. A conventional ruminant feeding study.

5. Identification of residues found in eggs from metabolism studies with ring-labelled carbosulfan.

6. Further information on storage conditions and times for Brassica samples. Additional field trials data may be required with a short harvest-to-analysis interval, depending on the information provided.

From the present Meeting:

7. Clarification of whether Spanish GAP for uses on citrus fruit includes application rates of 25-37.5 g ai/100l or 50-75 g ai/100l. Conflicting information was received, the first rate from a current label and the second from 'Data on registered uses (member country Spain) to be considered by the EEC'.

8. Information on the sampling-to-analysis interval in the Israeli trials on oranges (FMC, 1991b).

Desirable

From 1984 JMPR:

1. A citrus metabolism study.

2. Grain processing studies.

3. Further information on storage conditions and intervals for pome fruits.

4. Additional storage stability data, especially with field-incurred residues.

5. In addition to other carbosulfan metabolites determined, analyses of poultry tissues and eggs for 3-hydroxy-N-hydroxy-carbofuran, which has been found in metabolism studies. If found in cow tissues at significant levels during metabolism studies, those tissues and milk should also be analysed for this compound in conventional feeding studies.

6. Information on poultry, egg and tissue residues of dibutylamine from studies in which it was fed at 10 ppm in the diet.

4.11 CHLORPYRIFOS-METHYL (090)

TOXICOLOGY

Chlorpyrifos-methyl was evaluated by the 1975 JMPR, which allocated an ADI of 0-0.01 mg/kg bw/day.

Chlorpyrifos-methyl is moderately acutely toxic by the oral route. No significant differences between sexes were observed.

In a 28-day study in mice at dietary concentrations of 0, 1, 5, 10, 1000 or 10000 ppm, the NOAEL was 10 ppm, equal to 1.37 and 1.45 mg/kg bw/day for males and females respectively based on brain cholinesterase inhibition and alterations in the adrenal glands at 1000 ppm.

In a 13-week study in rats at dietary concentrations yielding doses of 0, 0.1, 1, 10, or 250 mg/kg bw/day, the NOAEL was 1 mg/kg bw/day based on histological alterations in the adrenals at 10 mg/kg bw/day.

In a 13-week study in dogs at dietary concentrations yielding doses of 0, 0.1, 10, or 50 mg/kg bw/day, the NOAEL was 10 mg/kg bw/day based on brain acetylcholinesterase inhibition, increased liver weight and reduction of body weight gain at 50 mg/kg bw/day.

In a 78-week study in mice at dietary concentrations of 0, 1, 5, 50 or 500 ppm the NOAEL was 50 ppm, equal to 4.4 and 3.9 mg/kg bw/day in males and females respectively. At 500 ppm, 50% inhibition of brain acetylcholinesterase occurred; other effects noted at this dietary concentration were centrilobular hepatocellular fatty change and cortical cellular swelling of the adrenals. The incidence of neoplastic lesions was similar in all groups.

In a 2-year dietary study in rats the NOAEL was 0.1 mg/kg bw/day based on dose-related alterations in adrenal glands detected at 1 and 50 mg/kg bw/day. There was no evidence of carcinogenicity in rodents.

Chlorpyrifos-methyl did not cause delayed neurotoxicity in hens.

A teratology study in rabbits was negative at all doses tested. The NOAEL was 16 mg/kg bw/day, the highest dose tested.

After consideration of all available *in vitro* and *in vivo* genotoxicity data, the Meeting concluded that chlorpyrifos-methyl was not genotoxic, despite a significant clastogenic response in an *in vitro* study.

The ADI was based on the results of the 2-year study in rats using a 100-fold safety factor. The Meeting was not able to use the human acetylcholinesterase inhibition data reviewed in 1975 as the basis for the ADI because adverse effects on adrenals were observed in rats in the absence of cholinesterase inhibition.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 50 ppm, equal to 3.9 mg/kg bw/day
Rat: 0.1 mg/kg bw/day
Human: 0.1 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.001 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Further observations in humans

RESIDUE AND ANALYTICAL ASPECTS

A review of chlorpyrifos-methyl was requested at the 21st (1989) Session of the CCPR (ALINORM 89/24A, Appendix V).

The Meeting has received information on GAP and reports from supervised trials on crops for which MRLs have been proposed (apples, peaches, cabbage, lettuce and peppers) and on additional crops (dates, grapes, oranges, peas, strawberries, mushrooms, potatoes, onions and sugar beets).

New information was also received on residues from post-harvest treatments of grain, peas and rape seed, and residues in fractions of processed grains. New feeding experiments have been conducted on goats and laying hens.

The new residue data on apples, peaches, cabbage and lettuce are in agreement with data evaluated at earlier Meetings, although residues in lettuce from trials in Spain were considerably lower. The Meeting confirmed its earlier estimates of residues on those crops. New data from Spain on peppers indicate a need for a higher MRL than the existing 0.1 mg/kg.

Residue data from trials on dates, grapes, oranges and mushrooms enabled the Meeting to estimate maximum residue levels, but data from trials on pears, strawberries, and potatoes were insufficient. This was also the case for onions and sugar beets where trials from another year or location are needed to propose residue limits. Data from trials on pears were very few and residues were much lower than those in apples reviewed at an earlier meeting: it was therefore not possible to estimate a maximum level for pome fruit.

Many experiments were carried out to determine residues in cereal grains, peas and rape seed after post-harvest treatments. MRLs are already established on wheat, maize and sorghum, and the new data support those limits. Post-harvest

treatments were also carried out on barley, oats, milo, peas and rape seed. The residues in all these crops were at the same level as in wheat, maize and sorghum and were very persistent, except in peas.

Additional information was also received on residues in process fractions from grains. Residue limits are already established on wheat bran, flour, wholemeal and bread, and the new information supports them. It is remarkable that crude and also refined and bleached refined oils from maize with a content of 3.8 mg/kg in the grains, contain residues of approximately 100 mg/kg, implying that vegetable oil should not be produced from maize after post-harvest treatment with chlorpyrifos-methyl. In investigations of fractions from barley, residues in malt were considerably lower than in the grains, and no residues were detectable in beer produced from the malt.

A metabolic study on lactating goats with ^{14}C-labelled chlorpyrifos-methyl showed that the primary route of excretion was via urine, where the excretion products were free and conjugated 3,5,6-trichloro-2-pyridinol and the desmethyl metabolite of chlorpyrifos-methyl. Total ^{14}C- residues in milk were low (0.02-0.03 mg/kg) and were identified as the parent compound and trichloropyridinol. Total ^{14}C-residues in muscle tissues were 0.03-0.05 mg/kg and in fat, liver and kidney somewhat higher. In tissues and organs residues consisted mainly of trichloropyridinol with only trace levels of the parent compound and its desmethyl metabolite. In fat, residues comprised the parent compound and trichloropyridinol. A similar study was carried out on laying hens.

On the basis of the data from supervised trials the Meeting concluded that the maximum residue levels listed in Annex 1 are suitable for use as MRLs. The residue limit for rape seed should be temporary until information is received on residues in oil from rape seed after post-harvest application.

FURTHER WORK OR INFORMATION

Required (by 1993)

1. Further information on the influence of commercial refining processes on residues in oil from maize after post-harvest treatment and full details of the commercial processes used.

2. Information on residues in crude and refined oil from rape seed after post-harvest treatment with full details of commercial processes.

Desirable

Additional data from trials on pears, strawberries, onions, potatoes and sugar beets.

4.12 CYHEXATIN (067)

TOXICOLOGY

Cyhexatin was last evaluated by the JMPR in 1989 when the ADI of 0-0.008 mg/kg bw was continued unchanged. It was recommended that the compound be reviewed again in 1991. Additional studies were submitted for evaluation at the present Meeting.

In rats, blood levels of tin following administrations of cyhexatin peaked in 3-4 hours and then declined almost to control values in 24 hours. An oral study in rats using technical and micronized cyhexatin resulted in peak blood levels of tin at 3 hours with technical material and 4 hours with micronized material. Levels with micronized material were higher than those with technical material. Dermal exposure of rabbits resulted in similar blood levels of tin with both technical and micronized material.

In pregnant rabbits administered 3.0 mg technical cyhexatin kg bw/day on days 6-18 of gestation, peak maternal blood tin levels were achieved about 3 hours after dosing. Tin half-life in maternal blood was 8.17 ± 1.59 hours. Tin levels in amniotic fluid, placentae, and pups were significantly increased on day 19. Tin levels in pup brains were also elevated. By day 26, tin levels in treated animals were comparable to those in control animals, except in brain where levels were slightly elevated. On day 19 mean pup weights were comparable to controls, but were reduced by day 26. No fetal malformations were reported in this study.

Following both oral and dermal dosing with cyhexatin in rats and rabbits, the tin was eliminated in both urine and faeces. The major route of elimination was via the urine.

A rabbit teratology study using two different technical samples, one from the USA and the other from The Netherlands (The Netherlands material had a smaller particle size), and one pure sample of cyhexatin indicated differences in the severity of cyhexatin maternal toxicity, which appeared to be related to the product particle size, a smaller particle size resulting in increased toxicity. When the two technical samples were compared (high mortality with the pure material prevented valid interpretation of comparative data), pre- and post-implantation losses, fetotoxicity, and reduction in litter size followed a pattern similar to maternal toxicity. A high incidence of folded retinas (exceeding the control range) was noted with both technical samples at the lowest dose tested (0.75 mg/kg bw/day); the significance of this

finding was uncertain. An increase in the occurrence of dilation of the third and/or lateral ventricle of the brain was noted with the US technical material and with the pure material at 3.0 mg/kg bw/day. There was no evidence of hydrocephaly at 0.75 mg/kg bw/day with technical cyhexatin.

Two studies in rats were available. The first study utilized doses of 0, 0.1, 0.5 or 6 mg technical cyhexatin/kg bw/day in a two-generation study with 1 or 2 litters/generation. The NOAEL in this study was 0.1 mg/kg bw/day, with decreased weight gain occurring in females at 0.5 mg/kg bw/day. Reproductive parameters were unaffected in this study, except for reduced post-natal pup weight gain at 6 mg/kg bw/day. There was no evidence of induced abnormal development of pups *in utero*. The second study, utilizing dietary concentrations of 0, 10, 30 or 100 ppm, which incorporated a teratology component, indicated a NOEL of 10 ppm, equivalent to 0.5 mg/kg bw/day. Decreased body-weight gain in pups during lactation and reduced pup survival in F_0-F_{1a} offspring were observed at 30 ppm. There was no evidence of compound-induced developmental abnormalities.

The ADI was estimated on the basis of the multigeneration study in rats (NOAEL 0.1 mg/kg bw/day), applying a 100-fold safety factor.

Additional data on the particle size of micronized the material was received during the Meeting but there was not sufficient time to interpret and relate these data to all the relevant studies.

The Meeting recommended that cyhexatin be reviewed again in 1994 when the results of ongoing work and the studies listed below should be available.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 3 mg/kg bw/day
Rat: 0.1 mg/kg bw/day (multigeneration study)
Rabbit: < 0.75 mg/kg bw/day (teratology)
Dog: 0.75 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.001 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

1. Observations in humans

2. Clarification of the influence of particle size on the toxicokinetics and toxicity of cyhexatin

3. Determination of the effect of restricted food intake on reproduction parameters, preferably by a limited paired feeding study on rats during gestation and lactation.

4. Information on the particle size of cyhexatin residues on food.

RESIDUE AND ANALYTICAL ASPECTS

The 1988 Session of the CCPR noted that the original manufacturer had ceased distribution of cyhexatin, and recommended the toxicological re-evaluation of cyhexatin together with azocyclotin, and a review of the current use patterns.

Cyhexatin is still registered in a number of countries. In others the MRLs have been maintained even if the registration of cyhexatin has been withdrawn. Canada has cancelled the MRLs.

Owing to its consistent activity against mites, cyhexatin is very useful in implementing anti-resistance strategies in combination or alternation with other acaricides, particularly ovicides. It is usually applied once or twice at a rate of 200-1200 g ai/ha.

Field trials reflecting the current recommended use patterns have been carried out recently in France, Italy and the UK to assess residues of cyhexatin on apples, grapes, kiwifruit, peaches, pears, strawberries and hops. These trials and the earlier ones which were in accord with current GAP were considered together by the Meeting. The results indicated that maximum residue levels in apples, pears, peaches and strawberries would not exceed 0.5 mg/kg if current use patterns were followed.

In the trials evaluated by previous Meetings, the residues of cyhexatin (sum of parent compound, dicyclohexyltin oxide and cyclohexylstannoic acid) were determined together by a method based on the measurement of the total organotin residue. The limited information available (1973 evaluation) indicated that the residues on oranges consisted predominantly of the parent cyhexatin. Subsequently, the comparative studies carried out on apples, applying in parallel the 25WP formulations of cyhexatin and azocyclotin, revealed that there was no significant difference between the results of residue determinations by the spectrophotometric (total tin) method and by GLC with individual detection of the residue components (1983 evaluation). Since cyhexatin was found to be the major residue component shortly after treatments with azocyclotin, the composition of the residue from the two pesticides is very similar. Consequently the proportions of the metabolites in the residues after treatment with cyhexatin may be assessed from the detailed residue data obtained with the specific GLC

methods applied in the case of azocyclotin. Those results (see Appraisal of the current azocyclotin evaluation) indicated that in addition to the parent cyhexatin, dicyclohexyltin oxide was the major residue component on beans, grapes, nectarines and peaches, reaching its highest concentration (up to about 25% of the total residue) between 20 and 40 days after application. Cyclohexylstannoic acid was present at negligible levels (less than 10% of the total) in all samples.

The samples from recent supervised trials evaluated by the present Meeting were analyzed either by an atomic absorption spectrophotometric method (AAS) or by liquid chromatography (HPLC). The AAS method measured the organic and inorganic tin compounds separately, but did not distinguish between cyhexatin (tricyclohexyltin hydroxide), dicyclohexyltin oxide and cyclohexylstannoic acid, while with HPLC only the parent cyhexatin was determined. Since, however, the residues measured as organic tin consist mainly of the parent cyhexatin on apples and oranges (FAO 1971, 1974), as well as on other commodities discussed in the current evaluation of azocyclotin, the residue data give a good indication of the true residue levels.

The residue data from trials carried out in accordance with current GAP enabled the Meeting to estimate maximum residue levels for some commodities. The estimates also cover the residues resulting from the use of azocyclotin.

In view of the availability of specific HPLC and GLC residue analytical methods developed recently for the separate determination of cyhexatin, dicyclohexyltin oxide and cyclohexylstannoic acid (Weber, 1988), and taking into account that dicyclohexyltin oxide generally amounted to less then 30% of the total residue, the Meeting recommended that the definition of the residue should be changed and cyhexatin used as an indicator compound for the total organotin residue. The re-definition of the residue does not affect the limits recommended by previous Meetings.

Definition of azocyclotin residue: sum of azocyclotin and cyhexatin, expressed as cyhexatin.

Definition of cyhexatin residue: cyhexatin.

FURTHER WORK OR INFORMATION

Desirable

Information on current GAP for hops and kiwifruit.

4.13 DAMINOZIDE (104)

TOXICOLOGY

Daminozide was considered by the JMPR in 1977, 1983, and 1989. The 1989 Meeting allocated an ADI of 0-0.5 mg/kg bw for daminozide containing less than 30 mg/kg UDMH.

Because of concern over the possible carcinogenic potential of its contaminant and degradation product unsymmetrical dimethylhydrazine (UDMH), the 1989 JMPR requested the results of ongoing carcinogenicity bioassays of UDMH in rats and mice and quantitative data on the conversion of daminozide to UDMH in experimental animals, as well as results of observations in humans.

Administration of drinking water containing 0, 1, 5, 10 (male), 20 (female), 40 or 80 ppm UDMH to mice for two years was associated with an increased incidence of pulmonary neoplasms in female mice at 20 ppm but not at 5 ppm (equal to 1.4 mg/kg bw/day) or in male mice up to 10 ppm. At higher doses of 40 and 80 ppm, hepatotoxicity and high mortality confounded interpretation, although pulmonary and hepatic neoplasms occurred in both sexes.

UDMH similarly administered to rats in drinking water at 0, 1, 50, or 100 ppm, induced hepatocellular neoplasms in females at 50 ppm and 100 ppm but not in males at any concentration. The incidence of pituitary adenomas was also increased in females at 100 ppm. Nonetheless, UDMH was without carcinogenic activity to rats at 1 ppm (equal to 0.09 mg/kg bw/day).

The Meeting noted the lack of carcinogenic potential of daminozide and UDMH in a novel rapid *in vivo* bioassay system in F344 male rats.

The Meeting concluded that the results of these bioassays were consistent with its previous evaluation of the carcinogenicity of daminozide containing up to 30 mg/kg UDMH and confirmed its previous estimate of the ADI which was based upon the most sensitive toxicological end-point, effects seen in a rat multigeneration study, using a 100-fold safety factor.

Quantitative data on the conversion of daminozide to UDMH in experimental animals, which had been requested, were not submitted. Comparative *in vitro* studies of this conversion using appropriate human and rat systems would be particularly relevant.

4.14 DISULFOTON (074)

TOXICOLOGY

Disulfoton was previously evaluated by the JMPR in 1973 and 1975. An ADI of 0-0.002 mg/kg bw was allocated in 1975.

Disulfoton is rapidly absorbed in rats after oral dosing and approximately 90% is excreted via the urine within 24 hours. The biotransformation pathway consists of hydrolysis and oxidation to metabolites such as disulfoton sulphone, disulfoton oxon sulphoxide and disulfoton oxon sulphone.

Disulfoton has high acute oral toxicity to mice, rats and dogs. It is classified by WHO as "extremely hazardous".

Cholinesterase inhibition and related clinical effects were the only significant findings in long-term bioassays in mice and rats. In a 99-week study in mice at dietary concentrations of 0, 1, 4, or 16 ppm, the NOAEL was 4 ppm, equal to 0.55 mg/kg bw/day. At the 16 ppm concentration brain acetylcholinesterase inhibition was reported. There was no evidence of carcinogenicity.

In a long-term study in rats at dietary concentrations of 0, 1, 4, or 16 ppm the NOAEL was 1 ppm, equal to 0.06 mg/kg bw/day. At higher concentrations clinical signs of toxicity and inhibition of plasma, erythrocyte and brain cholinesterase activities were observed. No carcinogenic effect was detected.

In a 2-year study in dogs at dietary concentrations of 0, 0.5, 1, or 2/5/8 ppm, the NOAEL was 1 ppm, equal to 0.03 mg/kg bw/day. At the next highest dose inhibition of brain acetylcholinesterase was observed. Treatment-related histopathological changes were not found.

Disulfoton did not cause delayed neuropathy in adult hens.

Disulfoton was not teratogenic in rats or rabbits. In rats given 0, 0.1, 0.3 or 1 mg/kg bw/day, the NOAELs for embryotoxicity and maternal toxicity were 0.1 and 0.3 mg/kg bw/day respectively. In rabbits given 0, 0.3, 1 or 3/2/1.5 mg/kg bw/day, the NOAELs for embryotoxicity and maternal toxicity were 1.5 and 0.3 mg/kg bw/day, respectively.

In a 2-litter 2 generation reproduction study in rats at dietary concentrations of 0, 1, 3 or 9 ppm, the NOAEL for toxicity was 3 ppm (equivalent to 0.15 mg/kg bw/day), based on signs of maternal toxicity at 9 ppm. The NOAEL for reproductive effects was 1 ppm (equivalent to 0.05 mg/kg bw/day) based on decreased brain acetylcholinesterase, body-weight gain and survival of pups at 3 ppm.

Although there was one positive reverse mutation assay it was concluded, after review of all available *in vivo* and *in vitro* genotoxicity data, that there was no evidence of genotoxicity.

The human volunteer study reviewed by the 1975 JMPR was reported in summary form only and was considered inadequate for the estimation of an ADI.

The ADI was based on the 2-year study in dogs, using a 100-fold safety factor.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 4 ppm in the diet, equal to 0.55 mg/kg bw
Rat: 1 ppm in the diet, equal to 0.06 mg/kg bw
Dog: 1 ppm in the diet, equal to 0.03 mg/kg bw
Man: 0.75 mg/man/day, equivalent to 0.01 mg/kg bw

Estimate of acceptable daily intake for humans

0-0.0003 mg/kg bw.

Studies which will provide information valuable in the continued evaluation of the compound

Further observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Disulfoton has been evaluated several times by the JMPR, in 1973, 1975, 1979, 1981 and 1985.

New residue data from supervised trials on several crops together with other data on use patterns, fate in the environment, storage stability, fate during processing, methods of residue analysis, and national MRLs were provided. Monitoring data were also made available.

In view of the extensive new data available to supplement the earlier evaluations, the Meeting undertook a complete re-evaluation of the compound.

Disulfoton is a systemic insecticide and acaricide and is also effective as a nematicide. It is formulated as granules and emulsifiable concentrates and is registered world-wide for use on many crops. The main applications are on coffee, tobacco, maize, vegetables, potatoes, rice and cotton.

The effect of frozen storage on disulfoton and its main metabolites in several commodities was studied. In most cases disulfoton and its metabolites were only slightly degraded under frozen storage conditions.

Processing studies on potatoes, maize and wheat showed no increase of disulfoton residues in the processed commodities. In tomato a slight increase occurred in paste, dry pulp and puree. Residues in crude peanut oil were significantly higher (0.06 mg/kg) than in the unprocessed nutmeat (0.01 mg/kg).

The USFDA informed the Meeting that in the routine regulatory monitoring programme of the FDA for 1988, 1989 and 1990, residues were found in several plant samples, namely brassica vegetables, lettuce, potato, parsley, beans, grapes, sweet potatoes, strawberries, hay and wheat straw. In five brassica and one pea samples residues exceeded the proposed MRLs. The total number of samples analysed was not reported, but it is known that from 1988 to 1990, 17,000 - 20,000 commercial shipments of food were controlled each year.

Some modifications to previously reported GLC methods

for the determination of disulfoton residues were brought to the attention of the Meeting. The limits of determination were 0.01 - 0.05 mg/kg.

The Meeting concluded that the MRLs for clover hay or fodder and rice should be maintained because there is no important change in GAP and the residue data reviewed in the 1973 evaluation are still valid.

The Meeting proposed that the MRLs for cereal grain (except rice and maize), forage crops (green) and vegetables should be withdrawn because separate maximum residue levels for the corresponding individual crops could now be estimated.

On the basis of the residues found in supervised trials and feeding studies the Meeting concluded that the residue levels listed in Annex I are suitable for establishing MRLs.

The Meeting was unable to make recommendations for the commodities listed below either because information on GAP was inadequate or because available residue data from supervised trials were not suitable for evaluation in terms of current GAP.

VS 0624	Celery
VD 0541	Soya bean (dry)

FURTHER WORK OR INFORMATION

Desirable

1. Further results from supervised trials, and fully documented details of the trials already summarized in the 1973 Evaluations, on crops where GAP is reported but maximum residue levels could not be estimated e.g. soya bean, egg plant, Brussels sprouts, Chinese cabbage, onions, peppers, spinach.

2. Further information on the possible occurrence of residues in food in commerce or at consumption.

4.15 FENTIN (040)

TOXICOLOGY

Fentin was previously evaluated by the JMPR in 1963, 1965, and 1970. An ADI of 0-0.0005 mg/kg bw was allocated in 1970.

Most toxicological studies on fentin were carried out with triphenyltin hydroxide (TPTH). Since triphenyltin acetate (TPTA) is hydrolysed rapidly to TPTH in an aqueous medium,

studies with both compounds have been used for the evaluation of fentin.

After oral administration of ^{14}C-labelled TPTH the radioactivity was mainly eliminated via the faeces (50-70%), but also via the urine (20-25%). Biliary excretion was also demonstrated. After 7 days residual radioactivity was present with the highest concentration in the liver and the next highest in the kidneys. After oral administration of ^{113}Sn-labelled TPTH, elimination was almost exclusively via faeces. In both cases faecal elimination was biphasic with half-lives of 9 and 50-60 hours. With ^{113}Sn-labelled TPTH the highest concentration was found in the kidneys. After administration of the ^{14}C-labelled compound, radioactivity in the faeces of the rat consisted of parent compound and di- and monophenyltin as well as non-extractable bound residues and tin (measured as Sn). It was reported that benzene was found in the faeces. Sulphate conjugates of phenol, hydroquinone, catechol and resorcinol as well as phenylmercapturic acid were present in the urine. Phenyltin compounds were not found in the urine.

TPTH is toxic to rats after acute oral administration with LD_{50} values of about 160 mg/kg bw. TPTA showed similar acute toxicity.

In a 3-month study in mice at dietary concentrations of TPTH of 0, 4, 20 or 100 ppm, a number of effects were observed at 100 ppm. The main effects were a decrease in haemoglobin concentration and erythrocyte count and an increase in Heinz bodies. Immunoglobulins were decreased and liver weight was increased. The NOAEL was 20 ppm, equal to 3.4 and 4.1 mg/kg bw/day for males and females, respectively.

Dietary concentrations of TPTH of 0, 4, 20 or 100 ppm were tested in a 13-week study in rats. The NOAEL was 4 ppm, equal to 0.30 and 0.35 mg/kg bw/day for males and females respectively, based on a decrease in white blood cells and plasma albumin and an increase in plasma aspartate aminotransferase at 20 ppm.

In a 52-week study in dogs (dietary concentrations of TPTH of 0, 2, 6 or 18 ppm) the NOAEL was 6 ppm, equal to 0.2 mg/kg bw/day based on a decreased albumin level and an increase in relative liver weight at 18 ppm.

Two long-term/carcinogenicity studies in mice and one in rats were performed in which there was no evidence of carcinogenicity. However, there were indications in each of these studies that the doses received by the animals may have been lower than intended owing to instability of the test compound in the diet.

In a third long-term/carcinogenicity study in mice at dietary concentrations of TPTH of 0, 5, 20 or 80 ppm,

increased liver and decreased kidney weights, increased nodular hyperplasia and hepatocellular adenoma and carcinoma occurred at 80 ppm only. The NOAEL was of 5 ppm, equal to 0.85 mg/kg bw/day for males and 1.36 mg/kg bw/day for females, based on decreased body-weight gain at 20 ppm.

In a second long-term/carcinogenicity study in rats (with dietary concentrations of TPTH of 0, 5, 20 or 80 ppm), an increase in mortality was observed at all dose levels. A NOAEL could not be established at the lowest concentration of 5 ppm, equal to 0.3 and 0.4 mg/kg bw/day for males and females respectively. The incidence of pituitary adenomas was increased in females at 20 and 80 ppm. At 80 ppm, the incidence of Leydig cell tumours was increased. These changes were accompanied by non-neoplastic lesions in the pituitary and the testes.

In a 2-generation reproduction study in rats with one litter per generation (dietary concentrations of TPTH of 0, 5, 18.5 or 50 ppm) fertility was not affected. The NOAEL was 5 ppm (equal to 0.4 mg/kg bw/day) based on decreased litter size, decreased pup weight and decreased relative spleen and thymus weight in the weanlings.

In several teratogenicity studies with rats, hamsters, and rabbits, TPTA or TPTH caused maternal and embryo toxicity, but irreversible structural effects were not observed. In rabbits, the most sensitive species, the NOAEL for embryo/fetotoxicity was 0.3 mg/kg bw/day in a study that utilized doses of 0, 0.1, 0.3 or 0.9 mg/kg bw/day TPTA. In this study the NOAEL for maternal toxicity was 0.1 mg//kg bw/day.

Most *in vitro* and *in vivo* genotoxicity tests were negative. However, two human lymphocyte chromosomal aberration assays and two mouse lymphoma mutation assays were positive. The latter responses may have been caused by a variety of effects, including chromosomal aberrations. Since two *in vivo* studies for chromosomal aberrations (a micronucleus test in mice and a cytogenetic test in Chinese hamsters) were negative, it would appear that any genotoxic properties are of low potency. It was therefore concluded that fentin does not present a genotoxic hazard for man.

Effects on the immune system were observed in short- as well as in long-term toxicity studies. In special studies with mice and rats, TPTH showed immunosuppressive properties (lymphopenia and lymphocyte
depletion of spleen and thymus), resulting in altered humoral and cellular immunity. The NOAEL in mice was 5 ppm, equal to 1 mg/kg bw/day, based on a decrease in splenic weight found at 25 ppm. In rats, the NOAEL was 25 ppm, equal to 1.7 and 1.8 mg/kg bw/day for males and females respectively, based upon a significant decrease in immunoglobulin G and a marginal decrease in leucocyte and lymphocyte counts at 50 ppm.

The Meeting noted that there was increased mortality at the lowest dose tested in the most recent long-term study in rats (0.3 mg/kg bw/day). Applying a 500-fold safety factor to this LOAEL would result in approximately the same ADI as the previously established ADI based upon a NOAEL of 0.1 mg/kg bw/day in an earlier long-term study in rats. The previous ADI was therefore retained. This ADI is supported by NOAELs derived from recent studies, including the NOAEL of 0.4 mg/kg bw/day in the 2-generation reproduction study, the NOAELs in short-term studies in rats (0.3 mg/kg bw/day) and dogs (0.2 mg/kg bw/day) and in a teratology study in rabbits (0.1 mg/kg bw/day for maternal toxicity).

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse:	5 ppm in the diet, equal to 1 mg/kg bw/day
Rat: (long-term/carcinogenicity study)	< 5 ppm in the diet, equal to < 0.3 mg/kg bw/day
	5 ppm in the diet, equal to 0.4 mg/kg bw/day (multigeneration reproduction study)
Dog:	6 ppm, equal to 0.2 mg/kg bw/day
Rabbit:	0.1 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.0005 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

1. Ongoing studies on the endocrinological effects of fentin

2. Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Fentin was re-evaluated in response to a request from the CCPR (ALINORM 89/24A, Appendix V).

The 1970 JMPR estimated maximum residue levels for several crops e.g. potatoes, sugar beet, celery, celeriac and carrots. In 1972 maximum levels were estimated for other crops including rice.

In 1970 the residue was defined as "total triphenyltin compounds (not including diphenyl and monophenyl tin and inorganic tin) calculated as triphenyltin hydroxide". It has to be recognized that the analysis of samples from the trials up to 1972, and thus the maximum residue levels estimated, may have included small amounts of the diphenyl- and monophenyltin metabolites, but since the proportions of these in the total

residue are low, the residue levels estimated by the 1970 and 1972 Meetings are restricted to the total triphenyltin compounds, excluding the diphenyl- and monophenyltin metabolites.

Since 1972 no additional residue data have been were received by the JMPR. In 1986, on a proposal of the CCPR, the JMPR changed the definition of the fentin residue without changing the estimated maximum residue levels. Since then residues are calculated and expressed as fentin and no longer calculated as triphenyltin hydroxide.

The present Meeting received updated information on GAP in various countries and data on residues from supervised trials on the main crops on which the use of fentin is currently registered. Fentin products are mainly used on potatoes, sugar beets and hops, and to a lesser extent on other crops such as rice, peppers, tomatoes and peanuts.

Extensive information was also provided on environmental aspects of the large-scale use of fentin, e.g. toxicity for several water organisms, including fish-food organisms. From this information it may be deduced that gross contamination of surface water should be avoided.

The additional data on residues from supervised trials on potatoes, sugar beets, and rice are in reasonable agreement with those presented at the 1970 and 1972 Meetings. No amendments need to be made to the MRLs for these commodities. No maximum residue level could be estimated for sweet peppers because information on GAP in the country in which the trials were carried out was insufficient.

The residue data from supervised trials on onions and garlic (from only one country) and tomatoes were insufficient to estimate maximum residue levels.

The residues from supervised trials on hops treated according to GAP ranged from 0.05 to about 1 mg/kg on the dried hops, depending on the method of analysis used.

A simple and rapid method of analysis currently recommended and other available methods all show deficiencies with regard to specificity and sensitivity. The total organotin residue is converted to tin by treating the residue with nitric and sulphuric acids. The tin is then treated with sodium hydroxide to reduce it to the stannous form which is determined by atomic absorption spectrophotometry and calculated as triphenyltin acetate.

The multi-detection method S 24 of the Deutsche Forschungsgemeinschaft is suitable for regulatory purposes. It involves separate analysis of triphenyltin and diphenyltin compounds by GLC with flame-photometric detection. The limit of determination of both compounds is 0.01 mg/kg.

An improved GLC method of analysis with flame-photometric detection provides for separate analysis of the triphenyl parent compound and the di- and monophenyl metabolites.

The Meeting confirmed its estimates of maximum residue levels for potatoes (0.1 mg/kg), sugar beets (0.1 mg/kg) and rice (0.1 mg/kg). Other maximum residue levels suitable for use as MRLs were estimated.

The Meeting was unable to make recommendations for the commodities listed below, either because GAP information was inadequate or because available residue data from supervised trials were not suitable in terms of current GAP.

SB 0715	Cacao beans	SB 0716	Coffee beans
VR 0577	CarrotSO 0697	Peanut	
VR 0570	Celeriac	TN 0672	Pecan
VS 0624	Celery		

FURTHER WORK OR INFORMATION

Required (by 1994)

Residue data from supervised trials according to current GAP on crops for which the use of fentin compounds is still registered in various countries, e.g. pecan, peanut, celery, celeriac, together with information on the current GAP in the countries concerned.

4.16 FLUSILAZOLE (165)

RESIDUE AND ANALYTICAL ASPECTS

Flusilazole was first reviewed by the 1989 JMPR which estimated an ADI and several MRLs, some of which were considered temporary pending the receipt of additional required information.

The Meeting reviewed information from the manufacturer in response to the requests of the 1989 JMPR, additional GAP and supervised trials residue information from other sources, and a country comment on proposed limits for grapes and raisins.

In response to a country comment the Meeting re-examined the data and GAP basis for the currently proposed MRL of 0.5 mg/kg for grapes and confirmed that 0.3 mg/kg (or 0.5 mg/kg if rounded up) would be required to accommodate European uses if the trials in Germany reviewed by the 1989 JMPR reflect European GAP. The Meeting was informed that there is no GAP for flusilazole on grapes in Germany and that current GAP for grapes would be available for the 1993 JMPR. The Meeting

confirmed the 1 mg/kg estimate for dried grapes.

Revised GAP in Spain suggests that the current 0.2 mg/kg proposal for pome fruit could be too low in view of trials in other European countries. However, the Meeting concluded that any required increase in the 0.2 mg/kg proposal would need to be supported by supervised trials which reflected the revised GAP and included use of the approved formulation.

Detailed summary data from residue trials in New Zealand on nectarines and peaches, which reflected New Zealand GAP, reported residues of <0.01 mg/kg. However, these data are of limited use because information on the analytical method used, the sample handling and storage conditions, and the storage-to-analysis intervals was not provided. Maximum residues on peaches in French trials provided by the Spanish government and reflecting Spanish GAP were 0.09 mg/kg. This level is consistent with the Spanish national limit of 0.1 mg/kg. The Meeting was informed that data from four additional trials in Italy could be available for the 1993 JMPR.

Additional but limited data on supervised trials on wheat showed residues in the grain consistent with those on which the 1989 JMPR estimated a temporary maximum residue level of 0.1 mg/kg and required no change in that estimate.

A simulated wheat grain processing study on field-treated wheat grain was submitted in response to a requirement of the 1989 JMPR . Although residues were detected in the grain, shorts and germ, middlings, bran, and patent flour, no concentration of residues was observed. The highest residue was in bran (0.017 mg/kg average) compared to 0.046 mg/kg in the grain.

No baking study, which had also been requested, was conducted and processing studies had not been done on metabolites because it was noted that most grain residues were conjugates of chemicals whose synthesis had not been possible. The Meeting agreed that it would not be necessary to conduct a baking study for flusilazole in grain in view of the very low residues (0.013 mg/kg) found in the flour. The Meeting concluded that it should be feasible to analyse for the silanol metabolite F 7321 in treated grain and its processed fractions and that this information was still desirable.

A summary report of a study of the freezer storage stability of residues in wheat grain was provided in response a requirement of the 1989 JMPR. It suggests that flusilazole *per se* is stable in wheat grain under freezer conditions for 36.5 months. This information tentatively confirms the validity of the data from residue trials reviewed in 1989 and is consistent with findings for residues in apples and grapes (1989 Evaluations). However, details of the storage conditions for the new study were not provided, and are needed to confirm this tentative conclusion. The Meeting was informed that additional information could be provided for the 1993 JMPR.

Requested information on the stability of major metabolites in grain has not been provided. The reasons given were that authentic standards are lacking and that the metabolites in grain are conjugates. For the reasons given above, the Meeting concluded that it should be feasible to study the freezer storage stability at least of the metabolite F 7321 in cereal grain and/or straw in order to confirm the validity of the supervised trials data on this metabolite in those commodities. The study of the storage stability of cereal grain metabolites is no longer an absolute requirement. The Meeting was informed that freezer storage stability studies for flusilazole metabolites in cereals could be available for the 1993 JMPR.

A re-submitted study of soil leaching gives additional support to the 1989 JMPR conclusion that flusilazole *per se* is not readily leached from soils. The Meeting was informed that final reports of interim soil studies could be provided for the 1993 JMPR.

As requested, the Meeting received additional explanations of the reported differences between the ruminant and poultry metabolism studies reviewed by the 1989 JMPR. Differences were attributed to variations between species, with more extensive metabolism in poultry than in ruminants. It was suggested that there is little evidence that the additional metabolites identified in poultry metabolism studies occur in ruminants. It appeared that the metabolism had been studied in more detail in hens, but the Meeting could not conclude definitely from the information available that metabolism is more extensive in poultry than in ruminants. It could not be concluded, therefore, that all uncertainties about the metabolism of flusilazole in animals had been removed. Submission of one hen metabolism study cited, but not provided (Smyser, 1990), may help to remove some of the remaining uncertainties.

Even with some uncertainties remaining however, in view of the new information provided to supplement that previously available and the expectation that no residues of flusilazole *per se* would occur above the limit of determination in animal food products from the use of flusilazole according to GAP, the Meeting tentatively concluded that the metabolism of flusilazole in animals is reasonably well understood. Submission of the 1990 hen metabolism study (Smyser, 1990) is needed for further clarification. The Meeting was informed that this could be provided for the 1993 JMPR.

The Meeting was informed that no additional work is planned or in progress to provide the information on residues in rape seed oil, sugar beet pulp and molasses, or those occurring in commerce or at consumption, which were considered desirable by the 1989 JMPR.

FURTHER WORK OR INFORMATION

Required (by 1993)

Information on GAP and additional supervised trials data (including data on major metabolites) for nectarines and peaches reflecting that GAP from additional countries.

Desirable

1. Additional information on GAP for flusilazole on grapes in Europe, including information on the number of applications permitted.

2. Details of storage conditions (e.g. sample sizes, temperature, containers, whole grain or extract, relevance to storage conditions of field trials samples) and analyses (sample chromatograms) in the wheat grain freezer storage stability study (Guinivan, 1987).

3. Information on the stability of flusilazole metabolites (especially IN-F7321) in cereal grains and/or plant parts under freezer storage conditions (from 1989 JMPR).

4. Submission of the hen metabolism study cited but not provided (Smyser, 1990).

5. Information on residues of the major flusilazole metabolites (especially IN-F7321, the silanol) in processed fractions of cereal grain from field-treated cereal with measurable grain residues.

6. Submission of final reports of the interim soil studies reviewed by the 1989 JMPR (Stadalius, 1986; Fujinari, 1986b) (from 1989 JMPR).

4.17 GLUFOSINATE-AMMONIUM (175)

Ammonium 4-[hydroxy(methyl)phosphinoyl]-DL-homoalaninate.

Glufosinate-ammonium was considered for the first time by the present Meeting. It is a non-selective herbicide used as a desiccant and for weed control with a contact and systemic effect on mono- and dicotyledonous weeds.

TOXICOLOGY

The toxicokinetics of glufosinate-ammonium were investigated in rats and dogs as well as in livestock (goats and hens). The substance was rapidly excreted in all test species regardless of the route of administration. About 80-90% of an oral dose of glufosinate-ammonium remained unabsorbed and was eliminated unchanged in the faeces over 48

hours, while about 10-15% was eliminated in the urine.

The main metabolite of glufosinate-ammonium found in urine and in faeces was 3-[hydroxy(methyl)phosphinoyl]propionic acid[v]. Its half-life was 6-7 hours in vivo. Rats given a single oral dose of 20 mg/kg bw 3-[hydroxy(methyl)phosphinoyl]propionic acid excreted 92% in the urine and 3.5% in faeces after 4 days.

Glufosinate-ammonium competitively inhibits glutamine synthetase in mammals. However, even at high (sublethal) doses, glutamate, ammonia and glutamine levels in brain, liver and kidney tissues were unaffected. No effect was seen on enzymes which have glutamate as a substrate nor on the metabolism of amino acids, glutathione or carbohydrates. The substance did not impair the oxidative metabolism in mitochondria *in vitro*.

The compound showed slight to moderate acute oral toxicity in rats, mice and dogs, with the last being the most sensitive species.

Short-term toxicity studies were performed in rats, mice and dogs. In mice, the NOAEL was 80 ppm, equal to 17 and 19 mg/kg bw/day in males and females respectively, based upon increased plasma potassium levels at the next highest dose (67 mg/kg bw/day). In rats, effects on absolute kidney weights were seen at dose levels as low as 0.52 mg/kg bw/day. These effects on kidney weight were not found in the long-term bioassay in rats. In dogs, the NOAEL was 4.5 mg/kg bw/day, based on decreased body weight at higher doses. CNS excitation was seen only in dogs.

When 3-[hydroxy[methyl]phosphinoyl]propionic acid, the primary metabolite of glufosinate-ammonium, was administered in the diet to rats for 28 days at concentrations of 50-5000 ppm, the NOAEL was 2500 ppm, equal to 280 mg/kg bw/day. An increase in liver weight was seen in the high-dose females. Hepatic glutamine synthetase was unaffected by treatment.

Glufosinate-ammonium was not teratogenic in rats or rabbits. The NOAELs for maternal and embryo/fetal toxicity was 6.3 mg/kg bw/day in rabbits and 2.2 mg/kg bw/day in rats.

Glufosinate-ammonium was not carcinogenic in long-term/carcinogenicity studies in rats and mice. In mice fed 0, 20, 80, or 160 ppm (males) and 0, 20, 80, or 320 ppm (females), the NOAEL was 80 ppm (equal to 11 mg/kg bw/day), with increased male mortality at higher dietary concentrations. In rats fed 0, 40, 140 or 500 ppm, the NOAEL was 40 ppm (equal to 2.1 mg/kg bw/day) with increased kidney weight at 140 ppm. Additional effects noted at higher doses were a reduction in glutathione level in liver and blood and significant increases in renal weight.

In a two-generation study in rats the only effect on

reproduction was a reduction in litter size in animals fed 360 ppm glufosinate-ammonium. The NOAEL was 120 ppm, equivalent to 6 mg/kg bw/day.

After reviewing the available *in vitro* and *in vivo* genotoxicity data, it was concluded that there was no evidence of genotoxicity.

The ADI was based upon the NOAEL determined from the long-term study in rats, using a 100-fold safety factor.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 80 ppm in the diet, equal to 11 mg/kg bw/day
Rat: 40 ppm in the diet, equal to 2.1 mg/kg bw/day
Rabbit: 6.3 mg/kg bw/day
Dog: 4.5 mg/kg bw/day

Estimate of acceptable daily intake for man

0-0.02 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

1. Further observations in humans.

2. Clarification of the biological significance of the increased renal glutamate synthetase activity observed in rats.

RESIDUE AND ANALYTICAL ASPECTS

Information was provided on residues from supervised trials, in which the compound was used as a desiccant on potatoes, rape, sunflowers, peas, beans, soya beans, alfalfa, cotton, lentils, wheat and barley and for weed control on pome fruit, stone fruit, citrus fruit, bananas, grapes, kiwifruit and soya beans. In all trials residues were determined as the parent compound and its main metabolite 3-[hydroxy(methyl)phosphinoyl]propionic acid[4]. When used as a desiccant residues were usually present and at levels up to 2 mg/kg. Residues from applications for weed control are always low. Both the application rate and the PHI seem to have only a limited influence on the residue levels. When used as a desiccant on potatoes, the residue level appears to be dependent on the degree of senescence of the plant.

In animal feeding studies on lactating cows and laying hens, residues were present in milk and eggs only when the feed contained an unrealistically high content of the compound and its main metabolites. No residues were detectable in the meat, and one sample of fat showed a residue of the parent compound near the limit of determination.

Metabolic or degradation studies were carried out on plants (soya beans, apples, maize, potatoes, lettuce and vines), animals (lactating goats and poultry), soil and water. ^{14}C-glufosinate-ammonium labelled at 3,4C was used in all

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[4]The name 3-methylphosphinico-propionic acid was used in reports provided to the Meeting.

experiments. All studies showed the general degradation steps of deamination and subsequent decarboxylation to form the main metabolite 3-[hydroxy(methyl)phosphinoyl]propionic acid. In plants further metabolism mainly occurred by complete degradation of the molecule to compounds which were incorporated into natural plant constituents. No other metabolites were identified in plants: if present, the levels were too low for identification.

In goats, 97% of the total radioactivity was recovered in urine and faeces. In milk, tissues and organs, residues consisted exclusively of 3-[hydroxy(methyl)phosphinoyl]propionic acid. Similar results were obtained when the compound was administered to laying hens.

In soil the degradation rate was dependent on the initial concentration applied to the soil and the soil type. The qualitative degradation route in all soils was via 3-[hydroxy(methyl)phosphinoyl]propionic acid and 2-[hydroxy(methyl)phosphinoyl]acetic acid. Other compounds appeared as traces. The total mineralization of glufosinate-ammonium to CO_2 after 120 days amounted to 20-60% of the applied radioactivity, depending on the soil type. In water, degradation was dependent on the presence of micro-organisms.

On the basis of the data on residues from supervised trials the Meeting concluded that the residue levels listed in Annex I are suitable for use as MRLs. The limits refer to the sum of glufosinate-ammonium and 3-[hydroxy(methyl)phosphinoyl]propionic acid, expressed as glufosinate (free acid).

FURTHER WORK OR INFORMATION

Desirable

1. Analytical methods for determining residues in plants containing vegetable oils, and in meat, milk and eggs.

2. Information on GAP in the use of glufosinate-ammonium as a desiccant on grains, peas and beans.

4.18 HEPTACHLOR (043)

TOXICOLOGY

An ADI of 0 - 0.0005 mg/kg bw was allocated for heptachlor by the JMPR in 1970.

Heptachlor is well absorbed through the GI tract and metabolized to a large extent to heptachlor epoxide and minor

metabolites. Heptachlor epoxide has been shown to accumulate in adipose tissue, and to cross the placenta, but it was not found in the brain. In rats, the major route of elimination is via the faeces.

In both short- and long-term studies in dogs, rats, and mice, the liver was found to be the target organ. In a 30-day feeding study in mice at dietary concentrations of 0, 1, 5, 10, 25 or 50 ppm, histopathology findings indicated that males at 5 ppm or above and females at 10 ppm or above had enlargement of centralobular and midzonal hepatocytes. The severity was dose-related. Based upon these results, the NOAEL was 1 ppm, equivalent to 0.15 mg/kg bw/day.

Several long-term/carcinogenicity studies in rats were reviewed, but the majority of them had severe methodological limitations. In one study, rats received time-weighted dietary concentrations of 39 or 78 ppm (males) and 26 or 51 ppm (females)of heptachlor for 80 weeks. On the basis of decreased body-weight in high-dose males and increases in mortality in high-dose males and females, the NOAEL was 26 ppm, equivalent to 1.3 mg/kg bw/day. Deficiencies in this study precluded proper evaluation of the carcinogenic potential of heptachlor in rats.

In a 2-year feeding study, dogs fed heptachlor epoxide at dietary concentrations of 0, 1, 3, 5, 7 or 10 ppm, exhibited an increase in liver weight at 10 ppm and an increase in the incidence of liver histopathological changes at 3 ppm and above. The histopathological changes were enlargement and vacuolation of centralobular or scattered hepatocytes. Similar histological changes persisted through six months of the recovery period. The NOAEL based upon these findings was 1 ppm, equivalent to 0.025 mg/kg bw/day.

Heptachlor/heptachlor epoxide is carcinogenic in mice; two studies demonstrated an increase in liver tumour incidence in male and female Charles River CD-1 and $B_6C_3F_1$ mice.

Heptachlor/heptachlor epoxide also caused a marginal increase in the incidence of hepatocytomegaly in all treated CD-1 mice; a NOAEL was not established in this study.

In a 2-generation reproduction study in dogs at dietary concentrations of 1, 3, 5, 7, or 10 ppm of heptachlor epoxide, there was an increase in mortality of F_2 pups at 3 ppm and above. The NOAEL based on this finding was 1 ppm.

The available epidemiology studies have not shown a clear relationship between any effects in humans and exposure to heptachlor.

After reviewing the available *in vitro* and *in vivo* short-term test data, it was concluded that, although it can interfere with intercellular communication, heptachlor is not genotoxic.

Many studies available for evaluation were conducted more than 20 years ago and have severe deficiencies. Because of these deficiencies, its carcinogenicity in mice and its ability to bioaccumulate, the Meeting recommended that heptachlor should not be used directly on food crops and its use in the production of food commodities should be phased out. Because of its environmental persistence it is found as a contaminant in food commodities. The Meeting therefore maintained an ADI, basing it on the NOAELs derived from studies in dogs. However, recognizing the inadequacy of the data base, the Meeting increased the safety factor to 200-fold. This ADI will provide a guideline for assessing the significance of dietary exposure to heptachlor residues.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Rat: 26 ppm, equivalent to 1.3 mg/kg bw/day
Dog: 1 ppm, equivalent to 0.025 mg/kg bw/day (reproduction study)
1 ppm, equivalent to 0.025 mg/kg bw/day (2-year study)

Estimate of acceptable daily intake for humans

0-0.0001 mg/kg bw

RESIDUE AND ANALYTICAL ASPECTS

Heptachlor has been evaluated several times by the JMPR. The 1987 Meeting noted that all the limits were Extraneous Residue Limits (ERLs).

The 1990 CCPR postponed consideration of the possible withdrawal of the ERL for vegetables for one year, awaiting further data.

GAP and monitoring data from the manufacturer and several countries were provided to the Meeting. Heptachlor is used, mainly as a soil or seed treatment, on cotton, sugar cane, sunflower, citrus, coffee, oil palm, nut trees, bananas, pineapples and cereals (wheat, barley, maize, rye, oats, millet and sorghum) in tropical and sub-tropical areas. It is used against ants, termites, wireworms, cutworms, bollworms, seedling maggots and flea beetles. No registered uses on vegetables were reported.

In Canadian monitoring data from 1984 to 1989 residues of heptachlor, including the metabolite heptachlor epoxide, were detected in only a few commodities, namely beef, beef-fat, goose, lamb, milk, pork, pork-fat, carrots and cucumbers. Except in milk, where residues up to 0.007 mg/kg were found,

no residues exceeded the Extraneous Residue Limits. Most of the commodities were totally free from detectable residues.

Additional monitoring data were provided from the USA (1988, 1989 and 1990) by the FDA. Residues occurred in several crop samples, e.g. carrots (4 samples), celery (1), parsely root (1), parsnip (1), potato (4), squash (15), zucchini (5), pumpkin (1). Only five samples exceeded the ERL of 0.05 mg/kg for vegetables (squash 0.07, 0.12, zucchini 0.08, 0.16 and parsley root 0.08). The FDA reported that their sampling coverage extended to approximately 17,000 - 20,000 commercial shipments (domestic and imported) of food each year. In the USFDA Total Diet Study for 1988, 1989 and 1990, intakes of heptachlor (and its epoxide) were respectively 0.0017, 0.0008 and 0.0005 ìg/kg body wt/day for a 14-16-year-old male, and thus show a decrease over the years.

In Swedish monitoring data on squash, of 76 samples analysed for heptachlor epoxide only one (at a level of 0.07 mg/kg) exceeded the ERL of 0.05 mg/kg.

The Meeting recommended that the current ERLs listed in Annex I should be converted to Temporary ERLs pending the receipt of further information.

FURTHER WORK OR INFORMATION

Required (by 1993)

Monitoring data and information on the possible occurrence of residues in food in commerce or at consumption (see 1990 report, section 2.7, for details of type of information required).

4.19 HEXACONAZOLE (17O)

RESIDUE AND ANALYTICAL ASPECTS

Concern was expressed at the 23rd (1991) Sessivon of the CCPR that the 0.05 mg/kg maximum residue level estimated for hexaconazole on bananas might not be high enough to accommodate GAP. The JMPR was requested (ALINORM 91/24A, para 231) to re-examine the data.

It appeared that the 1990 JMPR estimate was based on the observation that residues in 13 of the 14 samples reflecting GAP were not greater than 0.05 mg/kg and most were well below that level. Because there was no compelling reason to conclude that the highest value of 0.07 mg/kg resulting from GAP was not a valid value, and because the distribution of values up to that level was fairly even, the Meeting concluded that a maximum level of 0.1 mg/kg limit could be estimated.

4.20 HEXYTHIAZOX (176)

(4RS,5RS)-5-(4-chlorophenyl)-N-cyclohexyl-4-methyl-2-oxo-1,3-thiazolidine-3-carboxamide.

Hexythiazox was considered for the first time by the present Meeting. It is a specific acaricide used in controlling many kinds of phytophagous mites. It acts as an ovicide, larvicide and nymphicide. It is formulated as 5%, 10% and 50% wettable powders and 5% and 10% emulsifiable concentrates.

TOXICOLOGY

After oral administration to rats, hexythiazox was eliminated rapidly, two-thirds via the faeces and one-third via the urine. Low levels were recovered in the tissues and organs, with the highest concentrations in the fat, liver, adrenals and in the gastrointestinal tract and its contents. In the faeces about 20% was excreted as the parent compound. Many metabolites were found in the urine and faeces, although only 10% of those in the urine and 50% of those in the faeces could be identified. Metabolism occurs via oxidation, and finally cleavage, of the cyclohexane ring.

The compound shows low acute toxicity in the species examined. WHO has classified hexythiazox as unlikely to present acute hazard in normal use.

Short-term administration of hexythiazox to rats and dogs revealed the liver and the adrenals as target organs. In a 90-day study in rats the NOAEL was 70 ppm, equal to 4.9 and 5.3 mg/kg bw/day for males and females respectively. In a one-year study in dogs the NOAEL was 100 ppm, equal to 2.9 mg/kg bw/day in males and 3.2 mg/kg bw/day in females.

In a 2-year feeding study in mice at dietary concentrations of 0, 40, 250 or 1500 ppm there was an increased incidence of liver nodules in both sexes at 1500 ppm. The incidences of liver adenomas and hepatocarcinomas was increased in females at 1500 ppm. Three haemangiopericytomas in the liver were observed in males at 1500 ppm. These were subsequently re-evaluated as hepatoblastomas. At the lowest concentration of 40 ppm, equal to 6.7 and 8.4 mg/kg bw/day in males and females respectively, reduced body-weight gain in male animals was observed. A NOAEL was not established.

In a long-term carcinogenicity study in rats at dietary concentrations of 0, 60, 430 or 3000 ppm, there were no treatment-related increases in neoplasias. There was a reduction in body-weight gain and an increase in some organ weights at 430 ppm. The NOAEL was 60 ppm, equal to 3.2 and 4.2 mg/kg bw/day for males and females respectively.

In a 2-generation, 2-litters-per-generation reproduction study in rats at 0, 60, 400 or 2400 ppm, no adverse effects on reproduction were found. The NOAEL was 60 ppm, equivalent to 3 mg/kg bw/day, based on increased liver and kidney weights at 400 ppm.

Maternal toxicity (reduced weight gains) and embryotoxicity (delayed development) were observed in a teratogenicity study in rats at doses of 0, 240, 720, or 2160 mg/kg bw/day. The NOAEL was 240 mg/kg bw/day. In a teratogenicity study in rabbits at doses of 0, 120, 360 or 1080 mg/kg bw/day, slight embryotoxicity was observed at the highest dose. The NOAEL was 360 mg/kg bw/day. No teratogenic effects were observed in either species.

After reviewing all available *in vitro* and *in vivo* short-term tests on hexythiazox it was concluded that there was no evidence of genotoxicity.

An ADI was established which was based on NOAELs in the 2-year feeding and reproduction studies in rats and a 1-year study in dogs, using a 100-fold safety factor.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Rat: 60 ppm in the diet, equal to 3.2 mg/kg bw/day (2-year study)
Rat: 60 ppm in the diet, equivalent to 3 mg/kg bw/day

(reproduction study)
Dog: 100 ppm in the diet, equal to 2.9 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Hexythiazox is registered and used in 36 countries. It is mainly applied on orchard and fruiting vegetables, one or two applications, at a rate of 25-210 g ai/ha.

Extensive information on residues from supervised trials on apples, pears, peaches, cherries, citrus fruits, grapes, strawberries, cucumbers and tomatoes was available for evaluation. Some limited data were provided for several other crops.

The residue on various crops generally declined slowly: about 40-60% of the initial residue was detected 30 days after application. The residues on treated crops were low, ranging from not detected to 0.5 mg/kg at harvest.

In processing studies on grapes and citrus fruit, grape juice, wine and citrus pulp were all free from detectable residues (<0.05 mg/kg).

The fate of hexythiazox was investigated in plants, animals, soil and water.

In plants, translocation of hexythiazox was minimal. On the surface of the plants the active ingredient was degraded relatively slowly. During 30 to 90 days after application, unchanged hexythiazox was the major extractable residue with small amounts of metabolites containing the 4-chlorophenyl-2-oxothiazolidine moiety. When various crop samples were analyzed, the results were similar within the error of the analyses regardless of whether the parent compound or the total residue was determined.

In animals hexythiazox was metabolized more extensively than in plants, but the degradation pathways were similar. The predominant route of elimination was in the faeces. In a dairy cattle feeding study, the total residues in organs and milk were below the limit of detection (0.05 mg/kg).

In soil hexythiazox is finally degraded to carbon dioxide after elimination of the cyclohexane ring. The half-life of the

parent compound varied from 6 to 25 days, and half-lives of the des-cyclohexane compounds were between 12 and 28 days. The uptake of soil residues by rotational crops was low except by wheat. Hexythiazox was leached to a moderate extent.

Hexythiazox was not hydrolysed in water, but in a water/sediment system it was degraded by micro-organisms with a half-life of 42 days.

The photodegradation of hexythiazox on the soil surface under natural sunlight took place with a half-life of 116 days, while in water under a mercury lamp it was much faster with a half-life of 2.5 hours.

Storage-stability tests indicated that the residues in both field-treated and fortified samples were stable in chopped samples stored at -30°C, but some decomposition occurred in homogenized samples, especially in grapes.

Analytical methods have been developed to determine either the parent compound alone or the total residue containing the 4-chlorophenyl-2-oxothiazolidine moiety. The limits of determination in plant materials and soil were 0.01 mg/kg, in animal tissues and milk 0.05 mg/kg, and in water 0.0001 mg/l.

On the basis of the available information the Meeting estimated maximum residue levels for a number of commodities.

4.21 IMAZALIL (110)

TOXICOLOGY

Imazalil was evaluated by the JMPR in 1977, when a temporary ADI of 0 - 0.01 mg/kg bw was estimated. The compound was last re-evaluated in 1986, when an ADI of 0 - 0.01 mg/kg bw, based on a study in dogs, was allocated. Observations in humans were regarded as being useful to provide information valuable for the continued evaluation of the compound. Data in this area, as well as an additional dog study, were available to the Meeting.

In a 12-month study in dogs at dose levels of 0, 1.25, 2.5 or 20 mg/kg bw/day administered by capsule, a NOAEL of 2.5 mg/kg bw was determined. This was based on clinical signs, decreased body-weight gain, and increased liver weight at higher doses.

Imazalil was used in the therapy of alternariosis in a female patient unresponsive to conventional therapy. Oral administration was initiated at a dose of 50 mg daily and gradually increased to 1200 mg daily. For six months the drug was tolerated without evident toxicity. Measurements of serum concentrations over time found a short half-life with no

accumulation or effects on clearance after repeated administration. These findings are similar to those observed in rodents after the administration of imazalil.

An ADI was allocated on the basis of the NOAEL established for the newly evaluated study in dogs utilizing a 100-fold factor.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Rat: 100 ppm, equal to 5 mg/kg bw/day
Dog: 2.5 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Further observations in humans.

4.22 METHOMYL (094)

RESIDUE AND ANALYTICAL ASPECTS

Methomyl was reviewed by the JMPR in 1975-1978 and 1986-1990 and numerous maximum residue levels were estimated or revised. Although proposals for grapes (5 mg/kg), pome fruit (2 mg/kg) and cabbage (5 mg/kg) have been advanced to step 8 of the Codex procedure, additional information has been requested and submitted owing to some reservations on the proposed limits (See ALINORM 91/24A, para. 127).

In the case of grapes extensive new data have been received from the United States, reflecting GAP of 1 kg ai/ha and PHIs of 1 day for fresh grapes and 14 days for wine grapes. Maximum residues of 5.6 mg/kg after 1 day and 3.9 mg/kg after 14 days at GAP rates support the 5 mg/kg limit. This is consistent with the confirmation provided by the 1988 JMPR.

Concern has been expressed at the CCPR on the possibility of residues in wine resulting from the field use of methomyl on grapes. Recent studies in France indicate that no residues of methomyl are likely above the limits of determination of 0.05 mg/kg in grapes and 0.02 mg/kg in wine, must and lees, when the grapes are harvested 28 to 34 days after 2 to 4 treatments at 400 g ai/ha under the trial conditions and locations. When grapes

harvested one day after the last application were processed, residues in the wine and lees were about half those in the grapes, and in must about the same as in the grapes. These concentration factors can be used to estimate residues in wine resulting from other residue levels in grapes.

These results are relevant to other data reviewed by the Meeting which show residues in wine grapes (at the 14 day PHI for wine grapes) approaching the current 5 mg/kg MRL, although generally below 2 mg/kg. Residues of the order of 1 mg/kg and possibly 2.5 mg/kg are therefore possible in wine from grapes containing methomyl at the MRL level, but residues in grapes close to 5 mg/kg would not be likely to occur frequently and hence residues above 0.5 mg/kg in wine would be rare. The fact that residues in must were of the same order as those in grapes draws attention to the need for information on residues in ready-to-bottle grape juice. The Meeting was informed that consideration will be given to the possibility of developing data for grape juice during planned trials on grapes.

It should be noted that data summaries in earlier monographs did not distinguish between table and wine grapes.

Limited residue data (and summary information) reflecting GAP for pears with application rates of 0.28 mg/kg showed residues well below the CXL for pome fruit of 2 mg/kg and provide no basis for its revision. In view of the studies evaluated by the 1988 JMPR in which one residue exceeded the 2 mg/kg proposal for pome fruit and information that additional trials are planned, the Meeting recommended that the situation for pome fruits should be re-examined when relevant residue data and information on GAP become available. The Meeting was informed that additional trials data on apples as well as freezer storage stability studies on apples and grapes could be available for the 1993 JMPR.

Limited summary data showed methomyl residues in head cabbage resulting from a single 0.2 kg/ha application in one country of $\leq$0.5 mg/kg after 7 days. The submission was intended to demonstrate that the current 5 mg/kg CXL is too high. The Meeting noted that the 5 mg/kg limit had been estimated on the basis of GAP which included multiple applications up to 1 kg/ha and a 1-day PHI. The 1988 JMPR had confirmed the need for 5 mg/kg to accommodate this GAP which was verified as still current by the 1989 JMPR. The present Meeting agreed that the new summary data suggested (and previously provided data also supported the view) that a limit lower than 5 mg/kg would be adequate for longer PHIs, but pointed out that such a lower limit would not allow for the shorter PHIs which are still GAP.

The analytical method used for the development of methomyl data on pears and grapes was provided and is based on determination by HPLC with UV detection. It determines methomyl *per se* as compared with GLC methods in which residues are converted to the oxime.

On the basis of current information on GAP and new and previously reviewed residue data, the Meeting recommended that revision of the CXLs for pome fruit, grapes and head cabbages should not be proposed at this time, but that the situation for pome fruit and grapes should be re-examined when new residue data from planned or current trials and relevant information on GAP become available.

FURTHER WORK OR INFORMATION

Desirable

1. Submission of freezer storage stability studies on grapes and pears reported to be in progress.

2. Submission of additional residue trials data on apples when available.

3. Information on methomyl residues in ready-to-bottle grape juice resulting from maximum GAP applications to wine grapes harvested at the GAP PHI.

4.23 MONOCROTOPHOS (054)

TOXICOLOGY

Monocrotophos was previously evaluated by the JMPR in 1972 and in 1975. An ADI of 0 - 0.0006 mg/kg bw was allocated in 1975.

In a 13-week study in rats at dietary concentrations of 0, 0.1, 0.25, 0.5, 2 or 8 ppm, the NOAEL was 0.5 ppm, equivalent to 0.025 mg/kg bw/day, based on brain acetylcholinesterase inhibition at 2 ppm.

In a 2-year study in mice at dietary concentrations of 0, 1, 2, 5 or 10 ppm a NOAEL could not be established because brain acetylcholinesterase inhibition was detected at the lowest dietary concentration (approximately 20% inhibition). There was no evidence of a treatment-related carcinogenic effect.

In a 2-year study in rats at dietary concentrations of 0, 0.01, 0.03, 0.1, 1.0 or 10 ppm the NOAEL was 0.1 ppm, equivalent to 0.005 mg/kg bw/day, based on brain acetylcholinesterase inhibition at the next higher dose. Again, there was no evidence of carcinogenicity.

Monocrotophos did not cause delayed neuropathy in hens.

In a multigeneration reproduction study in rats at dietary concentrations of 0, 0.1, 1, 3, or 10 ppm, the NOAEL was 1 ppm, equivalent to 0.05 mg/kg bw/day, based on toxicity in pups seen in the F_2 generation at 3 ppm.

In a teratology study in rats at doses of 0, 0.3, 1 or 2 mg/kg bw/day, the NOAEL was 0.3 mg/kg bw/day for both maternal toxicity and teratogenicity. There was a slightly increased incidence of malformed and/or misshapen brain at all dose levels (0.3 mg/kg bw/day included). A dose-effect relationship for this uncommon malformation was lacking and historical control data were not available.

Substantial variations in the purity of the test material used in the genetic toxicology studies hampered thorough evaluation for genotoxicity. When purity was at the level of technical grade monocrotophos (78%) there were significant responses in tests for mutagenicity in bacteria and sister chromatid exchange in Chinese hamster ovary cells; *in vivo* studies for clastogenic activity were negative.

The Meeting concluded that the significance of the brain malformations observed in the teratology study in rats warranted clarification, as did the genotoxic potential of monocrotophos. Accordingly, the Meeting recommended that monocrotophos be reviewed in 1994.

An ADI was allocated on the basis of the 2-year study in rats using a 100-fold safety factor.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse:< 1 ppm in the diet, equivalent to < 0.15 mg/kg bw/day
Rat: 0.1 ppm in the diet, equivalent to 0.005 mg/kg bw/day

Estimate of acceptable daily intake for humans

0-0.00005 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

1. Genotoxicity studies, known to exist, with commercial and purified monocrotophos.

2. Historical control data on the incidence of brain malformations in rats at the relevant laboratory.

RESIDUE AND ANALYTICAL ASPECTS

At the 21st (1989) Session of the CCPR a re-evaluation of monocrotophos was requested (ALINORM 89/24A, Appendix V). The Meeting has received information on GAP in many countries and reports of supervised trials on crops for which MRLs are established (citrus fruit, beans, cabbage, onions, potatoes, maize, soya beans, tomatoes, coffee beans and cotton seeds) and on other crops (bananas, grapes, egg plants, Chili peppers, watermelons, mangoes, cereal grains, rice, peanuts, sunflowers, sugar cane, cacao beans and tea).

Additional information was also received on metabolic studies on monocrotophos in plants and soil and on investigations of adsorption and leaching in soil. The effect on residues of processing was studied in citrus, sunflower seeds and tea.

The new data on beans, cabbage, onions, potatoes, tomatoes, maize, soya beans, coffee beans and cotton seed were generally in agreement with data evaluated at earlier Meetings, and supported existing CXLs.

Residues from trials on egg plants, Chili peppers, watermelons, wheat, peanuts and sugar cane enabled the Meeting to estimate maximum residue levels, but more data from trials and/or information on relevant approved uses are needed to propose residue limits for bananas, grapes, mangoes, barley, oats, sunflower seeds and cacao.

New studies were carried out on the metabolism of monocrotophos in plants and its degradation in soil. The degradation products previously found were O-desmethyl-monocrotophos, dimethyl phosphate and N-hydroxymethyl-monocrotophos. Maize grains and fodder were analyzed for trimethyl phosphate at various intervals after treatment but residues of this compound were not detectable. Residues of N-hydroxymethyl-monocrotophos, which occurs as a glycoside in crops, were determined in maize and sugar cane. Residues in the edible parts of crops were not detectable but were present in foliage and fodder.

The aerobic and anaerobic degradation of monocrotophos was studied in three different soil types, showing half-lives for monocrotophos of 2.5 - 5 days. The degradation products under aerobic conditions were N-hydroxymethyl-monocrotophos and N-methylacetoacetamide, but monocrotophos and its metabolites were rapidly mineralized to CO_2. Degradation was slower under anaerobic conditions. Adsorption and leaching experiments showed a correlation between the organic matter content of the soil and adsorption. Adsorption is weak and most of the monocrotophos added to the soil was leached, whereas the degradation products were less mobile.

On the basis of the data on residues from supervised trials,

the Meeting concluded that the residue levels listed in Annex I are suitable for use as MRLs.

FURTHER WORK OR INFORMATION

Desirable

1. Information on GAP, especially for grapes and rice, from countries where residue trials have been carried out.

2. Additional supervised trials on bananas, mangoes, barley, oats, sunflowers and cacao. The analyses of bananas and mangoes should include the determination of residues in the whole fruit.

4.24 PARATHION (058)

RESIDUE AND ANALYTICAL ASPECTS

Parathion was first evaluated in 1965. When the new Codex Classification of Foods and Animal Feeds was introduced information was requested to enable general commodity descriptions such as "Fruit" and "Vegetables" to be replaced by more specific descriptions (ALINORM 91/24A, paras 238, 252).

Parathion is a very widely used insecticide with registrations in many countries for foliar application to a wide range of horticultural and agricultural crops. It is no longer used in New Zealand and there are no current authorised uses in Germany.

Most uses in the USA were voluntarily cancelled in September 1991. Uses remained on alfalfa, barley, canola, maize, cotton, sorghum, soya beans, sunflower and wheat.

Information was provided on residues from supervised trials in the USA, Germany and Portugal. For many of the commodities it was not possible to estimate maximum residue levels because the conditions in the supervised trials did not match current GAP.

Residue data from supervised trials were supplied on grapefruit, lemons, oranges, tangelos, apples, pears, cherries, plums, apricots, prunes, currants, grapes, strawberries, blackberries, olives, leeks, broccoli, cabbages, cucumbers, tomatoes, peppers, sweet corn, lettuce, spinach, beans, peas, soya beans (dry), potatoes, celery, maize, rice, sorghum, almonds, cotton seed, sunflower seed, legume animal feeds and the straw, fodder and forage of cereal grains.

A trial on lemons in Portugal reported residues of 0.22

mg/kg 21 days after spraying.

In Portugal, two trials on tangelos produced residues of 0.34 and 0.47 mg/kg 21 days (the recommended PHI) after spraying, and two trials on oranges showed residues of 0.38 mg/kg after treatment according to GAP.

Parathion residues in apples ranged up to 0.05 mg/kg in a series of trials in Germany in the 1960s (PHI 14 or 15 days).

Trials in Portugal suggest that when parathion is used according to GAP, residues in olives should not exceed 0.5 mg/kg. Parathion residues in crude olive oil were on average 4.5 times the level in the olives.

Residues in leeks were not detectable (<0.01 mg/kg) when parathion was used according to Belgian GAP. Data were limited. Neither parathion nor paraoxon was detected (<0.05 mg/kg) in beans (dry) and soya beans (dry) in supervised trials in the USA.

Three trials from Germany in 1977 suggest that parathion residues in potatoes treated according to GAP in The Netherlands should not exceed 0.02 mg/kg.

The use of parathion on maize in the USA according to GAP should not produce residues exceeding 0.1 mg/kg.

Supervised trials in the USA on sorghum suggest a maximum residue level of 5 mg/kg. Paraoxon was detected in every sample.

Parathion residues in cotton seed ranged up to 0.97 mg/kg in supervised USA trials, but residues in sunflower seed were not detected (<0.05 mg/kg). Sunflower seed consisted of the whole commodity.

Copious trials data were provided from the USA on residues in animal feeds. The results of animal transfer studies would need to be assessed before MRLs could be estimated on the feeds and animal commodities.

Information on the fate of parathion and paraoxon during the processing of citrus fruit, apples, grapes, cereals and cotton seed was made available to the Meeting.

Residues of parathion, an oil-soluble compound, were very high in citrus oils. Residues in lemon peel were of the same order as those in the lemons. Parathion residues in citrus juices were much lower than those in the whole fruit, while paraoxon was not detectable (<0.05 mg/kg).

In apple juice produced from peeled and cored apples, residues of parathion and paraoxon were not detectable (<0.05 mg/kg). Residues in juice and pomace were much higher when the peel was included.

Residues in grapes declined during the drying process to produce raisins. During grape crushing, residues were retained in the pomace fraction and depleted in the juice. Residues of parathion were not detected (<0.01 mg/kg) in wine made from grapes containing up to 0.26 mg/kg parathion.

Parathion residues in maize processing fractions were not substantially different from those in the maize grain.

Residues in oat flour, bran and rolled oats were 30-70% of the residues in the oat grain.

Parathion and paraoxon residues in sorghum bran were higher than in the grain, while residues in the flour were lower.

Parathion residues in all the processed fractions of cotton seed were lower than those in the seed. The relation between the residues in crude oil, meal and refined oil is not clear: two studies provided quite different processing ratios.

Monitoring data on parathion residues in fruit and vegetables were provided from Thailand, Tunisia and the USA. Generally parathion was detected in only a few per cent of the samples.

Parathion and paraoxon residues can be measured by relatively simple GLC methods.

FURTHER WORK OR INFORMATION

Desirable

Animal transfer studies are needed before maximum residue levels can be estimated on animal feeds.

4.25 PARATHION-METHYL

RESIDUE AND ANALYTICAL ASPECTS

Parathion-methyl was scheduled for evaluation at the 1991 JMPR, and residue data were received from Germany. The Meeting was aware that residue data had recently been generated in the USA under a re-registration programme. It was expected that reports would be available by the end of 1991.

The Meeting decided to await the new data and evaluate all available parathion-methyl information at one time.

4.26 PERMETHRIN (120)

RESIDUE AND ANALYTICAL ASPECTS

Permethrin has been evaluated at each JMPR from 1979 to 1989. At the 1980 Meeting it was reviewed as a grain protectant for post-harvest treatment, and TMRLs of 2 mg/kg for cereal grains and wheat flour (wholemeal), 0.5 mg/kg for wheat flour (white), and 10 mg/kg for wheat bran were recommended.

At the 1988, 1989, 1990 and 1989 Sessions of the CCPR, the JMPR was requested to evaluate permethrin residue studies in commercial-scale milling. The Australian delegation agreed to provide these data. Data from supervised processing trials, mainly carried out in Australia, were provided to the Meeting which enabled it to estimate new maximum residue levels.

Permethrin is authorized or registered for use as a grain protectant in Australia, some African countries such as Cameroon, Ivory Coast, Kenya, Malawi, Tanzania, and Sudan, and European countries such as Spain and Poland. Recommended maximum application rates range from 1 to 3 g ai/t.

The recommended application rate in Australia is 1 g ai/t. Processing trials were carried out at 1 g ai/t and an exaggerated rate of 1.5 g ai/t. In each trial approximately 200 tonnes of wheat were treated. Two commercial flour mills participated in the trials. The methods of residue analysis used for the trials

were simple and accurate, with a limit of determination of 0.01 mg/kg. The mean recovery from wheat treated at 0.2 mg/kg (6 samples) was 104% (CV 9%)

The Meeting concluded that the new data from large-scale commercial trials reflecting current GAP were more reliable for estimating maximum residue levels than previously provided data from small-scale trials. The Meeting estimated maximum levels for wheat flour, wheat wholemeal and wheat bran, unprocessed, of 0.5, 2 and 5 mg/kg respectively, to replace the current TMRLs. A new maximum residue level of 2 mg/kg was estimated for wheat germ.

FURTHER WORK OR INFORMATION

Desirable

1Additional residue data from the post-harvest treatment of cereals with permethrin from countries where GAP permits application rates greater than 1.5 g ai/t.

2. Additional monitoring data and information on the possible occurrence of residues in grain in commerce or at consumption.

4.27 PHORATE (112)

RESIDUE AND ANALYTICAL ASPECTS

Phorate was reviewed by the JMPR in 1977, 1982, 1983, 1984, 1985 and 1990 (for residues in the underlined years). In response to discussions and requests for data at the 23rd Session of the CCPR (ALINORM 91/24A, paras. 145, 147, 148) information was provided to the Meeting on maize, sweet corn, peanuts and potatoes, including processing information on potatoes. No additional information was provided on carrots.

The Meeting reviewed additional data on peanuts because it had been suggested at the CCPR that the 0.05 mg/kg limit was too low. In view of the validated limit of determination of 0.05 mg/kg with control values well below that level in the studies, the apparent variability in residue levels, the occurrence of residues of 0.05 mg/kg from applications below the maximum allowed by GAP reviewed by the 1977 JMPR and maximum residues of the order of 0.08 mg/kg from uses according to GAP, the Meeting concluded that the current MRL of 0.05 mg/kg may be exceeded on some occasions from GAP.

The Meeting confirmed the 1990 estimate of 0.1 mg/kg (fresh wt) for maize fodder. New data on residues in sweet corn plants indicate that the 0.1 mg/kg limit for maize forage (fresh wt.) may be exceeded on occasion. Data reflecting GAP indicate apparent residues of <0.01 mg/kg in maize grain and up to 0.03 mg/kg in

sweet corn. While estimates of dietary intake for field corn should be based on 0.01 mg/kg levels, relatively high control values (0.004 mg/kg average), average recoveries of 131.7% (105.6-150.9%) at 0.01 mg/kg fortification levels where control values were not subtracted, and the appearance of sample chromatograms all suggest that a 0.05 mg/kg limit of determination is reasonable for maize grain. Limits of determination of 0.02 mg/kg for sweet corn (kernel + cob) and 0.1 mg/kg for maize forage (fresh wt.) are reasonable.

Additional small-scale processing studies on maize provided to the Meeting allowed the estimation of approximate concentration factors for total phorate-related residues in processed fractions: meal (3X); crude oil (4X, from expeller); crude oil from solvent extraction (5X); refined oil (6X); deodorized oil (<1X); grits (<1X); flour (2X); hulls (12X); expeller presscake (<1X) and solvent extracted presscake (1X).

Extensive and relatively detailed summary data from unsupervised uses of phorate on potatoes in Canada by farmers according to GAP show that most residues are $\leq$0.05 mg/kg with maximum residues up to 0.15, 0.16 and 0.27 mg/kg, although the latter value was suspect. This is consistent with earlier findings and the 1990 JMPR estimate of a maximum residue of 0.2 mg/kg. The Meeting confirmed the 1990 estimate.

A potato cooking study according to good laboratory practices showed residue reductions of the order of 77-87 % for baking, 43% for French frying and 45-50% for boiling (78% for peels). There was no evidence of residue reduction resulting from washing, not unexpectedly for a systemic pesticide. It could not be determined from the data provided whether peeling lowered residue levels, although reduction by this route would not necessarily be expected for a systemic pesticide such as phorate.

Processing of field-treated potatoes into chips, flakes and granules resulted in residue concentration in flakes (1.6 times) and granules (3.7 times), but not in chips. The Meeting was informed that two additional potato cooking studies and one additional potato processing study are being conducted: reports are expected in January 1992.

Results of studies of the stability of total phorate-related residues in processed corn meal and refined corn oil during freezer storage were highly variable, but suggest that residues are stable for a period up to 1 year.

FURTHER WORK OR INFORMATION

Desirable

1. Potato freezer storage stability study C-3005 cited in C-3520.

2. Analytical method M-1705 and its potato validation study C-2867 cited in C-3520, and method M-1620 and its potato validation study C-2710 cited in C-3291.

3. Method M-1672 and its corn oil/meal validation Report C-2908.1 cited in Report C-2996.

4. Recovery analyses reported in Report C-2996.

5. Submission of potato processing and cooking studies currently under way.

4.28 PROPICONAZOLE

RESIDUE AND ANALYTICAL ASPECTS

In response to a request of the 1990 CCPR (ALINORM 91/24, para 222), the Meeting reviewed the residue data on cereals summarized in the 1987 monograph and concluded that the maximum residue limit for cereals should be replaced by individual limits for oats, rye and wheat at or about the limit of determination. In view of the available data the limit for barley was replaced by a temporary estimate of 0.2 mg/kg. The Meeting did not have sufficient information to estimate maximum residue levels for maize or rice.

Additional residue data from supervised trials were provided on melons, peppers, rice and tomatoes, but were too limited to allow the estimation of maximum residue levels.

FURTHER WORK OR INFORMATION

Required (by 1993)

1. Residues measured as the parent compound on barley and rice from supervised trials carried out in accordance with current GAP (from 1987 JMPR)

2. Information on registered use patterns of propiconazole on barley and rice.

Desirable

Additional residue data on melons, peppers and tomatoes from trials carried out according to established GAP, to provide sufficient information to estimate maximum residue levels.

4.29 PROPOXUR (073)

RESIDUE AND ANALYTICAL ASPECTS

Propoxur has been evaluated several times by the JMPR, for the first in time in 1973. The 22nd (1990) CCPR decided to delete the MRL for vegetables if no information on GAP and residues is supplied.

Extensive new residue data from supervised trials on vegetables were provided to the Meeting. Data on GAP and monitoring data from several countries were also made available. On the basis of these data, together with those evaluated previously, the Meeting re-evaluated the whole vegetable group.

The compound is registered and used on vegetables in 11 countries, mainly as a wettable powder (500 g ai/kg) and an emulsifiable concentrate (200 g/l). The application rate varies between 0.2 and 3.00 kg/ha.

Residue data were obtained from trials on vegetables such as broad beans, common beans, garden peas, red cabbage, white cabbage, cauliflower, kale, kohlrabi, carrots, cucumbers, tomatoes, spinach, leeks and potatoes.

For legume vegetables supervised trials were carried out on broad beans, common beans and garden peas. Seven days after the last application residues in broad beans were all below the limit of determination (0.02 mg/g). In common beans residues are unlikely to exceed 1 mg/kg 3 - 10 days after the last application. Garden peas (fresh without pods) did not show any residues, but residues up to 0.07 mg/kg were found in pods after 11 days. In peas with pods residues are unlikely to exceed 0.05 mg/kg 7 - 10 days after the last application.

For brassica vegetables supervised trials were carried out on red and white cabbage, Savoy cabbage, cauliflower, kale and kohlrabi. The data on red and white cabbage, cauliflower and kale are insufficient to estimate maximum residue levels. The results of six trials on Savoy cabbage according to GAP in Germany would support an MRL of 0.5 mg/kg. Six trials on kohlrabi all showed residues below 0.2 mg/kg after 7 days (the PHI in Germany).

Supervised trials on fruiting vegetables were on cucumbers, peppers and tomatoes. The single result for peppers reported in the 1973 Evaluations is not sufficient to propose an MRL. Two glasshouse trials on cucumbers were reported in the 1973 Evaluations: three further outdoor trials from Germany support the assessment that three days after the last application residues are unlikely to exceed 0.1 mg/kg. All results for tomatoes (indoor and outdoor

use) show that after the shortest reported PHI of 3 days the residues are below 0.05 mg/kg.

For leafy vegetables supervised trials have been carried out on lettuce and spinach. Residues in lettuce 7 days after the last outdoor application or 14 days after indoor application are unlikely to exceed 3 mg/kg. In addition to the results already reported in the 1973 Evaluations, seven new trials for spinach were brought to the attention of the Meeting. Residues were well below 2 mg/kg seven days after the last application.

Some results for carrots were reported in the 1973 monograph. In a further 6 trials from Germany, residues in the carrots 10 days after the last application were all below limit of determination (0.02 mg/kg).

Taking into account the results of 12 available trials on leeks, the Meeting estimated a maximum residue level of 1 mg/kg based on a PHI of 7 days.

The results of 7 trials on potatoes brought to the attention of the Meeting show that residues are likely to be below the limit of determination (0.1 mg/kg).

The results of 9 trials on onions in Germany already summarized in the 1973 Evaluations were re-evaluated by the Meeting. Except for one trial where significant residues occurred and where the parchment skin was not removed before analysis, residues were all below the limit of determination.

The Meeting proposed that the MRLs for "Root and tuber vegetables" and "Vegetables" should be withdrawn because separate maximum residue levels for the individual crops could now be estimated.

Monitoring data were provided from Poland, Thailand and the USA. Residues were not detectable.

FURTHER WORK OR INFORMATION

Desirable

1. Additional results from supervised residue trials where a maximum residue level could not be estimated by the Meeting, e.g. head cabbage (except Savoy cabbage), cauliflower, kale and peppers.

2. Results of supervised residue trials on crops for which GAP is reported, e.g. artichokes and melons.

4.30 TRIAZOPHOS (143)

TOXICOLOGY

In 1986 the temporary ADI of 0 - 0.0002 mg/kg bw was extended pending the submission of a carcinogenicity study.

In a 52-week study in dogs, employing dietary concentrations of 0, 0.2, 0.4, 4 or 80 ppm triazophos, the only signs of reaction to treatment were associated with inhibition of plasma and erythrocyte cholinesterase activity. The NOAEL was 4 ppm (equal to 0.12 mg/kg bw/day), based on inhibition of plasma and erythrocyte cholinesterase activity and mortality at 80 ppm.

Long-term/carcinogenicity studies in rats and mice at dietary concentrations of 0, 3, 27 or 243 ppm and 0, 6, 30 or 150 ppm demonstrated that triazophos has no carcinogenic potential in either species. In rats an increased incidence of hyperplasia of the exocrine pancreas was observed at 27 and 243 ppm and inhibition of brain acetylcholinesterase in females at 243 ppm. The NOAEL was 3 ppm, equal to 0.17 mg/kg bw/day. In mice, slightly increased mortality at 150 ppm and inhibition of brain acetylcholinesterase in females at 150 ppm were observed. The NOAEL was 30 ppm, equal to 4.5 mg/kg bw/day.

In a two-generation reproduction study in rats at dietary concentrations of 3, 27 or 243 ppm triazophos, marked clinical signs, including mortality, decreased survival and reduced weight gain in pups were seen at 243 ppm. The NOAEL was 27 ppm, equal to 2-3 mg/kg bw/day.

There were two additional delayed neurotoxicity tests in hens. In the first, atropine and oxime antidotes were used with a dose of triazophos about 7 times the unprotected LD_{50} of 7.5 mg/kg bw. In the group treated with triazophos, high mortality was seen and only 4 hens survived to termination. Among these 4 hens, signs of ataxia were seen in 2 hens and histological lesions were seen in the nervous

tissue of 3 animals. In the second study, at lower doses (about twice the unprotected LD_{50}), triazophos displayed no neurotoxic effects.

A 90-day neurotoxicity study in hens at dietary concentrations of 0, 50, 110 or 250 ppm, was preceded by a 20-day preliminary study. In the preliminary study, at dietary levels up to 200 ppm, there were no neurotoxic symptoms and neuropathy target esterase (NTE) activity remained undisturbed by treatment. Histopathology was not performed. In the main study, cholinergic signs were seen at the high dose of 250 ppm and one hen (of 10) died on day 76. This hen, and one other, displayed clinical signs of neurotoxicity. Plasma cholinesterase activity was markedly reduced at all doses, but NTE activity was not investigated. Morphological lesions characteristic of neurotoxicity were reported in the spinal cord and peripheral nerves. The study report stated that lesions were more severe and seen more frequently in hens treated with triazophos than in controls. The Meeting concluded that it was difficult to interpret these histopathology findings since, most unusually, lesions were frequently seen in the spinal cord, but very infrequently in the peripheral nerves, of control animals.

The Meeting reviewed the results of male and female human volunteer studies previously summarized in the 1982 monograph. A series of experiments had been conducted, including a three-week trial with 25 volunteers. The present Meeting agreed with the conclusion of the 1982 JMPR regarding that trial: a dose of 0.0125 mg/kg bw/day of triazophos was a minimal effect level with regard to plasma cholinesterase activity but was without effect on erythrocyte acetylcholinesterase.

In view of the uncertainty regarding the potential for triazophos to cause delayed neurotoxicity, the Meeting extended the temporary ADI, basing it on the NOAEL in dogs, utilizing a 500-fold safety factor. (0.1 mg/kg bw/day).

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 30 ppm in the diet, equal to 4.5 mg/kg bw/day
Rat: 3 ppm in the diet, equal to 0.17 mg/kg bw/day (long term study)
27 ppm in the diet, equal to 2-3 mg/kg bw/day (multigeneration study)
Dog: 4 ppm in the diet, equal to 0.12 mg/kg bw/day
Human: 0.0125 mg/kg bw/day

Estimate of temporary acceptable daily intake for humans

0-0.0002 mg/kg bw

Studies without which the determination of a full ADI is impractical

To be submitted to WHO by 1992:

1. Clarification of the potential for triazophos to cause delayed neurotoxicity through an acute delayed neurotoxicity study in hens combined with measurements of acetylcholinesterase and neuropathy target esterase inhibition in nervous tissue.

2. Submission of ongoing studies, including those on antidotes to acute poisoning.

5. RECOMMENDATIONS

5.1 In the interests of public health and agriculture and in view of the needs of the Codex Committee on Pesticide Residues, the Meeting recommends that Joint Meetings on Pesticide Residues should continue to be held annually.

5.2 The Meeting recommends (Section 2.2) that results of food monitoring surveys suitable for estimates of dietary intake should be reported in full. They should include null results and report the limits of determination.

5.3 The Meeting recommends (Section 2.7) that analytical chemists conducting regulatory analysis for pesticide residues should report the reproducibility of their analyses and ensure that regulatory agencies are aware of the variability inherent in the reported results when interpreting them.

5.4 The Meeting recommends (Section 3.1) that further studies (*in vivo* and *in vitro*) into the mechanisms governing the enhancement of spontaneously occurring tumours in rodents should be pursued on compounds associated with the induction of such tumours.

5.5 The Meeting recommends (Section 3.3) that if a pesticide residue consists of a single compound, the octanol-water partition coefficient of that compound should be the main factor considered in determining whether the residue should be classified as fat-soluble. The Meeting further recommends that the data supporting (1) the apparently anomalous classification of methidathion and phosmet as fat-soluble and of cyhexatin, phorate and phosalone as not being fat-soluble, and (2) inconsistencies in the expression of the residues of the fat-soluble pesticides fensulfothion, isofenphos and pirimiphos-methyl in meat, should be re-examined at a future Meeting.

5.6 The Meeting recommends (Section 4.12) that cyhexatin be reviewed again in 1994.

5.7 The Meeting recommends (Section 4.18) that heptachlor should not be applied directly to food crops, and that its use in the production of food commodities should be phased out.

5.8 The Meeting recommends (Section 4.23) that monocrotophos should be reviewed in 1994.

6. FUTURE WORK

The following items should be considered at the 1992 or 1993 Meeting. Compounds recommended for priority attention by the 23rd or earlier Sessions of the CCPR which have not yet been evaluated are marked with an asterisk (*). All other compounds are for re-evaluation.

6.1 1992 Meeting (tentative)

Toxicological Evaluation

*Abamectin
Aldicarb
*Bifenthrin
*Cycloxydim
Dicofol
*Dithianon
Fenbutatin oxide
Iprodione
Methidathion
*Myclobutanil
*Penconazole
Piperonyl butoxide
*Propham
Pyrazophos
Thiram
Vinclozolin

Residue Evaluation

*Abamectin
Aldrin/dieldrin
Anilazine
Benalaxyl
Benomyl
*Bifenthrin
Bromide ion (Inorganic bromide)
Bromomethane (Methyl bromide)
Bromopropylate
Captan
Carbendazim
Chlorothalonil
*Cycloxydim
Cyfluthrin
Demeton compounds
Deltamethrin
Dicofol
Dimethoate
Dinocap
*Dithianon
Endrin
Etrimfos
Fenbutatin oxide
Flucythrinate
Folpet
Metalaxyl
Methacrifos
Methidathion
*Myclobutanil
Omethoate
*Penconazole
Piperonyl butoxide
Procymidone
Profenofos
*Propham
Pyrazophos
Thiophanate-methyl
Triazophos
Vamidothion
Vinclozolin

6.2 1993 Meeting (tentative)

Toxicological Evaluation

Amitrole
Captan
Carbaryl
*Chlorpropham
Diazinon
Dichlorvos
Diquat
Ethephon
Ethylenethiourea (ETU)
*Etofenprox
*Fenpropathrin
Folpet
Mancozeb
Maneb
*Metiram
Phosalone
Propineb
Propylenethiourea (PTU)
Quintozene
Triazophos
Zineb

Residue Evaluation

Acephate
Aldicarb
Amitrole
Azinphos-methyl
Bendiocarb
Carbaryl
Carbosulfan
*Chlorpropham
Chlorpyrifos-methyl
Cyfluthrin
DDT
Diazinon
Dichlorvos
Endosulfan
Ethephon
Ethion
Ethylenethiourea (ETU)
*Etofenprox
*Fenpropathrin
Ferbam
Flusilazole
Heptachlor
Hexaconazole
Mancozeb
Maneb
Methamidophos
*Metiram
Phosalone
Propineb
Propiconazole
Propylenethiourea (PTU)
Quintozene
Thiram
Zineb
Ziram

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FAO/WHO. 1979b Pesticide residues in food: 1978 evaluations. FAO Plant Production and Protection Paper 15 Sup.

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FAO Plant Production and Protection Paper 20.

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FAO Plant Production and Protection Paper 20 Sup.

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FAO/WHO. 1981b Pesticide residues in food: 1980 evaluations.
FAO Plant Production and Protection Paper 26 Sup.

FAO/WHO. 1982a Pesticide residues in food - 1981. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 37.

FAO/WHO. 1982b Pesticide residues in food: 1981 evaluations.
FAO Plant Production and Protection Paper 42.

FAO/WHO. 1983a Pesticide residues in food - 1982. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 46.

FAO/WHO. 1983b Pesticide residues in food: 1982 evaluations.
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FAO/WHO. 1986d Pesticide residues in food - 1986. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues.
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FAO/WHO. 1987a Pesticide residues in food: 1986 evaluations. Part II - Toxicology. FAO Plant Production and Protection Paper 78/2.

FAO/WHO. 1987b Pesticide residues in food - 1987. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues.
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FAO Plant Production and Protection Paper 86/1.

FAO/WHO. 1988b Pesticide residues in food: 1987 evaluations. Part II - Toxicology.
FAO Plant Production and Protection Paper 86/2.

FAO/WHO. 1988c Pesticide residues in food - 1988. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues.
FAO Plant Production and Protection Paper 92.

FAO/WHO. 1988d Pesticide residues in food: 1988 evaluations. Part I - Residues.
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FAO/WHO. 1989a Pesticide residues in food: 1988 evaluations. Part II - Toxicology.
FAO Plant Production and Protection Paper 93/2.

FAO/WHO. 1989b Pesticide residues in food - 1989. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues.
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FAO/WHO. 1990a Pesticide residues in food: 1989 evaluations. Part I - Residues.
FAO Plant Production and Protection Paper 100.

FAO/WHO. 1990b Pesticide residues in food: 1989 evaluations. Part II - Toxicology.
FAO Plant Production and Protection Paper 100/2.

FAO/WHO. 1990d Pesticide residues in food - 1990. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues.
FAO Plant Production and Protection Paper 102.

FAO/WHO. 1991a Pesticide residues in food: 1990 evaluations. Part I - Residues. FAO Plant Production and Protection Paper 103/1.

FAO/WHO. 1991b Pesticide residues in food: 1990 evaluations - Toxicology.
WHO/PCS/91.47.

CORRIGENDA TO REPORT AND RESIDUE EVALUATIONS OF 1990 JMPR

Additions and alterations are shown **bold**. Minor typographical errors, except in chemical, common, or trade names, are not included.

REPORT

Page	Para	Line	
xi		9:	Change 10-2 to 10^{-2}
xii		13:	Change 103 to 10^{3}
1	3	8:	Change 'man' to '**humans**'
5	6	5-6:	**Run on** to read 'number of samples with residues below limit of determination or limit of reporting'
58	6	2:	Change N,N-dimethyl-N-phenylsulphamide to N,N-dimethyl-**N'**-phenylsulphamide

ANNEX I

Page 78: PROCHLORAZ, lines 3-4: **Transpose (1983) from col. 1 to col. 6,** to read:

1983,1985,1987	FI	0350	Papaya	1 Po	1 Po	T **(1983)**
1988,1989	FS	0012	Stone fruits	0.05	1	T (1983)

Page 79: PROCYMIDONE: **Delete the entry.** (No changes were made to the existing recommendations).

ANNEX II

Errors or omissions are corrected in Annex II to the present report.

EVALUATIONS

Page

vii, line 9: Change 10-2 to **10^{-2}**

viii, line 13: Change 103 to **10^{3}**

1, Citrus fruits, line 2: Change 0.058 to **0.58**

2, Table 1, line 1: Change acephate residue from 2.0 to **2.05**

Page 7, Table 6, lines 1-2: Change to read:

	acephate	methamidophos	acephate	methamidophos
Whole mature fruit	1.65 (1.2-1.6)	0.04 (0.02-0.05)		
Whole fruit washed			0.20 (0.03-0.32)	0.02 (0.01-0.03)

Page

14, Table 2: In the entries for Greece, **transpose the figure 0.70 from col. 3 to col. 2.** Col. 3 should be blank.

15, National MRLs, line 11: Change 0.5* to **0.05***

21, Table 1, lines 8-9: (Sheep and Goat) **Change cols. 4 and 5** to read:

Formulation	Rate	
125 g/l plus **diazinon**	1 in 4	

29, Table 1. Headings of cols. 2-5 should read:

Formulation	Application **g ai/hl**	Application **kg ai/ha**	PHI, **days**

38, Table 2: All formulations should read **EC 500**

79, Table 4: Headings of cols. 2 and 5 should read '**Rate, g ai/ha**' and '**Interval** between applicns. (weeks)' respectively.

Page

83, Table 7, line 1 (Brazil): **Delete** the residue 0.10 under melamine, 0-2 days
line 2 (Denmark): **Delete** the entry '1' in col. 5.

137, Table 2: Col. 5 should be sub-headed **'Formulation'**

146, Table 1: Change to read 'Beans, green ?[3]'

158, Table 1: Col. 4 should be headed: Active ingredient **g/ha** (g/100 1)

169, Table 1, line 1: Cols. 2 and 3 should read **'50%WP'** and **'130'** respectively.

186, Table 3: Residues from the GB, 1987 trial should read 0.13, 0.13, 0.10 and 0.21 mg/kg at **14** days, with no entries at any other interval.

187, Table 4, penultimate line: **Delete** the entry 0.02 mg/kg at 28-30 days.

191, Table 5, line 10: (CO, 1988, Whole) The hexaconazole residue should read **0.01,** not <0.01, mg/kg.

218, **In processing,** para 2,
line 2: Change to read '... at the proposed rate of 2 x 40 **g** ai/ha and at 2 x 80 **g** ai/ha'.

222-227: Since references are given only by number in the Tables, **they should be understood as being numbered consecutively from 1 to 83.**

329, Table 5: Change '...carbomoyl...' to' '...carb**a**moyl...' in chemical name of prochloraz.

331, Table 7, col. 1: **Delete 'Peritoneal'** in heading.

392, Table 2, line 3, col. 2: Change '197' to '**1976**'

393, Table 3, lines 5-6: The residues in flowerhead and leaves should be <0.006 and 0.02 respectively at **28** days, and <0.006 and 0.04 at **35** days.

line 9: The residue <0.006 in leaves should be at **35** days.

ANNEX I

426, PROCYMIDONE: **Delete the entry**. (No changes were made to the existing recommendations).

ANNEX I

ACCEPTABLE DAILY INTAKES AND RESIDUE LIMITS PROPOSED AT THE 1991 MEETING

These figures are additional to, or amend, those recorded in Annexes of the reports of earlier meetings. Limits recommended at meetings from 1965 to 1977 inclusive are summarized in document FAO/WHO 1978c.

This table includes maximum Acceptable Daily Intakes (ADIs) and Maximum Residue Limits (MRLs). It should be noted that MRLs include draft MRLS and Codex MRLs (CXLs). The MRLs recommended by the JMPR on the basis of its estimates of maximum residue levels enter the Codex procedure as draft MRLs. They become Codex MRLs when they have passed through the procedure and have been adopted by the Codex Alimentarius Commission.

Some ADIs are temporary: this is indicated by the year in which re-evaluation is scheduled in parenthesis below the ADI. All recommended MRLs for compounds with temporary ADIs are necessarily temporary.

The following qualifications and abbreviations are used.

*	At or about the limit of determination
E	Extraneous Residue Limit (ERL).
F (following MRLS for milk)	The residue is fat-soluble and MRLs for milk and milk products are derived as explained in the introduction to Part 2 of the Guide to Codex Maximum Limits for Pesticide Residues and to Volume XIII of the Codex Alimentarius.
(fat) (following MRLs for meat)	The MRL applies to the fat of meat.
Po	The (T)MRL accommodates post-harvest treatment of the commodity.
PoP (following (T)MRLs for processed foods (classes D and E in the Codex Classification)	The (T)MRL accommodates post-harvest treatment of the primary food commodity.
T	The MRL is temporary, irrespective of the status of the ADI, until required information has been provided and evaluated.
V (following (T)MRLs for commodities of	The (T)MRL accommodates veterinary uses.

animal origin)

W (in place of an MRL) The previous recommendation is withdrawn.

If a recommended MRL is an amendment, the previous value is also recorded, together with the year in which the level was estimated. The absence of a figure in the "Previous" column indicates that the recommendation is the first for the commodity or group concerned.

The table includes the Codex Classification Numbers (CCNs) of both the compounds and the commodities listed, to facilitate reference to the Guide to Codex Maximum Limits for Pesticide Residues. Commodities are listed in the order of the "Types" in the revised Codex Classification, and within each Type in (English) alphabetical order. Different Types are not differentiated by sub-headings, but are separated from one another by spaces. The Types are listed in the following order:

Type	Code
Fruits	01
Vegetables	02
Grasses	03
Nuts and seeds	04
Herbs and spices	05
Mammalian products	06
Poultry products	07
Primary animal feed commodities of plant origin	11
Secondary food commodities of plant origin	12
Derived products of plant origin	13

ACCEPTABLE DAILY INTAKES (ADIs) AND MAXIMUM RESIDUE LIMITS (MRLs)

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Recommended Name	MRL or ERL (mg/kg) New	Previous
AZINPHOS-METHYL (002) 1965,1968 1972,1973, 1974	0.005	FP 0226	Apple	2	1[1]
		FS 0240	Apricot	W	2
		FB 0020	Blueberry	5	1[1]
		FS 0013	Cherries	2	1[1]
		FC 0001	Citrus fruits	W	2
		FB 0265	Cranberry	0.1	1[1]
			Fruits (except as otherwise listed)	W	1
		FS 0245	Nectarine	2	1[1]
		FS 0247	Peach	2	4
		FP 0230	Pear	2	1[1]
		FS 0014	Plums(including Prunes)	2	1[1]
		VB 0402	Brussels sprouts	W	1
		VS 0624	Celery	W	2
		VC 0424	Cucumber	0.2	0.5[2]
		VC 0046	Melons, except watermelon	0.2	2
		VO 0445	Peppers, sweet	1	0.5[2]
		VR 0589	Potato	0.05*	0.2
		VD 0541	Soya bean, dry	0.05*	0.2
		VO 0448	Tomato	1	0.5[2]
			Vegetables (except as otherwise listed)	W	0.5
		VC 0432	Watermelon	0.2	0.5[2]
		GS 0659	Sugar cane	0.2	-
		GC 0654	Wheat	0.2	0.2 for cereal grains
		TN 0660	Almonds	0.3	0.2
		TN 0672	Pecan	0.3	-
		SO 0702	Sunflower seed	W	0.2
		TN 0678	Walnut	0.3	-
		AL 1021	Alfalfa forage (green)	5	2
		AL 1020	Alfalfa hay 10	-	

AL 1031	Clover hay	5	-
AL 0528	Pea vines, green	W	2

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Name	Recommended MRL or ERL (mg/kg) New	Previous
AZINPHOS-METHYL (contd.)		AS 0654	Wheat straw and fodder, dry	1 T	-
		[1]MRL for Fruits (except as otherwise listed) [2]MRL for Vegetables (except as otherwise listed)			
		Residue: azinphos-methyl			
		Remarks: ADI increased from 0.0025 mg/kg			
AZOCYCLOTIN (129) 1979,1981,1982, 1983,1985,1989	0.001	FP 0226	Apple	5	2[1]
		FC 0001	Citrus fruits	2	2[2]
		FB 0269	Grapes	0.2	2[3]
		FI 0341	Kiwifruit	W	5[2]
		FS 0245	Nectarine	1	-
		FS 0247	Peach	1	5[2]
		FP 0230	Pear	2	2[2]
		FS 0014	Plums (including Prunes)	2	2[2]
		FB 0275	Strawberry	0.5	2[1]
		VP 0526	Common bean	0.2	0.2[1]
		VC 0424	Cucumber	0.5	0.5[2]
		VO 0440	Egg plant	0.1*	0.1*[3]
		VC 0425	Gherkin	1	1[2]
		VC 0046	Melons, except watermelon	0.5	0.5[2]
		VO 0445	Peppers, sweet	0.5	0.5[2]
		VO 0448	Tomato	2	2[2]
		MM 0095	Meat	0.2	0.2[2]
			Milk products	0.05*	0.05*[2]
		ML 0106	Milks	0.05*	0.05*[2]
		DT 1114	Tea, Green, Black	W	2[2]
		[1]Previous limit for cyhexatin and azocyclotin. [2]Previous limit for cyhexatin only. [3]Previous limit for azocyclotin only.			
Residue:		sum of azocyclotin and cyhexatin, expressed as cyhexatin			

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Name	MRL or ERL (mg/kg) New	Previous
AZOCYCLOTIN (contd.)	Remarks: ADI lowered from 0.003 mg/kg bw. Recommended MRLs for azocyclotin and cyhexatin are now identical. The above list therefore replaces all previous recommendations (and includes unchanged proposals). Note changed definition of residue				
BENTAZONE (172) (pods and/or	0.1	VD 0071	Beans, dry	0.05*	-
		VD 0561	Broad bean, dry	0.05*	-
		VP 0526	Common bean immature seed)	0.2	-
		VD 0561	Field pea, dry	0.05*	-
		VP 0528	Garden pea (young pods)	0.2	-
		VP 0534	Lima bean (young pods and/or immature beans)	0.05	-
		VA 0385	Onion, Bulb	0.1	-
		VR 0589	Potato	0.1	-
		VD 0541	Soya bean, dry	0.05*	-
		GC 0640	Barley	0.05*	-
		GC 0645	Maize	0.05*	-
		GC 0647	Oats	0.05*	-
		GC 0649	Rice	0.1	-
		GC 0650	Rye	0.05*	-
		GC 0651	Sorghum	0.05*	-
		GC 0654	Wheat	0.05*	-
		SO 0693	Linseed	0.1	-
		SO 0699	Peanut	0.05	-
		MM 0095	Meat	0.05*	-
		ML 0106	Milks	0.05*	-
		PE 0112	Eggs	0.05*	-
		AL 1021	Alfalfa forage (green)	2	-
		AF 0645	Maize fodder	3	-

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Name	Recommended MRL or ERL (mg/kg) New	Previous
BENTAZONE (contd.)	Residue: Plant materials: sum of bentazone, 6-hydroxy-bentazone and 8-hydroxy-bentazone, expressed as bentazone. Animal materials: sum of bentazone and 2-amino-N-isopropylbenzamide, expressed as bentazone				
BIORESMETHRIN (093)	0.03	GC 0654	Wheat	1 Po	5 Po for cereal grains 1975,1976
		CM 0654	Wheat bran, unprocessed	5 PoP))	5 PoP for milled cereal products
		CF 1211	Wheat flour	1 PoP)	
		CF 1210	Wheat germ	3 PoP)	
		CF 1212	Wheat wholemeal	1 PoP)	
			Cooked cereal products including bread	W PoP	0.05*
		Residue:	bioresmethrin		
	Remarks: Previous limits were GIs. As an ADI has been estimated, limits are now recommended as MRLs				
BITERTANOL (144) 1983,1984, 1986,1987, 1988,1989	0.01	FS 0240	Apricot	1	-
		FS 0245	Nectarine	1	-
		FS 0247	Peach	1	-
		Residue:	bitertanol		
BUPROFEZIN (173)	0.01	FC 0004	Oranges, Sweet, Sour	0.3 T	-
		VC 0424	Cucumber	0.3 T	-
		VO 0448	Tomato	0.5 T	-

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Recommended Name	MRL or ERL (mg/kg) New	Previous
BUPROFEZIN (contd.)		Residue:	buprofezin		
Remarks:	Limits are temporary until required information on chemistry is provided, irrespective of the status of the ADI				
CADUSAFOS (174)	0.0003	FI 0327	Banana	0.01*	-
		VR 0589	Potato	0.02	-
		Residue:	cadusafos		
CARBOFURAN (096) 1976,1979, 1980,1982	0.01	FC 0001	Citrus fruits	2[1]	-
		Residue:	sum of carbofuran and 3-hydroxy-carbofuran, expressed as carbofuran		
Remarks:	[1]Resulting from the use of carbosulfan				
CARBOSULFAN (145) 1984,1986	0.01	Residue:	carbosulfan		
Remarks:	Note changed definition of residue				
CHLORPYRIFOS-METHYL (090) 1975,1976, 1979,1990	0.001	FT 0295	Date	0.05	-
		FB 0269	Grapes	0.2	-
		FC 0004	Oranges, Sweet, Sour	0.5	-
		VO 0450	Mushrooms	0.01*	-
		VO 0051	Peppers	0.5	0.1
		GC 0640	Barley	10 Po	-
		GC 0647	Oats	10 Po	-
		SO 0495	Rape seed	10 Po T	-

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Recommended Name	MRL or ERL (mg/kg) New	Previous
CHLORPYRIFOS-METHYL (contd.)		Residue:	chlorpyrifos-methyl (fat-soluble)		
		Remarks:	ADI lowered from 0.01 mg/kg		
CYHEXATIN (067) 1970, (as tricyclohexyltin hydroxide),1974, 1975,1977,1978, 1980,1981,1982, 1983,1985,1988,	0.001	FP 0226	Apple	5	2[1]
		FC 0001	Citrus fruits	2	2[2]
		FB 0269	Grapes	0.2	2[3]
		FI 0341	Kiwifruit	W	5[2]
		FS 0245	Nectarine	1	-
		FS 0247	Peach	1	5[2]
		FP 0230	Pear	2	2[2]
		FS 0014	Plums (including Prunes)	2	2[2]
		FB 0275	Strawberry	0.5	2[1]
		VP 0526	Common bean	0.2	0.2[1]
		VC 0424	Cucumber	0.5	0.5[2]
		VO 0440	Egg plant	0.1*	0.1*[3]
		VC 0425	Gherkin	1	1[2]
		VC 0046	Melons, except watermelon	0.5	0.5[2]
		VO 0445	Peppers, sweet	0.5	0.5[2]
		VO 0448	Tomato	2	2[2]
		MM 0095	Meat	0.2	0.2[2]
			Milk products	0.05*	0.05*[2]
		ML 0106	Milks	0.05*	0.05*[2]
		DT 1114	Tea, Green, Black	W	2[2]
			[1]Previous limit for cyhexatin and azocyclotin. [2]Previous limit for cyhexatin only.		
[3]Previous limit for azocyclotin only.					
		Residue:	cyhexatin		

Remarks: Recommended MRLs for azocyclotin and cyhexatin are now identical. The above list therefore replaces all previous recommendations (and includes unchanged proposals).
Note changed definition of residue.

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Recommended Name	MRL or ERL (mg/kg) New	Previous
DISULFOTON (074) 1973,1975, 1979,1981, 1984 (Pods and/or	0.0003	VS 0621	Asparagus	0.01*	0.5[1]
		VD 0071	Beans (dry)	0.01	-
		VB 0400	Broccoli	0.2	0.5[1]
		VB 0041	Cabbage, Head	0.2	0.5[1]
		VB 0404	Cauliflower	0.2	0.5[1]
		VP 0526	Common bean immature seeds)	0.2	0.5[1]
		VP 0529	Garden pea, shelled	0.01*	0.5[1]
		VP 0528	Garden pea, young pods	0.1	0.5[1]
		VL 0482	Lettuce, Head	1	0.5[1]
		VL 0483	Lettuce, Leaf	1	0.5[1]
		VR 0591	Radish, Japanese	0.2	0.5[1]
		VR 0596	Sugar beet	0.2	0.5
		VO 0447	Sweet corn (corn-on-the-cob)	0.01*	0.5[1]
		VO 1275	Sweet corn (kernels)	0.01*	0.5[1]
		VO 0448	Tomato	0.1	0.5[1]
			Vegetables	W	0.5
		GC 0640	Barley	0.2	0.2[2]
		GC 0081	Cereal grain (except rice and maize)	W	0.2
		GC 0645	Maize	0.01	0.5
		GC 0647	Oats	0.01*	0.2[2]
		GC 0649	Rice	0.5 T	0.5
		GC 0651	Sorghum	0.5	0.2[2]
		GC 0654	Wheat	0.2	0.2[2]
		SB 0716	Coffee beans	0.2	0.1*
		SO 0691	Cotton seed	0.1	-
		SO 0697	Peanut (kernels)	0.1	0.1*
		TN 0672	Pecan	0.01*	0.1*
		ML 0107	Milk of cattle, goats and sheep	0.02	-
		PE 0840	Chicken eggs	0.001*	-
		PM 0110	Poultry meat	0.01*	-
		AL 1020	Alfalfa fodder (dry wt)	5	10
		AS 0640	Barley straw	3	-

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Recommended Name	MRL or ERL (mg/kg) New	Previous
DISULFOTON (contd.)		AL 1031	Clover hay or fodder	10 T	10
			Forage crops	W	5
		AS 0645	Maize fodder (dry wt)	3	-
		AF 0645	Maize forage	1	5[3]
		AF 0647	Oat forage (green)	0.5	5[3]
		AS 0647	Oat straw	0.05	-
		AF 0651	Sorghum forage (green)	20	5[3]
		AV 0596	Sugar beet leaves or tops	2	5[3]
		AF 0654	Wheat forage	2	5[3]
		AS 0654	Wheat straw	10	-
		[1]MRL for vegetables [2]MRL for cereals (except rice and maize) [3]MRL for forage crops (green)			
	Residue:	sum of disulfoton, demeton-S and their sulphoxides and sulphones, expressed as disulfoton			
		Remarks:	ADI lowered from 0.002 mg/kg		
FENTIN (040) 1965,1970, 1972,1986	0.0005	DH 1100	Hops, dry	1	-
		Residue:	fentin, excluding inorganic tin and di- and mono- phenyltin		
FLUSILAZOLE (165) 1989,1990	0.001	FS 0245	Nectarine	0.1 T[1]	-
		FS 0247	Peach	0.1 T[1]	-
		GC 0640	Barley	0.1	0.1 T
		GC 0650	Rye	0.1	0.1 T
		GC 0654	Wheat	0.1	0.1 T
		MM 0812	Cattle meat	0.01*	0.01* T
		MO 0812	Cattle, edible offal of	0.02*	0.02* T
		MF 0812	Cattle fat	0.01*	0.01* T
		ML 0812	Cattle milk	0.01*	0.01* T

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Recommended Name	MRL or ERL (mg/kg) New	Previous
FLUSILAZOLE (contd.)		AS 0640	Barley straw and fodder, dry	2	2 T
		AS 0650	Rye straw and fodder, dry	2	2 T
		AS 0654	Wheat straw and fodder, dry	2	2 T
		Residue:	flusilazole		
Remarks:	[1]Temporary pending evaluation of information on GAP and data on residue trials from additional countries				
GLUFOSINATE-AMMONIUM (175) 1991	0.01	FI 0327	Banana	0.05*	-
		FB 0018	Berries and other small fruits	0.1	-
		FC 0001	Citrus fruits	0.1	-
		FB 0269	Grapes	0.1	-
		FI 0341	Kiwifruit	0.05*	-
		FP 0009	Pome fruits	0.05*	-
		FS 0012	Stone fruits	0.05*	-
		VR 0589	Potato	0.5	
	-	VD 0541	Soya beans	0.5	-
		GC 0645	Maize	0.05*	-
		SO 0495	Rape seed	1	-
		SO 0702	Sunflower seed	1	-
Residue:	sum of glufosinate-ammonium and 3-[hydroxy(methyl)phosphinoyl]propio=nic acid, expressed as glufosinate (free acid)				
HEPTACHLOR (043) 1965,1966, 1967,1968, 1969,1970, 1974,1975, 1977,1987	0.0001	VR 0527	Carrot	0.2E T	0.2E
		VO 0448	Tomato	0.02E T	0.02E
			Vegetables, except as otherwise listed	0.05E T	0.05E

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Recommended Name	MRL or ERL (mg/kg) New	Previous
HEPTACHLOR (contd.)		Residue:	sum of heptachlor and heptachlor epoxide (fat-soluble)		
		Remarks:	ADI lowered from 0.0005 mg/kg		
HEXACONAZOLE (170) 1990	0.005	FI 0327	Banana	0.1	0.05
		Residue:	hexaconazole		
HEXYTHIAZOX (176)	0.03	FP 0226	Apple	0.5	-
		FS 0013	Cherries	1	-
		FC 0001	Citrus fruits	0.5	-
		FB 0279	Currant, Red, White	0.2	-
		FB 0269	Grapes	1	-
		FS 0247	Peach	1	-
		FP 0230	Pear	0.5	-
		FS 0014	Plums including Prunes)	0.2	-
		FB 0275	Strawberry	0.5	-
		VP 0526	Common bean	0.5	-
		VC 0424	Cucumber	0.1	-
		VO 0448	Tomato	0.1	-
		Residue:	hexythiazox		
IMAZALIL (110) 1977,1980, 1984,1985, 1986,1988, 1989	0.03	Residue:	imazalil		
		Remarks:	ADI increased from 0.01 mg/kg		
MONOCROTOPHOS (054) 1972,1975	0.00005	VO 0440	Egg plant	0.2	-
		VO 0444	Peppers, Chili	0.2	-
		VC 0432	Watermelon	0.1	-
		GC 0654	Wheat	0.02*	-
		GS 0659	Sugar cane	0.02*	-

		SO 0697	Peanut	0.05*	-

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Recommended Name	MRL or ERL (mg/kg) New	Previous
MONOCROTOPHOS (contd.)		DT 1114	Tea, Green, Black	0.5	-
		Residue:	monocrotophos		
PARATHION (058) 1965,1967, 1969,1970, 1984	0.005	FP 0226	Apple	0.05*	0.5[1]
		FC 0204	Lemon	0.5	1[2]
		FC 0206	Mandarin	0.5	1[2]
		FT 0305	Olives	0.5	0.5[1]
		FC 0004	Oranges, Sweet, Sour	0.5	1[2]
		VA 0384	Leek	0.05*	0.7[3]
		VR 0589	Potato	0.05*	0.7[3]
		VD 0541	Soya bean (dry)	0.05*	0.7[3]
		GC 0645	Maize	0.1	-
		GC 0651	Sorghum	5	-
		SO 0691	Cotton seed	1	-
		SO 0702	Sunflower seed	0.05*	-
		OC 0305	Olive oil, crude	2	-
		Residue:	parathion		
Remarks: [1]General limit for fruits, with certain exceptions [2]Group limit for Citrus fruits [3]General limit for vegetables, with certain exceptions					
PERMETHRIN (120) 1979,1980, 1981,1982, 1983,1984, 1985,1986, 1987,1988,	0.05[1]	CM 0654	Wheat bran, unprocessed	5 PoP	10 PoP T
		CF 1211	Wheat flour	0.5 PoP	0.5PoP T
		CF 1212	Wheat wholemeal	2 PoP	2 PoP T
		CF 1210	Wheat germ	2 PoP	-
	[1]Applies to the nominal 40% *cis*-, 60% *trans*- and 25% *cis*-, 75% *trans*- materials only				
		Residue:	permethrin (sum of isomers)		

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Name	MRL or ERL (mg/kg) New	Previous
PHORATE (112) 1977,1982, 1983,1984, 1985,1990	0.0002	VO 0447	Sweet corn (corn-on-the-cob)	0.05	-
		GC 0645	Maize	0.05*[1]	-
		SO 0697	Peanut	0.1	0.05
		AF 0645	Maize forage (fresh wt)	0.2 (fresh wt)	0.1
Residue:	Sum of phorate, its oxygen analogue, and their sulphoxides and sulphones, expressed as phorate				
Remarks:	[1]At or about the limit of determination. Residues are unlikely to exceed 0.01 mg/kg				
PROPICONAZOLE (160) 1987	0.04	GC 0640	Barley	0.2 T	0.1[1]
		GC 0080	Cereal grains (except rice)	W	0.1
		GC 0647	Oats	0.05*	0.1[1]
		GC 0650	Rye	0.05*	0.1[1]
		GC 0654	Wheat	0.05*	0.1[1]
		Residue:	propiconazole		
Remarks:	[1]:Included in limit for Cereals (except rice)				
PROPOXUR (075) 1973,1977, 1981,1983, 1989	0.02	VP 0522	Broad bean (green pods and immature seeds)	0.02*	3[1]
		VB 0403	Cabbage, Savoy	0.5	3[1]
		VR 0577	Carrot	0.02*	0.5[2]
		VP 0526	Common bean (pods and/or immature seeds)	1	3[1]
		VC 0424	Cucumber	0.1	3[1]
		VP 0528	Garden pea (young pods)	0.05	3[1]
		VB 0405	Kohlrabi	0.2	3[1]
		VA 0384	Leek	1	3[1]
		VL 0482	Lettuce, Head	3	3[1]

Pesticide (CCN) Year(s) of previous evaluations	Rec. max. ADI (mg/kg bw)	Commodity CCN	Name	Recommended MRL or ERL (mg/kg) New	Previous
PROPOXUR (contd.)		VA 0385	Onion, Bulb	0.05*	3[1]
		VR 0589	Potato	0.1*	0.5[2]
		VR 0075	Root and tuber vegetables	W	0.5
		VL 0502	Spinach	2	3[1]
		VO 0448	Tomato	0.05	3[1]
			Vegetables	W	3
			[1]MRL for vegetables [2]MRL for root and tuber vegetables		
		Residue:	propoxur		
TRIAZOPHOS (143) 1982,1983, 1984 (corr. to 1983),1986, 1990 1986,1990	0.0002 (T)	Residue: triazophos			
		Remarks:	Temporary ADI extended. Toxicological studies to be provided by 1992.		

ANNEX II

INDEX OF REPORTS AND EVALUATIONS

Numbers in parentheses are Codex Classification Numbers.

ACEPHATE (095) 1976 (T,R)[vi], 1979 (R), 1981 (R), 1982 (T), 1984 (T,R), 1987 (T), 1988 (T), 1990 (T,R), 1991 (corr. to 1990 R evaluation)

ACRYLONITRILE 1965 (T,R)

ALDICARB (117) 1979 (T,R), 1982 (T,R), 1985 (R), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation)

ALDRIN (001) 1965 (T), 1966 (T,R), 1967 (R), 1974 (R), 1975 (R), 1977 (T), 1990 (R)

ALLETHRIN 1965 (T,R)

AMINOCARB (134) 1978 (T,R), 1979 (T,R)

AMITRAZ (122) 1980 (T,R), 1983 (R), 1984 (T,R), 1985 (R), 1986 (R), 1989 (R), 1990 (T,R), 1991 (R & corr. to 1990 R evaluation)

AMITROLE (079) 1974 (T,R), 1977 (T)

ANILAZINE (163) 1989 (T,R)

AZINPHOS-ETHYL (068) 1973 (T,R), 1983 (R)

AZINPHOS-METHYL (002) 1965 (T), 1968 (T,R), 1972 (R), 1973 (T), 1974 (R), 1991 (T,R)

AZOCYCLOTIN (129) 1979 (R), 1981 (T), 1982 (R),1983 (R), 1985 (R), 1989 (T,R), 1991 (R)

BENALAXYL (155) 1986 (R), 1987 (T), 1988 (R)

BENDIOCARB (137) 1982 (T,R), 1984 (T,R), 1989 (R), 1990 (R)

BENOMYL (069) 1973 (R), 1975 (T,R), 1978 (T,R), 1983 (T,R), 1988 (R), 1990 (R)

BENTAZONE (172) 1991 (T,R)

BHC (technical) 1965 (T), 1968 (T,R), 1973 (T,R) (see also lindane)

BINAPACRYL (003) 1969 (T,R), 1974 (R), 1982 (T), 1984 (R), 1985 (T,R)

BIORESMETHRIN (093) 1975 (R), 1976 (T,R), 1991 (T,R)

BIPHENYL see diphenyl

BITERTANOL (144) 1983 (T), 1984 (R), 1986 (R), 1987 (T), 1988 (R), 1989 (R), 1991 (R)

BROMIDE ION (047) 1968 (R), 1969 (T,R), 1971 (R), 1979 (R), 1981 (R), 1983 (R), 1988 (T,R), 1989 (R)

BROMOETHANE 1965 (T,R), 1966 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R), 1985 (R)

BROMOPHOS (004) 1972 (T,R), 1975 (R), 1977 (T,R), 1982 (R), 1984 (R), 1985 (R)

BROMOPHOS-ETHYL (005) 1972 (T,R), 1975 (T,R), 1977 (R)

BROMOPROPYLATE (070) 1973 (T,R)

BUTOCARBOXIM (139) 1983 (R), 1984 (T), 1985 (T), 1986 (R)

BUPROFEZIN (173) 1991 (T,R)

sec-BUTYLAMINE (089) 1975 (T,R), 1977 (R), 1978 (T,R), 1979 (R), 1980 (R), 1981 (T), 1984 (T,R: withdrawal of TADI, but no evaluation)

CADUSAFOS (174) 1991 (T,R)

CAMPHECHLOR (071) 1968 (T,R), 1973 (T,R)

CAPTAFOL (006) 1969 (T,R), 1973 (T,R), 1974 (R), 1976 (R), 1977 (T,R), 1982 (T), 1985 (T,R), 1986 (corr. to 1985 report), 1990 (R)

CAPTAN (007) 1965 (T), 1969 (T,R), 1973 (T), 1974 (R), 1977 (T,R), 1978 (T,R), 1980 (R), 1982 (T), 1984 (T,R), 1986 (R), 1987 (R and corr. to 1986 R evaluation), 1990 (T,R), 1991 (corr. to 1990 R evaluation)

CARBARYL (008) 1965 (T), 1966 (T,R), 1967 (T,R), 1968 (R), 1969 (T,R), 1970 (R), 1973 (T,R), 1975 (R), 1976 (R), 1977 (R), 1979 (R), 1984 (R)

CARBENDAZIM (072) 1973 (T,R), 1976 (R), 1977 (T), 1978 (R), 1983 (T,R), 1985 (T,R), 1987 (R), 1988 (R), 1990 (R)

CARBOFURAN (096) 1976 (T,R), 1979 (T,R), 1980 (T), 1982 (T), 1991 (R)

CARBON DISULPHIDE (009) 1965 (T,R), 1967 (R), 1968 (R), 1971 (R), 1985 (R)

CARBON TETRACHLORIDE (010) 1965 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R), 1985 (R)

CARBOPHENOTHION (011) 1972 (T,R), 1976 (T,R), 1977 (T,R), 1979(T,R), 1980(T,R), 1983(R)

CARBOSULFAN (145) 1984 (T,R), 1986 (T), 1991 (R)

CARTAP (097) 1976 (T,R), 1978 (T,R)

CHINOMETHIONAT (080) 1968 (T,R) (as oxythioquinox), 1974 (T,R), 1977 (T,R), 1981 (T,R), 1983 (R), 1984 (T,R), 1987 (T)

CHLORBENSIDE 1965 (T)

CHLORDANE (012) 1965 (T), 1967 (T,R), 1969 (R), 1970 (T,R), 1972 (R), 1974 (R), 1977 (T,R), 1982 (T), 1984 (T,R), 1986 (T)

CHLORDIMEFORM (013) 1971 (T,R), 1975 (T,R), 1977 (T), 1978 (T,R), 1979(T), 1980(T), 1985 (T), 1986 (R), 1987 (T)

CHLORFENSON 1965 (T)

CHLORFENVINPHOS (014) 1971 (T,R), 1984 (R)

CHLORMEQUAT (015) 1970 (T,R), 1972 (T,R), 1976 (R), 1985 (R)

CHLOROBENZILATE (016) 1965 (T), 1968 (T,R), 1972 (R), 1975 (R), 1977 (R), 1980(T)

CHLOROPICRIN 1965 (T,R)

CHLOROPROPYLATE 1968 (T,R), 1972 (R)

CHLOROTHALONIL (081) 1974 (T,R), 1977 (T,R), 1978 (R), 1979 (T,R), 1981 (T,R), 1983 (T,R), 1984 (corr. to 1983 report and T evaluation), 1985 (T,R), 1987 (T), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation)

CHLORPROPHAM 1965 (T)

CHLORPYRIFOS (017) 1972 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1981 (R), 1982(T,R), 1983 (R), 1989 (R)

CHLORPYRIFOS-METHYL 1975 (T,R), 1976 (R, Annex I only), 1979 (R), 1990 (R), 1991 (T,R)

CHLORTHION 1965 (T)

CLOFENTEZINE (156) 1986 (T,R), 1987 (R), 1989 (R), 1990 (R)

COUMAPHOS (018) 1968 (T,R), 1972 (R), 1975 (R), 1978 (R), 1980 (T,R), 1983(R),1987 (T), 1990 (T,R)

CRUFOMATE (019) 1968 (T,R), 1972 (R)

CYANOFENPHOS (091) 1975 (T,R), 1978 (T: ADI extended, but no evaluation), 1980, (T), 1982 (R), 1983 (T)

CYFLUTHRIN (157) 1986 (R), 1987 (T and correction to 1986 report), 1989 (R), 1990 (R)

CYHALOTHRIN (146) 1984 (T,R), 1986 (R), 1988 (R)

CYHEXATIN (TRICYCLO= HEXYLTIN HYDROXIDE) (067) 1970 (T,R), 1973 (T,R), 1974 (R), 1975(R), 1977 (T), 1978 (T,R), 1980 (T), 1981 (T), 1982 (R), 1983 (R), 1985 (R), 1988 (T), 1989 (T), 1991 (T,R)

CYPERMETHRIN (118) 1979 (T,R), 1981 (T,R), 1982 (R), 1983 (R), 1984 (R), 1985(R), 1986 (R), 1987 (corr. to 1986 Re-evaluation), 1988 (R), 1990 (R)

CYROMAZINE (169) 1990 (T,R), 1991 (corr. to 1990 R evaluation)

2,4-D (020) 1970 (T,R), 1971 (T,R), 1974 (T,R), 1975 (T,R), 1980 (R), 1985, (R), 1986 (R), 1987 (corr. to 1986 report, Annex I)

DAMINOZIDE (104) 1977 (T,R), 1983 (T), 1989 (T,R), 1991 (T)

DDT (021) 1965 (T), 1966 (T,R), 1967 (T,R),1968 (T,R), 1969 (T,R),1978,;(R) 1979 (T), 1980 (T), 1983 (T), 1984 (T)

DELTAMETHRIN (135) 1980 (T,R), 1981 (T,R), 1982 (T,R), 1984 (R), 1985 (R), 1986, (R), 1987 (R), 1988 (R), 1990 (R)

DEMETON (092) 1965 (T), 1967 (R), 1975 (R), 1982 (T)

DEMETON-S-METHYL (073) 1965 (T), 1967 (T), 1968 (R), 1973 (T,R), 1979 (R), 1982 (T), 1984 (T,R), 1989 (T,R)

DIALIFOS (098) 1976 (T,R), 1982 (T), 1985 (R)

DIAZINON (022) 1965 (T), 1966 (T), 1967 (R), 1968 (T,R), 1970 (T,R), 1975 (R), 1979 (R)

1,2-DIBROMOETHANE (023) 1965 (T,R), 1966 (T,R), 1967 (R), 1968 (R), 1971 (R), 1979 (R), 1985 (R)

DICHLOFLUANID (082) 1969 (T,R), 1974 (T,R), 1977 (T,R), 1979 (T,R), 1981 (R),1982 (R), 1983 (T,R), 1985 (R)

1,2-DICHLOROETHANE (024) 1965 (T,R), 1967 (R), 1971 (R), 1979 (R), 1985 (R)

DICHLORVOS (025) 1965 (T,R), 1966 (T,R), 1967 (T,R), 1969 (R), 1970 (T,R), 1974 (R), 1977 (T)

DICLORAN (083) 1974 (T,R), 1977 (T,R)

DICOFOL (026) 1968 (T,R), 1970 (R), 1974 (R)

DIELDRIN (001) 1965 (T), 1966 (T,R), 1967 (T,R), 1968 (R), 1969 (R), 1970, (T,R), 1974 (R), 1975 (R), 1977 (T), 1990 (R)

DIFLUBENZURON (130) 1981 (T,R), 1983 (R), 1984 (T,R), 1985 (T,R), 1988 (R)

DIMETHIPIN (151) 1985 (T,R), 1987 (T,R), 1988 (T,R)

DIMETHOATE (027) 1965 (T), 1966 (T), 1967 (T,R), 1970 (R), 1973 (R in evaluation of formothion), 1977 (R), 1978 (R), 1983 (R) 1984 (T,R) 1986(R), 1987 (T,R), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation)

DIMETHRIN, 1965 (T)

DINOCAP (087) 1969 (T,R), 1974 (T,R), 1989 (T,R)

DIOXATHION (028) 1968 (T,R), 1972 (R)

DIPHENYL (029) 1966 (T,R), 1967 (T)

DIPHENYLAMINE (030) 1969 (T,R), 1976 (T,R), 1979 (R), 1982 (T), 1984 (T,R)

DIQUAT (031) 1970 (T,R), 1972 (T,R), 1976 (R), 1977 (T,R), 1978 (R)

DISULFOTON (074) 1973 (T,R), 1975 (T,R), 1979 (R), 1981 (R), 1984 (R), 1991 (T,R)

DITHIOCARBAMATES 1965 (T), 1967 (T,R), 1970 (T,R), 1983 (R, propineb and thiram), 1984 (R, propineb), 1985 (R), 1987 (T, thiram), 1988 (R, thiram), 1990 (R), 1991 (corr. to 1990 evaluation)

DNOC 1965 (T)

DODINE (084) 1974 (T,R), 1976 (T,R), 1977 (R)

EDIFENPHOS (099) 1976 (T,R), 1979 (T,R), 1981 (T,R)

ENDOSULFAN (032) 1965 (T), 1967 (T,R), 1968 (T,R), 1971 (R), 1974 (R), 1975 (R), 1982 (T), 1985 (T,R), 1989 (T,R)

ENDRIN (033) 1965 (T), 1970 (T,R), 1974 (R), 1975 (R), 1990 (R)

ETHEPHON (106) 1977 (T,R), 1978 (T,R), 1983 (R), 1985 (R)

ETHIOFENCARB (107) 1977 (T,R), 1978 (R), 1981 (R), 1982 (T,R), 1983 (R)

ETHION (034) 1968 (T,R), 1969 (R), 1970 (R), 1972 (T,R), 1975 (R), 1982 (T), 1983 (R), 1985 (T), 1986 (T), 1989 (T), 1990 (T)

ETHOPROPHOS (149) 1983 (T), 1984 (R), 1987 (T)

ETHOXYQUIN (035) 1969 (T,R)

ETHYLENE DIBROMIDE see 1,2-dibromoethane

ETHYLENE DICHLORIDE see 1,2-dichloroethane

ETHYLENE OXIDE 1965 (T,R), 1968 (T,R), 1971 (R)

ETHYLENETHIOUREA (ETU) (108) 1974 (R), 1977 (T,R), 1986 (T,R), 1987 (R), 1988 (T,R), 1990 (R)

ETRIMFOS (123) 1980 (T,R), 1982 (T,R[5]), 1986 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R)

FENAMIPHOS (085) 1974 (T,R), 1977 (R), 1978 (R), 1980 (R), 1985 (T), 1987 (T)

FENBUTATIN OXIDE (109) 1977 (T,R), 1979 (R)

FENCHLORPHOS (036) 1968 (T,R), 1972 (R), 1983 (R)

FENITROTHION (037) 1969 (T,R), 1974 (T,R), 1976 (R), 1977 (T,R), 1979 (R), 1982, (T) 1983 (R), 1984 (T,R), 1986 (T,R), 1987 (R and corr. to 1986 R evaluation), 1988 (T), 1989 (R)

FENSULFOTHION (038) 1972 (T,R), 1982 (T), 1983 (R)

FENTHION (039) 1971 (T,R), 1975 (T,R), 1977 (R), 1978 (T,R), 1979 (T), 1980 (T), 1983 (R), 1989 (R)

FENTIN compounds (040) 1965 (T), 1970 (T,R), 1972 (R), 1986 (R), 1991 (T,R)

FENVALERATE (119) 1979 (T,R), 1981 (T,R), 1982 (T), 1984 (T,R), 1985 (R), 1986 (T,R), 1987 (R and corr. to 1986 report), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation)

FERBAM see dithiocarbamates, 1965 (T), 1967 (T,R)

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[5] **R evaluation omitted. Published 1986.**

FLUCYTHRINATE (152) 1985 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R)

FLUSILAZOLE (165) 1989 (T,R), 1990 (R), 1991 (R)

FOLPET (041) 1969 (T,R), 1973 (T), 1974 (R), 1982 (T), 1984 (T,R), 1986 (T), 1987 (R), 1990 (T,R), 1991 (corr. to 1990 R evaluation)

FORMOTHION (042) 1969 (T,R), 1972 (R), 1973 (T,R), 1978 (R)

GLYPHOSATE (158) 1986 (T,R), 1987 (R and correction to 1986 report), 1988 (R))

GUAZATINE (114) 1978 (T.R), 1980 (R)

HEPTACHLOR (043) 1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T,R), 1974 (R), 1975 (R), 1977 (R), 1987 (R), 1991 (T,R)

HEXACHLOROBENZENE (044) 1969 (T,R), 1973 (T,R), 1974 (T,R), 1978(T), 1985 (R)

HEXACONAZOLE (170) 1990 (T,R), 1991 (R & corr. to 1990 R evaluation)

HEXYTHIAZOX (176) 1991 (T,R)

HYDROGEN CYANIDE (045) 1965 (T,R)

HYDROGEN PHOSPHIDE (046) 1965 (T,R), 1966 (T,R), 1967 (R), 1969 (R), 1971 (R)

IMAZALIL (110) 1977 (T,R), 1980 (T,R), 1984 (T,R), 1985 (T,R), 1986 (T), 1988 (R), 1989 (R), 1991 (T)

IPRODIONE (111) 1977 (T,R), 1980 (R)

ISOFENPHOS (131) 1981 (T,R), 1982 (T,R), 1984 (R), 1985 (R), 1986 (T,R), 1988 (R)

LEAD ARSENATE 1965 (T), 1968 (T,R)

LEPTOPHOS (088) 1974 (T,R), 1975 (T,R), 1978 (T,R)

LINDANE (048) 1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T,R) (published as Annex VI to 1971 evaluations), 1973 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1978 (R), 1979 (R), 1989 (T,R)

MALATHION (049) 1965 (T), 1966 (T,R), 1967 (corr. to 1966 R), 1968 (R), 1969 (R), 1970 (R), 1973 (R), 1975 (R), 1977 (R), 1984 (R)

MALEIC HYDRAZIDE (102) 1976 (T,R), 1977 (T,R), 1980 (T), 1984 (T,R)

MANEB see dithiocarbamates, 1965 (T), 1967 (T,R), 1987 (T)

MANCOZEB (050) 1967 (T,R), 1970 (T,R), 1974 (R), 1977 (R), 1980 (T,R)

MECARBAM (124) 1980 (T,R), 1983 (T,R), 1985 (T,R), 1986 (T,R), 1987 (R)

METALAXYL (138) 1982 (T,R), 1984 (R), 1985 (R), 1986 (R), 1987 (R), 1989 (R), 1990 (R)

METHACRIFOS (125) 1980 (T,R), 1982 (T), 1986 (T), 1988 (T), 1990 (T,R)

METHAMIDOPHOS (100) 1976 (T,R), 1979 (R), 1981 (R), 1982 (T,R[6]), 1984 (R), 1985 (T), 1989 (R), 1990 (T,R)

METHIDATHION (051) 1972 (T,R), 1975 (T,R), 1979 (R)

METHIOCARB (132) 1981 (T,R), 1983 (T,R), 1984 (T), 1985 (T), 1986 (R), 1987 (T,R), 1988 (R)

METHOMYL (094) 1975 (R), 1976 (R), 1977 (R), 1978 (R), 1986 (T,R), 1987 (R), 1988 (R), 1989 (T,R), 1990 (R), 1991 (R)

METHOPRENE (147) 1984 (T,R), 1986 (R), 1987 (T and corr. to 1986 report), 1988 (R)

METHOXYCHLOR 1965 (T), 1977 (T)

METHYL BROMIDE (052) see bromomethane

MEVINPHOS (053) 1965 (T), 1972 (T,R)

MGK 264 1967 (T,R)

MONOCROTOPHOS (054) 1972 (T,R), 1975 (T,R), 1991 (T,R)

NABAM see dithiocarbamates, 1965 (T), 1976 (T,R)

NITROFEN (140) 1983 (T,R)

OMETHOATE (055) 1971 (T,R), 1975 (T,R), 1978 (T,R), 1979 (T), 1981(T,R),1984 (R), 1985 (T), 1986 (R), 1987 (R), 1988 (R), 1990 (R)

ORGANOMERCURY compounds 1965 (T), 1966 (T,R), 1967 (T,R)

OXAMYL (126) 1980 (T,R), 1983 (R), 1984 (T), 1985 (T,R), 1986 (R)

OXYDEMETON-METHYL 1965 (T), 1967 (T), 1968 (R), 1973 (T,R), 1984 (T), 1989 (T)

OXYTHIOQUINOX see chinomethionat

PACLOBUTRAZOL (161) 1988 (T,R), 1989 (R)

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[6] **R evaluation omitted. Published 1989.**

PARAQUAT (057) 1970 (T,R), 1972 (T,R), 1976 (T,R), 1978(R), 1981 (R), 1982 (T), 1985 (T), 1986 (T)

PARATHION (058) 1965 (T), 1967 (T,R), 1969 (R), 1970 (R), 1984 (R), 1991 (R)

PARATHION-METHYL (059) 1965 (T), 1968 (T,R), 1972 (R), 1975 (T,R), 1978 (T,R), 1979 (T), 1980 (T), 1982 (T), 1984 (T,R), 1991 (R)

PERMETHRIN (120) 1979 (T,R), 1980 (R), 1981 (T,R), 1982 (R), 1983 (R), 1984 (R), 1985 (R), 1986 (T,R), 1987 (T), 1988 (R), 1989 (R), 1991 (R)

2-PHENYLPHENOL (056) 1969 (T,R), 1975 (R), 1983 (T), 1985 (T,R), 1990 (T,R)

PHENOTHRIN (127) 1979 (R), 1980 (T,R), 1982 (T), 1984 (T), 1987 (R), 1988 (T,R)

PHENTHOATE (128) 1980 (T,R), 1981 (R), 1984 (T)

PHORATE (112) 1977 (T,R), 1982 (T), 1983 (T), 1984 (R), 1985 (T), 1990 (R), 1991 (R)

PHOSALONE (060) 1972 (T,R), 1975 (R), 1976 (R)

PHOSMET (103) 1976 (R), 1977 (corr. to 1976 R evaluation), 1978 (T,R), 1979 (T,R), 1981 (R), 1984 (R), 1985 (R), 1986 (R), 1987 (R and corr. to 1986 evaluation), 1988 (R)

PHOSPHINE see hydrogen phosphide

PHOSPHAMIDON (061) 1965 (T), 1966 (T), 1968 (T,R), 1969 (R), 1972 (R), 1974 (R), 1982 (T), 1985 (T), 1986 (T)

PHOXIM (141) 1982 (T), 1983 (R), 1984 (T,R), 1986 (R), 1987 (R), 1988 (R)

PIPERONYL BUTOXIDE (062) 1965 (T,R), 1966 (T,R), 1967 (R), 1969 (R), 1972 (T,R)

PIRIMICARB (101) 1976 (T,R), 1978 (T,R), 1979 (R), 1981 (T,R), 1982 (T), 1985 (R)

PIRIMIPHOS-METHYL (086) 1974 (T,R), 1976 (T,R), 1977 (R), 1979 (R), 1983 (R), 1985 (R)

PROCHLORAZ (142) 1983 (T,R), 1985 (R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1991 (R & corr. to 1990 report, Annex I, & evaluation)

PROCYMIDONE (136) 1981 (R), 1982 (T), 1989 (T,R), 1990 (R), 1991 (corr. to 1990 Annex I)

PROFENOFOS (171) 1990 (T,R)

PROPAMOCARB (148) 1984 (T,R), 1986 (T,R), 1987 (R)

PROPARGITE (113) 1977 (T,R), 1978 (R), 1979 (R), 1980 (T,R), 1982 (T,R)

PROPHAM 1965 (T)

PROPICONAZOLE (160) 1987 (T,R), 1991 (R)

PROPINEB 1977 (T,R), 1980 (T), 1983 (T), 1984 (R), 1985 (T,R)

PROPOXUR (075) 1973 (T,R), 1977 (R), 1981 (R), 1983 (R), 1989 (T), 1991 (R)

PYRAZOPHOS (153) 1985 (T,R), 1987 (R)

PYRETHRINS (063) 1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T), 1972 (T,R), 1974 (R)

QUINTOZENE (064) 1969 (T,R,) 1973 (T,R), 1974 (R), 1975 (T,R), 1976 (Annex I, corr. to 1975 R), 1977 (T,R)

2,4,5-T (121) 1970 (T,R), 1979 (T,R), 1981 (T)

TECNAZENE (115) 1974 (T,R), 1978 (T,R), 1981 (R), 1983 (T), 1987 (R), 1989 (R)

TERBUFOS (167) 1989 (T,R), 1990 (T,R)

THIABENDAZOLE (065) 1970 (T,R), 1971 (R), 1972 (R), 1975 (R), 1977 (T,R), 1979 (R), 1981 (R)

THIODICARB (154) 1985 (T,R), 1986 (T), 1987 (R), 1988 (R)

THIOMETON (076) 1969 (T,R), 1973 (T,R), 1976 (R), 1979 (T,R), 1988 (R)

THIOPHANATE-METHYL (077) 1973 (T,R), 1975 (T,R), 1977 (T), 1978 (R), 1988 (R), 1990 (R)

THIRAM (105) see dithiocarbamates, 1965 (T), 1967 (T,R), 1970 (T,R), 1974 (T), 1977 (T), 1983 (R), 1984 (R), 1985 (T,R), 1987 (T), 1988 (R), 1989 (R)

TOLYLFLUANID (162) 1988 (T,R), 1990 (R), 1991 (corr. to 1990 report)

TOXAPHENE see camphechlor

TRIADIMEFON (133) 1979 (R), 1981 (T,R), 1983 (T,R), 1984 (R), 1985 (T,R), 1986 (R), 1977 (R and corr. to 1986 evaluation), 1988 (R), 1989 (R)

TRIADIMENOL (168)	1989 (T,R)
TRIAZOLYLALANINE	1989 (T,R)
TRIAZOPHOS (143)	1982 (T), 1983 (R), 1984 (corr. to 1983 report, Annex I), 1986 (T,R), 1990 (R), 1991 (T & corr. to 1990 evaluation)
TRICHLORFON (066)	1971 (T,R), 1975 (T,R), 1978 (T,R), 1987 (R)
TRICHLORONAT	1971 (T,R)
TRICHLOROETHYLENE	1968 (R)
TRICYCLOHEXYLTIN HYDROXIDE	see cyhexatin
TRIFORINE (116)	1977 (T), 1978 (T,R)
TRIPHENYLTIN compounds	see fentin compounds

VAMIDOTHION (078)	1973 (T,R), 1982 (T), 1985 (T,R), 1987 (R), 1988 (T), 1990 (R)
VINCLOZOLIN (159)	1986 (T,R), 1987 (R and corr. to 1986 report and R evaluation), 1988 (T,R), 1989 (R), 1990 (R)

ZINEB (105)	see dithiocarbamates, 1965 (T), 1967 (T,R)
ZIRAM (105)	see dithiocarbamates, 1965 (T), 1967 (T,R)

ANNEX III

INTAKE PREDICTIONS

The Meeting considered the predicted intakes of residues of the pesticides on its agenda.

In carrying out EMDI (Estimated Maximum Daily Intake) calculations (WHO, 1989[vii]), information on residue levels in food as consumed was seldom available. There were, therefore, only limited possibilities to calculate EMDIs for those compounds for which the TMDI (Theoretical Maximum Daily Intake) exceeded the ADI.

For the following compounds the TMDI did not exceed the ADI or TADI. The TMDI calculations are based on ADIs, TADIs and MRLs current at the end of the present Meeting:

azinphos-methyl, azocyclotin, bentazone, bioresmethrin, bitertanol, buprofezin, cadusafos, carbofuran, carbosulfan, daminozide, fentin, flusilazole, glufosinate-ammonium, hexaconazole, hexythiazox, imazalil, parathion, parathion-methyl, permethrin, propiconazole and propoxur.

Additional data are required for the calculations of EMDIs for:

chlorpyrifos-methyl, cyhexatin, disulfoton, heptachlor, monocrotophos, phorate and triazophos.

ANNEX IV

ANNEX V

[i] *(WHO, 1989) Guidelines for predicting dietary intake of pesticide residues, World Health Organization, Geneva*

[ii] Freshe, H. and Timme, G. 1980. Quantitative residue analytical reliability: beatitude through the application of latitude. Residue Reviews, 73, 27-47.

[iii] WHO, 1990. Principles for the Toxicological Assessment of Pesticide Residues in Food, Geneva, World Health Organization (WHO Environmental Health Criteria, No. 104).

[iv] Bowman, B. T. and Sans, W.W. (1983) Determination of Octanol-Water Partitioning Coefficient (Kow) of 61 Organophosphorus and Carbamate Insecticides and their Relationship to Respective Water Solubility (S) Values.

[v] J. Environ. Sci. Health B18(6), 667-683.

[vi] The name 3-methylphosphinico-propionic acid was used in reports provided to the Meeting.

T = Toxicology

R = Residue and analytical aspects

[vii] WHO (1989). Guidelines for predicting dietary intake of pesticide residues, World Health Organization, Geneva.