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[1] T = Toxicology; R = Residue and analytical aspects
* = First evaluation
** = Evaluation in CCPR periodic review programme

1992 FAO/WHO JOINT MEETING ON PESTICIDE RESIDUES

Rome, 21-30 September 1992

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ABBREVIATIONS WHICH MAY BE USED

(chemical elements and pesticides are not included)

AChE	acetylcholinesterase
ADI	acceptable daily intake
ai	active ingredient
ALAT	alanine aminotransferase
approx.	approximate
ASAT	aspartate aminotransferase
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)
DP	dustable powder
DS	powder for dry seed treatment
EC	(1) emulsifiable concentrate (2) electron-capture [detector for chromatograph]
ECD	electron-capture detector
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
FID	flame-ionization detector
FPD	flame-photometric detector
g	gram
µg	microgram
GAP	good agricultural practice(s)
GC-MS	gas chromatography-mass spectrometry
G.I.	gastro-intestinal
GL	guideline level
GLC	gas-liquid chromatography
GPC	gel-permeation chromatography
GSH	glutathione

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
LOD	limit of determination (see also "*" at end of Table)
LSC	liquid scintillation counting or counter
m	metre
MFO	mixed function oxidase
mg	milligram
µg	microgram
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
SC	suspension concentrate (= flowable concentrate)
SD	standard deviation
SE	standard error
SG	water-soluble granule
SL	soluble concentrate
SP	water-soluble powder
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)
WG	water-dispersible granule
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
*	(following residue levels, e.g. 0.01* mg/kg): level at or about the limit of determination

PESTICIDE RESIDUES IN FOOD

REPORT OF THE 1992 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 Rome, Italy, from 21 to 30 September 1992. The FAO Panel of Experts had met in preparatory sessions on 17-18 September. The Meeting was opened by Dr. H. de Haen, Assistant Deputy Director-General, FAO, on behalf of the Directors-General of FAO and WHO. In his opening remarks, Dr. de Haen referred to the importance of the conclusions of the JMPR for the work of the Codex Committee on Pesticide Residues (CCPR) and other national and international organizations. He introduced Mr. W. J. Murray, the new FAO Joint Secretary to the JMPR.

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 the evaluation of the various pesticides considered. The supporting documents (Residue 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 Dr. O. E. (Gene) Paynter, who had made many distinguished scientific contributions over a period of many years as a participant in the Joint Meetings.

2. GENERAL CONSIDERATIONS

2.1 MODIFICATIONS TO THE AGENDA

The FAO Panel was unable to evaluate propham because the data were inadequate. It could not complete the evaluation of the residue aspects of cycloxydim in the time available. Several other compounds could not be evaluated for residues owing to lack of time and/or information.

2.2 CUMULATIVE INDEX TO SECTIONS 2 AND 3 OF JMPR REPORTS, 1965-1992

An index to the General Considerations (Section 2) and Specific Problems (Section 3) in all reports from 1965 to 1992 has been prepared and is included as Annex III to the present report.

It is proposed to issue periodical supplements to the index as Annexes to JMPR reports.

2.3 DATA REQUIREMENTS FOR COMPOUNDS IN THE CCPR PERIODIC REVIEW PROGRAMME

JMPR data requirements must be made explicit for member countries and industry supplying the relevant data for compounds in the CCPR periodic review programme. (See also Section 2.4).

At the 24th (1992) Session of the CCPR four recommendations were made by the *ad hoc* Working Group on Priorities to address the problems (ALINORM 93/24, Appendix V, Annex III):

"1. That submissions which are part of the periodic review programme should be clearly identified as such by the FAO Secretary when they are sent to JMPR reviewers.

"2. That the FAO Secretary provide guidance for JMPR reviewers on procedures to be followed for compounds being reviewed under the periodic review programme. For example, when no current GAP is available the withdrawal of the JMPR MRL recommendation is advised in the periodic review.

"3. That a document on JMPR FAO Panel procedural matters be developed for discussion at JMPR in 1992 and at CCPR 25. The intention is to include a section on such procedural matters in the FAO Guide.

"4. That submitters of data for new compounds, for significant expansions of uses, or for compounds in the periodic review programme, should provide lists of studies of the residue supporting information (metabolism studies, animal transfer studies, processing studies, analytical methods, and storage stability of analytical samples studies) which have been and are being supplied to JMPR. The lists will assist in identifying data gaps."

FAO DATA REQUIREMENTS FOR COMPOUNDS IN THE PERIODIC REVIEW PROGRAMME

Member countries and industry are requested to supply all relevant information on use patterns (registered and officially authorised uses), supervised residue trials, fate of residues (metabolism, storage and processing, stability in stored analytical samples), residues in food in commerce or at consumption, methods of residue analysis, and national maximum residue limits. The information should be supplied at the time of the periodic review irrespective of whether it has been previously supplied.

Until now in the periodic review programme no specific request has been made for the critical supporting studies. Critical supporting studies were previously referred to as residue supporting information in recommendation 4 arising from discussions at the 24th (1992) Session of the CCPR (ALINORM 93/24).

> The Meeting recommended that, for compounds in the periodic review programme, in addition to copies of the full studies, a detailed index of the available critical supporting studies (metabolism, animal transfer, processing, analytical methods, and storage stability of analytical samples) be prepared by the manufacturer and be included in the submission.

WHO DATA REQUIREMENTS FOR COMPOUNDS IN THE PERIODIC REVIEW PROGRAMME

In the past, when compounds with temporary ADIs were re-evaluated, the Joint Meeting examined only the new toxicological data made available in compliance with the further data requirements of previous Joint Meetings. In these instances, the Meeting did not usually re-examine and/or re-interpret the data reviewed by previous Joint Meetings. Temporary ADIs are no longer established for new compounds.

The recently introduced practice of reviewing old compounds in the CCPR periodic review programme requires that the full existing data-base on the compound be examined. This encompasses data already examined and interpreted by previous Joint Meetings as well as any new data (whether or not they have been developed since the last Joint Meeting evaluation).

It is essential that all of the available data be submitted at normally scheduled times to the Joint Meeting when it is re-evaluating a compound in the periodic review programme. The allocation of any ADIs resulting from such reviews is dependent on the appraisal of all the available data.

2.4 FAO DATA EVALUATION OF COMPOUNDS IN THE CCPR PERIODIC REVIEW PROGRAMME

At the 1991 Meeting it became apparent that JMPR procedures for reviewing compounds in the CCPR periodic review programme needed to be clarified, and the FAO methods of evaluating the data on such compounds better described (see also Report Section 2.3).

The Meeting compared the data evaluation of a periodic review compound with "normal" data evaluation (i.e. other than in the periodic review programme).

Residue data and GAP information

New MRLs. If no MRL exists for the individual commodity or the relevant commodity group there is little difference in the treatment of information supplied normally or under the periodic review programme.

Existing MRLs. For an individual commodity in the normal situation if new data are supplied where an MRL already exists the data are evaluated and the MRL may or may not require revision.

In the periodic review situation where adequate information is supplied on an individual commodity, the MRL is either revised or confirmed to be relevant to modern GAP.

In the normal situation when information on a single commodity included in a group commodity MRL is received evaluation would either show that the group MRL could remain or that an individual MRL and a group (except...) MRL could be recommended.

In a periodic review when information on only a single commodity included in a group commodity MRL is received it may be necessary to withdraw the group MRL and estimate a single-commodity MRL.

GAP information. Under normal circumstances if no new GAP information is supplied the MRL would remain. New GAP information may allow previously recorded residue data to be reinterpreted to permit estimation of a new maximum residue level.

In the normal situation where new residue data are to be evaluated judgement is required on a case-by-case basis to decide whether previously recorded GAP is still valid. GAP information recorded many years ago for some compounds may still be acceptable.

Under the periodic review programme the absence of GAP and residue information becomes significant. For example, if no GAP information is supplied for a particular commodity the JMPR reviewer can assume that there is no GAP for that commodity. Only GAP supplied for the purposes of re-evaluation is considered valid. If no GAP information is supplied, withdrawal of the MRL will be recommended.

Supporting Studies. Critical supporting studies (metabolism, animal transfer, processing, analytical methods, and storage stability of analytical samples) will be evaluated to assist with the interpretation of data from supervised residue trials, to influence the residue definition, to validate residue and other trials, and to provide further information on residues in food as consumed. Critical supporting studies were previously referred to as residue supporting information in recommendation 4 arising from discussions at the 24th (1992) Session of the CCPR (ALINORM 93/24).

RECOMMENDATIONS

The Meeting recommends that compounds in the periodic review programme be treated as follows.

Residue data and GAP

The JMPR will evaluate compounds in terms of current GAP and all available valid residue data.

If there is no current GAP information available, or if there are no residue data from trials conducted under the conditions of current GAP, the JMPR will recommend withdrawal of the relevant MRL. If sufficient information is available, the JMPR will either:

- confirm the existing MRL;

or

- recommend introduction of a new MRL and withdrawal of the existing MRL.

Group MRLs

If there is insufficient information to maintain a group (e.g., citrus fruits) MRL, but there is adequate information for one member (e.g., oranges), the JMPR will recommend withdrawal of the group MRL, and introduction of the single commodity MRL.

These procedures will be tempered by judgement in individual cases where extrapolation may be valid.

General Procedures

The periodic review programme requires different actions from those of a normal review; consequently, those compounds in the periodic review programme must be clearly identified in advance to the reviewer.

The Meeting recommends that the FAO Joint Secretary indicate which are the periodic review compounds in the list of reviewer-assigned compounds given to JMPR members.

2.5 SUBMITTED DATA IN WORDPERFECT FORMAT

The Meeting further discussed the standardized reporting of residue data and GAP summaries (see 1991 report, Section 2.10). It was recognized that similar considerations might also apply to the submission of compilations of national MRLs.

It was agreed that consideration should be given to working towards the submission of tables of summarized data prepared in a standardized format, in WordPerfect 5.1. This would facilitate the construction of data tables involved in the production of evaluations. It was reaffirmed that such summaries were to aid in the evaluation of submitted results and were to be provided in addition to the detailed data.

2.6 DIETARY INTAKE OF PESTICIDE RESIDUES

Following the methods described in *Guidelines for Predicting Dietary Intake of Pesticides*[1], Theoretical Maximum Daily Intake (TMDI) and, where applicable, Estimated Maximum Daily Intake (EMDI) calculations have been performed for the Joint Meeting by the International Programme on Chemical Safety (IPCS). See Annex IV.

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

A third draft of the Guide was briefly discussed by the FAO Panel. The second draft had been revised on the basis of discussions and subsequent written comments provided to the authors by the FAO Panel of the 1991 Meeting. A series of specific questions prepared by the GIFAP Working Group on Residues concerning the evaluation procedures and criteria employed by the FAO was used as one means of assessing the effectiveness of the revised Guide. Following discussion of the Guide it was agreed that additional comments on the revised draft would be provided by the members of the 1992 FAO Panel to the FAO Joint Secretary by the end of December. The fourth draft would be circulated to

[1] *Guidelines for predicting dietary intake of pesticide residues*, World Health Organization, Geneva, 1989.

Panel members early in 1993 and a small consultation would be convened prior to the 1993 CCPR. The aim is to have a final draft available for the consideration of the 1993 JMPR before circulation for government comment.

2.8 USE OF TEMPORARY MRLS BY THE FAO PANEL

A temporary maximum residue limit is a maximum residue limit for a specified, limited period, which is clearly related to required information.

As a general policy TMRLs will not be introduced for a new compound, or a compound in the periodic review programme, or when there is no established GAP.

Temporary MRLs may be recommended when some information, which is still lacking, is unlikely to affect the validity of the estimated maximum residue level and there is a clear commitment that the information will be available by a specified date.

The JMPR may recommend a TMRL in some special circumstances, decided on a case-by-case basis, for example:

- The JMPR is informed that experiments are in progress and data from residue or processing trials will be available for a specified Meeting in the future.

- Immediate withdrawal of an MRL may be too disruptive if insufficient opportunity has been given for comment and data submission.

The JMPR may also recommend conversion of an MRL to a TMRL when there is a significant change in GAP which would affect residue levels. The JMPR would require complete information to be supplied by a specified date.

TMRLs for specific commodities may be used to replace group commodity MRLs or "fruit" and "vegetable" MRLs where it is known that residue trials on those specific commodities are in progress. Such a situation has arisen when a group MRL has been scheduled for review, and residue data are being developed for some commodities in the group. It would not be correct to withdraw the group MRL without introducing some recognition of the continued validity of maximum residue levels estimated for those commodities while the work is in progress. In the absence of other information the TMRLs would be recommended at the same level as the group MRL to be withdrawn.

Each recommended TMRL will be directly related to an item of *Required* information. Each such item will have a due date specified. The information is to be available for review at the Joint Meeting in that specified year. If the required information is not supplied by the due date, the TMRL will be withdrawn.

2.9 JMPR MANUAL FOR FAO PANEL

The format and language of JMPR Evaluations and Reports have evolved over the lifetime of the CCPR-JMPR system. People who are familiar with JMPR publications should be readily able to find the information they are seeking expressed in a clear and consistent way.

A manual has been drafted to assist members of the FAO Panel to prepare documents for the Meeting in a consistent format. It may also be useful to people preparing submissions for review by the

FAO Panel. The manual is not intended to deal with the evaluation process or to provide guidance on MRL estimation.

The manual provides guidance on the word-processing style (standardized on WordPerfect 5.1) and format to be used, the preferred layout of tables, the headings to be used in monographs and reports, and preferred abbreviations and units.

Documents prepared in the correct format assist JMPR members to digest information quickly, and after the Meeting make it easier for the editor to produce final copy for publication. A working copy of the manual was available to FAO Panel members prior to the 1992 JMPR, which helped them to prepare documents in a uniform format. It is intended that the working copy will be developed further in the light of experience at the 1992 JMPR.

2.10 MRLS FOR ANIMAL FEEDS

At the 24th (1992) Session of the CCPR (ALINORM 93/24, para 189) the Committee decided to request countries to submit national approaches to requiring animal studies in relation to residues in animal feeds. The Committee would then ask the JMPR to elaborate general rules on when transfer studies were necessary.

Animal feeds are commodities of trade and therefore require Codex MRLs if pesticide uses result in detectable residues in the feeds. Residues in feeds may also lead to detectable residues in animal tissues, milk and eggs, necessitating MRLs for these commodities. In addition, some by-products of food commodities (e.g. apple pomace, grape pomace) and food commodities themselves (e.g. cereal grains) may be used as feedstuffs for food-producing animals.

An MRL set on a commodity used for food is not necessarily applicable to the commodity when used as an animal feed. In some situations the use of the commodity as a feed (containing residues at the MRL) could result in measurable residues in animal tissues, milk and eggs.

As a general principle, data should be available to demonstrate that when potential animal feed commodities containing residues within the established MRL are fed to food-producing animals, residues in animal tissues, milk and eggs will not exceed the MRLs for those commodities.

The Meeting noted that information on national approaches to requiring animal transfer studies had been requested by Circular Letter (CL 1992/12-PR, Part B, 3 (iii). It was recommended that this information should be considered in the development of the relevant section of the FAO Guide.

3. SPECIFIC PROBLEMS

3.1 CHOLINESTERASE REACTIVATION

In animal and human toxicology studies with anti-cholinesterase organophosphorus esters and anti-cholinesterase carbamates, the NOAEL is frequently based upon acetylcholinesterase depression in brain and/or erythrocytes. However, it is often not fully appreciated that carbamoylated and dimethylphosphorylated cholinesterases reactivate at varying but relatively rapid rates[1]. Reactivation may occur *in vivo* or *in vitro* (for example in the test tube after blood sampling). Very careful attention to experimental design and procedures is therefore necessary to prevent reactivation of inhibited enzyme before compound-induced changes can be quantified.

3.2 STABILITY OF PESTICIDE RESIDUES IN STORED ANALYTICAL SAMPLES

The Meeting welcomed and discussed the document drafted by GIFAP "Stability of Residue During Storage" (ALINORM 93/24, APPENDIX III, ANNEX I) which had been discussed by the CCPR Working Group on Methods of Analysis and endorsed by the CCPR as a basis for a procedure to be included in Part 7 of the Codex Guide after government comments (ALINORM 93/24, para 228). The Meeting considered this document to be entirely consistent with and supportive of its 1990 recommendation that studies on storage stability should be conducted when there is a need to store analytical samples (1990 Report, Section 2.10). The Meeting endorsed the concepts in the GIFAP draft and reiterated the 1990 JMPR recommendation that future FAO Guidelines on Estimating MRLs should provide guidance on conducting such studies. Joint Meetings have already implemented the 1990 JMPR recommendation to include a monograph Section entitled " Stability of Pesticide Residues in Stored Analytical Samples".

The Meeting drew attention to the fact that in addition to the primary purpose of storage stability studies to ensure the integrity of data submitted to the JMPR or national authorities, they are also a valuable source of information to regulatory authorities on how long they may store monitoring, enforcement, or other analytical samples before analysis.

The Meeting noted some other points that might be considered for inclusion, as follows.

1. While the guidance under discussion is concerned with "stored analytical samples", it should be emphasized that full details should also always be provided on the handling and storage conditions of samples from the time of field (or other) sampling to the time that storage of the analytical samples begins. Guidance on this is already available in the 1986 FAO *Guidelines on Pesticide Residue Trials to Provide Data for the Registration of Pesticides and the Establishment of Maximum Residue Limits*.

2. Because the GIFAP draft appears to be directed to stored analytical samples, the Meeting suggested that consideration might be given to adopting the title used in this report, "Stability of Pesticide Residues in Stored Analytical Samples".

3. When the analytical method determines a "total residue", storage stability studies should include separate analyses of all compounds of concern, not only the total residue.

4. If there is reason to believe residues may be degraded rapidly or are very volatile, some knowledge of storage stability in relevant sample matrices should be available before storage of field or other samples to assist in the selection of optimum analysis intervals during the storage

[1] *Organophosphorus insecticides - a general introduction*. Environmental Health Criteria No.63. Geneva, 1986. World Health Organization.

stability studies and to avoid possibly invalid results.

5. The JMPR may adjust maximum residue level estimates to accommodate residue losses demonstrated for the storage period and conditions if the loss is not severe (e.g. <30%). If the loss is >30% there is a danger that the results may be too uncertain for the estimation of maximum residue levels. Although the JMPR may make such adjustments, the submission of adjusted results is not acceptable.

6. The basic concepts embodied in the proposed guidance on storage stability studies should apply to all stored samples for residue determination (including those from metabolism and processing studies) to the extent that this is possible, not only to samples from supervised field trials and animal transfer studies.

7. In addition to the representative sample types mentioned in para 2, specific examples might usefully be given, for instance: water (e.g. leafy vegetable, citrus, apple)-, oil (e.g. oilseed)-, protein (e.g. legume vegetable)- and starch (e.g. potato, cereal)-containing crop materials...

8. Those conducting storage stability studies should be encouraged to keep reserve samples for a period in case additional analyses should be necessary to resolve unforeseen problems.

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 ABAMECTIN (177)

Abamectin is a mixture of components, B_{1a} (≥80%) and B_{1b} (≤20%). The systematic IUPAC names are:

Component B_{1a}: (2a*E*,4*E*,8*E*)-(5′*S*,6*S*,6′*R*,7*S*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6′-[(*S*)-*sec*-butyl]-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5′,6,8,19-tetramethyl-17-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranoside.

Component B_{1b}: (2a*E*,4*E*,8*E*)-(5′*S*,6*S*,6′*R*,7*S*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-6′-isopropyl-5′,6,8,19-tetramethyl-17-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranoside.

Abamectin is a macrocyclic lactone product derived from the soil microorganism *Streptomyces avermitilis*, which controls a number of plant-feeding mites and insects on agricultural and horticultural crops. It is most effective as an ingestion toxicant, but also has some contact activity. It is active against motile mites and insect larvae, but has no ovicidal activity.

The compound was considered for the first time by the present Meeting.

TOXICOLOGY

In addition to data on abamectin, human data on ivermectin, which is structurally similar, were considered.

Abamectin contains at least 80% avermectin B_{1a} and not more than 20% avermectin B_{1b} (see Figure 1). Because of the very similar biological and toxicological properties of the individual components, they can be considered to be equivalent. Abamectin is degraded photolytically to the _-8,9-isomer which therefore forms a part of the residue.

Figure 1. Structural formulae of abamectin and ivermectin*

** Source: WHO Technical Report Series, No. 799*

Following oral administration of abamectin to rats, 69-82% of the administered dose was eliminated in the faeces and only 1% in the urine. Biliary excretion was the major cause of the high level of faecal excretion. Biotransformation proceeds mainly by demethylation and hydroxylation.

Orally administered abamectin elicited dose-dependent CNS effects, including tremors and ataxia.

In a one-year dietary study in dogs at doses of 0, 0.25, 0.5 or 1 mg abamectin/kg bw/day, a borderline NOAEL of 0.25 mg/kg bw/day was determined, despite single instances of mydriasis at this lowest dose level.

In a two-year long-term/carcinogenicity study in mice, abamectin was administered in the diet at concentrations resulting in doses of 0, 2, 4 or 8 mg/kg bw/day. The NOAEL was 4 mg/kg bw/day, based on the occurrence of tremors, a higher mortality rate and reduced body-weight gain at 8 mg/kg bw/day. Abamectin was not carcinogenic in the mouse.

In a two-year long-term/carcinogenicity study in rats, abamectin was administered in the diet at concentrations resulting in doses of 0, 0.75, 1.5 or 2 mg/kg bw/day. The NOAEL was 1.5 mg/kg bw/day. Higher doses caused CMS toxicity. Abamectin was not carcinogenic in rats.

In two one-generation reproduction studies in rats avermectin B_{1a} was administered in the diet at concentrations resulting in dose levels ranging from 0.1 to 2 mg/kg bw/day. Maternotoxicity was observed at dose levels above 1 mg/kg bw/day. Fetotoxicity, consisting of reduced pup survival rates, reduced pup weight growth, and retardation, became evident at dose levels of 0.5 mg/kg bw/day and above. The NOAEL for fetotoxicity was 0.1 mg/kg bw/day.

In a two-generation reproduction study in rats at dose levels of 0.05, 0.12 or 0.4 mg abamectin/kg bw/day, the NOAEL for maternotoxicity was 0.05 mg/kg bw/day, based on reduced maternal body-weight gain during lactation at 0.12 mg/kg bw/day and above. The NOAEL for pup toxicity was 0.12 mg/kg bw/day, based on increased mortality and lowered pup weights at 0.4 mg/kg bw/day.

The teratogenic potential of abamectin administered by gavage was investigated in mice, rats and rabbits. Teratogenic effects, including cleft palates, omphaloceles and clubbed fore feet, were observed at maternotoxic doses in mice and rabbits. The NOAEL for teratogenicity in the most sensitive

species, the mouse (CF1 strain) was 0.2 mg/kg bw/day, while for maternotoxicity the NOAEL was 0.05 mg/kg bw/day, based on the occurrence of tremors and deaths at higher doses.

Various studies to investigate the teratogenic potential of the _-8,9-isomer have been conducted in mice and rats. Similar teratogenic effects to those seen with abamectin were observed in the most sensitive species, the mouse. The NOAELs for maternotoxicity in the mouse were 0.1 mg/kg bw/day, and for fetotoxicity/teratogenicity, 0.05 mg/kg bw/day.

After reviewing the available genotoxicity data, the Meeting concluded that abamectin was not genotoxic.

Although no human data were available on abamectin, extensive data on field and community-based trials with ivermectin in humans infected with Onchocera spp. were available[1]. The main effects noted were those arising from the death of parasites, the so-called Mazzotti reaction, which is characterized by arthralgia, pruritus, fever, hypertension, tachycardia, headache, and ocular changes. Very limited data in humans indicate that ivermectin does not increase the incidence of birth defects, although it is teratogenic in mice, rats and rabbits[2].

The available data provided adequate information to permit the allocation of an ADI for abamectin and its _-8,9-isomer, based on the NOAELs for abamectin of 0.05 mg/kg bw/day in the teratogenicity study in mice and in the two-generation reproduction study in rats. The NOAEL for the _-8,9-isomer were 0.05 mg/kg bw/day in the teratogenicity study in rats. A safety factor of 500 was used because of concern over the teratogenicity of the _-8,9-isomer which forms part of the residue in food.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Abamectin (and components avermectin B_{1a} and B_{1b}):

Mouse: 4 mg/kg bw/day (two-year feeding study)
0.05 mg/kg bw/day (teratology study, maternotoxicity)
0.2 mg/kg bw/day (teratology study, teratogenicity)

Rat: 1.5 mg/kg bw/day (2-year study)
0.1 mg/kg bw/day (1-generation reproduction study)
0.05 mg/kg bw/day (2-generation reproduction study, maternotoxicity)
0.12 (2-generation reproduction study, pup toxicity)

Dog: 0.25 mg/kg (borderline) (1-year study)

_-8,9-isomer

Mouse: 0.1 mg/kg bw/day (teratology study maternotoxicity)
0.05 mg/kg bw/day (teratology study teratogenicity)

Estimate of acceptable daily intake for humans (Abamectin and _-8,9-isomer)

0-0.0001 mg/kg bw.

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[1] *Toxicological evaluation of certain veterinary drug residues in food*. WHO Food Additive Series, No. 31, in preparation.

[2] *Evaluation of certain veterinary drug residues in food (Thirty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives)*. WHO Technical Report Series, No. 799, 1990.

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

1. Ongoing studies on the mechanism of central nervous system toxicity.
2. Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Abamectin has a low vapour pressure (<0.0004 mPa) and low water solubility (10 µg/l). It is soluble in organic solvents such as chloroform, acetone and ethanol (>10g/kg). It is stable to hydrolysis at pH 5, 7 and 9 at 25°C in the dark. The log P_{ow} (3.96) classifies abamectin as non-polar.

When avermectin B_{1a} was fed to rats two metabolites were identified in the tissues: 3″-*O*-demethyl avermectin B_{1a} (also described as 3″-desmethyl avermectin B_{1a} or 3″-*O*-desmethyl avermectin B_{1a}) and 24-hydroxymethyl avermectin B_{1a}, which together with avermectin B_{1a} accounted for more than 85% of tissue residues. The metabolism of the photolysis product Δ-8,9 isomer (8,9-*Z* isomer) in rats was parallel to that of avermectin B_{1a}; its metabolites were 24-hydroxymethyl-8,9-*Z*-avermectin B_{1a} and 3″-*O*-demethyl-8,9-*Z*-avermectin B_{1a} (also described as 3″-desmethyl-8,9-*Z*-avermectin B_{1a}).

A minor metabolite, 8-α-hydroxyavermectin B_{1a}, identified in metabolism studies on celery, citrus fruit and cotton leaves, and from exposure of avermectin B_{1a} to sunlight on glass, was also identified as a minor metabolite in the liver of rats dosed with avermectin B_{1a}.

In a 10-day oral lactating goat study with avermectin B_{1a} most of the dose was excreted in the faeces. Target tissues for the residue were liver, kidney and fat, with avermectin B_{1a} as a high percentage of the residue. Residue levels in goat's milk reached a plateau on day 4 of the dosing, and again avermectin B_{1a} constituted a high percentage of the residue.

In a 28-day oral lactating dairy cow study with avermectin B_{1a} doses at the equivalent of 0.01, 0.03 and 0.1 ppm in the feed, residues in the milk of the low and medium dose groups were not detected (<0.0005 mg/l). In the high dose group residues were mostly at 0.001 to 0.002 mg/l. Liver and fat were the main target tissues for residues; levels found in the 0.1 ppm feeding group were 0.018 mg/kg (liver), 0.002 mg/kg (muscle), 0.013 mg/kg (fat), and 0.004 mg/kg (kidney).

Metabolism studies with avermectin B_{1a} on citrus showed that it is not translocated from the treatment site and that it disappears relatively quickly, with 3-10% of the applied dose remaining as avermectin B_{1a} and 1-2% as Δ-8,9-isomer 1 week after treatment. Residues remained at the surface or in the peel; they were not detected in the inner pulp. Polar degradation products were the major fraction. Chromatography of these polar materials suggested that they were the same as those produced by photolysis of avermectin B_{1a}. The ratio of Δ-8,9-isomer to avermectin B_{1a} in the residues was in the range 10-30%.

Metabolism of avermectin B_{1a} in celery and cotton leaves and photolysis of avermectin B_{1a} on a glass plate provided the same patterns of products as in citrus. The products in all cases were a complex mixture of polar compounds, and produced similar HPLC profiles. Indications were that the characteristic diene structure had been lost, that the products contained one to six additional oxygen atoms and that numerous low molecular weight compounds, including sugar-related compounds, were formed. A less polar product identified was Δ-8,9-avermectin B_{1a}; 8α-hydroxyavermectin B_{1a} was also identified

Avermectin B_{1a} was classified as immobile in all six soils studied, including two sands. Aged residues were also immobile. Under anaerobic conditions very little soil degradation of avermectin B_{1a} occurred. Under aerobic conditions the half-life for avermectin B_{1a} disappearance was in the range 20 to 47 days in a fine sandy loam, a clay and a coarse sand. The main metabolite was identified as an equilibrium mixture of the 8α-hydroxy derivative and the corresponding ring-opened aldehyde derivative of avermectin B_{1a}.

Abamectin at 0.04 and 0.4 mg/kg soil had no effect on the rate of nitrification, suggesting no detrimental effect on soil microorganisms. The estimated LC_{50}s in soil for earthworms for the stated durations of exposure were: 62 ppm (7 days), 33 ppm (14 days), 28 ppm (28 days).

A rotational crop study using cotton, lettuce, sorghum, carrots and turnips concluded that abamectin would not be a detectable residue in the rotation crops.

Abamectin is registered for uses on cabbage, celery, Chinese cabbage, citrus, cotton, cruciferous crops, cucumber, eggplant, kale, mustard, pear, peppers, and tomato in one or more countries.

The Meeting received extensive residue data from supervised trials on these crops: oranges (Argentina, Brazil, USA), lemons (Argentina, USA), tangelos (USA), grapefruit (USA), pears (Argentina, Australia, France, Italy, Spain, USA), strawberries (Brazil, France, Italy, Spain, USA), celery (USA), cucumbers (France, Italy, Netherlands, Spain), lettuce (Netherlands, USA), Brassica leafy vegetables (Malaysia, Philippines, Thailand), white cabbage (Malaysia, Philippines, Taiwan), peppers (France, Italy, Netherlands), tomatoes (Argentina, Australia, Brazil, France, Italy, Netherlands, Spain, USA), cotton (Australia, Brazil, South Africa, USA), almonds, walnuts and pecans (USA).

Residue data in the trials include residues of avermectin B_{1a}, avermectin B_{1b} and Δ-8,9 isomer of avermectin B_{1a}, except in some of the early citrus trials where the method used at that time did not give a good recovery of the Δ-8,9 isomer. This had little influence on the results because avermectin B_{1a} is the major part of the residue.

Residue data from supervised trials on oranges, lemons, grapefruit and tangelos are mutually supportive. When pulp and peel were analyzed separately only occasionally were residues detected in the pulp (0.001 mg/kg). At the prescribed PHI, 7 days, residues in whole fruit did not exceed 0.005 mg/kg. Residues in peel were usually in the range 0.004-0.01 mg/kg, the highest being 0.014 mg/kg. Residues of avermectin B_{1a} in the whole fruit calculated from the relative weights of peel and pulp did not exceed 0.005 mg/kg. The data support an MRL of 0.01* mg/kg for citrus fruits; allowance must be made for addition of the two analytes, each with a limit of quantification at 0.005 mg/kg.

The authorised use pattern for abamectin on pears in France includes 1 or 2 applications and a 15 days PHI. Most of the trial data in France were produced with 3 applications and samples for analysis taken only up to 7 days after the final application. For the non-persistent abamectin the Meeting considered that the residues from 2 or 3 applications would be very similar. Residues at 7 days were mostly not detectable, which supports an MRL of 0.01* mg/kg for pears. Data for pears from Argentina and Italy support this conclusion. The same conditions of use in Australia and the USA appear to produce slightly higher residues, but Australia has no registered use on pears, and the proposed use in the USA will require a 21-days PHI.

There is no current official GAP for abamectin use on strawberries, but there are proposed uses in Italy and the USA (up to 0.022 and 0.026 kg ai/ha respectively) with a PHI of 3 days. Evaluation of the available data from supervised trials in Brazil, France, Italy, Spain and the USA in terms of the proposed GAP suggests that an MRL of 0.02 mg/kg would be suitable, but this recommendation should be postponed until official GAP is confirmed.

Copious celery residue trials data were supplied from the USA. As yet there is only proposed GAP in the USA (0.013-0.026 kg ai/ha with 7 days PHI). If the data are evaluated against the proposed use an MRL of 0.05 mg/kg would be suitable. This recommendation could proceed if the proposed GAP were confirmed as official. Residues in trimmed celery were at similar levels to residues in untrimmed celery.

Recommended GAP for cucumbers in France includes application of abamectin at up to 0.022 kg ai/ha with a PHI of 3 days. Data from supervised glasshouse trials in France suggest a need for an MRL of 0.05 mg/kg. Glasshouse trials in Italy, The Netherlands and Spain produced somewhat lower residues for the same nominal treatment. The variation between trials of residues at day 0 reflects likely variations of spray application efficiency.

The Netherlands has a proposed use on lettuce with a suggested 14 days PHI. Supervised glasshouse trials data from The Netherlands were mostly for 7 and 10 days after the final application, and so could not be evaluated even against the proposed use. The USA has a proposed use on lettuce, up to 0.021 kg ai/ha with a PHI of 7 days. Under these conditions most residues in lettuce were less than 0.01 mg/kg, but some trials produced residues in the 0.02-0.03 mg/kg range. An MRL of 0.05 mg/kg for head lettuce would be appropriate if the proposed use becomes official GAP.

Residue data from numerous supervised trials on Brassica leafy vegetables and white cabbage in Malaysia, the Philippines, Taiwan and Thailand were made available to the Meeting. The data could not be evaluated because of a lack of supporting information such as sample preparation: including or discarding external leaves can influence measured residue levels on these crops. In some white cabbage trials residues were not detected (<0.001 mg/kg) on the day of application, which requires explanation perhaps in terms of weather conditions or sample preparation.

France has an approved use for abamectin on sweet peppers with application at 0.022 kg ai/ha and a PHI of 3 days. Proposed uses in Italy and The Netherlands are in line with the use in France. Residue data from trials in France, Italy and The Netherlands all lead to the same pattern of residues. The Meeting recommended an MRL of 0.02 mg/kg for abamectin residues on sweet peppers.

Argentina, France, Mexico, Portugal, South Africa and Spain all have similar registered uses for abamectin on tomatoes, up to 0.023 kg ai/ha with a PHI of 3 days. Proposed uses in Brazil, Italy, The Netherlands and the USA also follow this use pattern. Supervised trials data from Argentina, Australia, Brazil, France, Italy, Spain and USA show that in a large majority of tomato samples treated according to this use pattern residues are below the limit of determination (0.005 mg/kg), but occasional samples have residues up to 0.02 mg/kg. Two glasshouse trials in The Netherlands produced higher residues, up to 0.06 mg/kg, but this is not current GAP. The Meeting concluded that 0.02 mg/kg would be a suitable MRL for tomatoes.

Supervised abamectin residue trials on cotton have been reported from Australia, Brazil, South Africa and the USA. Over a wide range of application rates, some of which were higher than label rates, and various intervals after the final application, residues were not detected (<0.005 mg/kg) in cotton seed. The Meeting recommended an MRL of 0.01* mg/kg for cotton seed.

Residues were not detected in almonds, pecans or walnuts in a series of supervised trials in the USA in 1988 and 1989. If the proposed uses in the USA become official suitable MRLs would be 0.01* mg/kg. A suitable MRL for almond hulls would be 0.1 mg/kg, based on the proposed 0.026 kg ai/ha application rate and a PHI of 21 days.

The lactating goat study and the lactating dairy cow study permit an estimation of the likely maximum residues arising in milk and meat from consumption of feed containing up to 0.1 ppm abamectin. The Meeting was able to estimate MRLs for meat, offal and milk.

Detailed information was provided to the Meeting on the fate of abamectin residues during the processing of oranges, tangerines, grapefruit, tangelos, apples and tomatoes.

The residue trials had shown that abamectin residues were not detectable in citrus pulp, and the processing trials confirmed that residues were not detectable in the juice. Residues were at much higher levels in the citrus oils than in other fractions, reflecting the lipid-soluble nature of abamectin.

In an apple processing study residues were not detectable in the juice or in apple sauce. Residues were depleted by washing and coring. Residues were mainly on the skin of the apple, which carried the residues through the process to the pomace. Unwashed apples containing abamectin residues at approximately 0.008 mg/kg produced wet pomace with residue levels of 0.04 mg/kg.

Tomatoes were processed to puree and pomace in a US study in 1986. Residues were not detected in the puree, but were carried through the process to the pomace. Residues were depleted by washing, but not by other parts of the process.

Extensive data were provided to show that avermectin B_{1a}, B_{1b} and Δ-8,9-B_{1a} in commodity sample matrices stored at freezer temperatures up to 3-4 years were stable. Matrices tested were: celery, cotton seed, grapefruit, grapefruit peel, grapefruit pulp, lemon, lemon peel, lemon pulp, orange, orange peel, orange pulp, pear, strawberry, and tomato.

Residues arising from the use of abamectin which need to be measured by an analytical method are avermectin B_{1a}, avermectin B_{1b} and Δ-8,9-avermectin B_{1a}. Analytical methods rely on conversion of these molecules to fluorescent derivatives, which are analyzed by HPLC.

Acetic anhydride or trifluoroacetic anhydride convert the cyclohexene ring to an aromatic ring,

which confers fluorescence on the molecule. The Δ-8,9-isomer yields the same derivative as avermectin B_{1a}. HPLC analysis is achieved on a reversed phase system with a C-18 column and 10% (v/v) water in methanol. The fluorescent derivative of avermectin B_{1a} and its Δ-8,9 isomer is eluted after the avermectin B_{1b} derivative. The fluorescent derivative has an excitation maximum of 365 nm and an emission maximum of 470 nm; consequently the fluorescence detector is set up with a 365 nm bandpass excitation filter and a 418 nm emission cut-off filter.

The sample extracting solvent depends on the matrix; extracting solvents which have been used are acetonitrile, methanol, and hexane/acetonitrile/ water. Most clean-up procedures require three columns: C_8, NH_2, and silica, but alumina is required for some crops. Pome fruit are treated with pectinase to reduce the amount of pectin prior to extraction; if not so treated the pectin clogs the filtration of the extraction solvent.

Limits of detection and quantification are generally reported as 0.002 and 0.005 mg/kg respectively. The method was extensively tested (about 400 recovery tests) on crops reported in the supervised trials at spiking levels of 0.005-0.1 mg/kg for avermectin B_{1a}, B_{1b} and Δ-8,9 isomer. Recoveries were in the range 70-110%.

Methods for soils, bovine tissues and milk, which rely on the same reactions but have different extraction solvents and clean-up, have also been extensively validated.

The fluorescent derivatives of ivermectin and abamectin are separated by the reversed phase HPLC system, so if both were present in the one sample there would be no confusion of identities.

Avermectin B_{1a} forms two different derivatives which are very useful for positive residue identification. Treatment with 1% sulphuric acid in methanol removes both of the sugar moieties to produce the aglycone. Only one sugar is removed by 1% sulphuric acid in isopropanol to produce the monosaccharide. Both of these molecules form fluorescent derivatives which are separated from each other and the parent by HPLC.

Although abamectin has a relatively high octanol/water partition coefficient (log P_{ow} 3.96) this results mainly from its very low water solubility. The Δ-8,9 isomer is less polar than avermectin B_{1a} on the evidence of elution order on reversed phase HPLC. No information was available on the distribution of the residue between the fat of milk and the remainder of the milk. Metabolism and animal transfer studies suggest that the residue does not continue to accumulate in fat; in the lactating goat study residues in milk reached a plateau on day 4. The Meeting decided that the residue would not be defined as fat-soluble.

The Meeting was provided with a list of proposed and established national maximum residue limits from ten countries.

FURTHER WORK OR INFORMATION

Desirable

1. Details of official GAP when available for almonds, celery, lettuce, pecans, strawberries and walnuts will permit the estimation of further MRLs from the data already supplied.

2. Supporting information (field information, sample preparation) for the supervised trials on brassica leafy vegetables and white cabbage is needed before the data can be evaluated.

3. Information on the distribution of abamectin between the fat and non-fat phases of milk.

4.2 ALDICARB (117)

Aldicarb is an *N*-methylcarbamate ester of an aliphatic oxime currently used as an insecticide and nematicide in agriculture. As with all carbamate insecticides, aldicarb interacts with cholinesterases in a rapidly reversible manner, its mode of action being associated with the inhibition of acetyl-cholinesterase at nerve synapses.

TOXICOLOGY

Aldicarb was evaluated for Acceptable Daily Intake by the 1979 and 1982 Joint Meetings. An ADI of 0-0.005 mg/kg bw was allocated by the 1982 Joint Meeting.

Aldicarb is rapidly absorbed, widely distributed in the body and rapidly excreted. Metabolism appears to be similar in all species studied, aldicarb being rapidly metabolised to its sulphoxide, which is more slowly degraded to aldicarb sulphone. All metabolites are quickly eliminated from the body, 80-90% being excreted within 24 hours. Elimination was complete by the fifth day after dosing and no bio-accumulation was seen.

Aldicarb has high acute toxicity in a wide variety of mammalian species. Signs of toxicity are those commonly associated with acetylcholinesterase inhibition by a carbamate insecticide: cholinergic signs of poisoning, which are alleviated rapidly on cessation of exposure. Aldicarb sulphoxide is a more potent inhibitor of acetylcholinesterase than aldicarb itself, while aldicarb sulphone is considerably less toxic than either aldicarb or the sulphoxide. WHO has classified aldicarb as extremely hazardous.

Short-term and long-term toxicity studies have been performed in mice, rats, and dogs with aldicarb and its metabolites, both individually and in combination. Toxicity tests employing mixtures of aldicarb or aldicarb sulphoxide with aldicarb sulphone are of interest because aldicarb sulphoxide and aldicarb sulphone are the terminal residues potentially consumed by humans. Cholinesterase depression is the most significant indicator of toxicity that can be evaluated. However, considerable attention must be paid to the methods of sample collection and determination of cholinesterase activity. Continuous administration of aldicarb to the test animals until collection of samples for analysis is important, as is rapid analysis under carefully controlled conditions.

No-effect levels in the various studies which included evaluation of cholinesterase inhibition, are summarized in Table 1. No distinction is made in this table between the methods of determining cholinesterase activity.

It is now considered inappropriate to use no-adverse effect levels from many of the earlier repeat-dose studies for the derivation of an ADI, because animals were not dosed for 24-48 hours before the collection of tissue samples for measurement of cholinesterase activity. In the most recent studies in dogs, which were conducted in a manner designed to maximise detection of cholinesterase depression, the overall NOEL was 0.02-0.03 mg/kg bw/day, but the NOAEL (which discounts inhibition of plasma cholinesterase only) was 0.05-0.06 mg/kg bw/day.

Results of repeat-dose studies with aldicarb demonstrate that the method of administering the test material to the test animals can greatly modify the apparent toxicity of aldicarb and its metabolites. Mice, rats and dogs have tolerated daily doses equal to the LD50 incorporated into the diet for 7 days to 2 years. Doses which caused death in less than 2 hours when administered as a bolus caused no death and only moderate cholinesterase depression when given in the diet.

Two dietary carcinogenicity studies have been conducted with aldicarb in rats and three in mice. A dermal carcinogenicity study has also been conducted with aldicarb in mice and dietary studies have been carried out with aldicarb sulphone in mice and aldicarb sulphoxide in rats. Aldicarb was not carcinogenic in mice or rats.

Two reproduction studies have been conducted in rats with aldicarb and one with aldicarb sulphone. There were no effects on reproductive performance at doses up to 0.7 mg/kg bw/day aldicarb or 9.6 mg/kg bw/day aldicarb sulphone. Aldicarb did not display any teratogenic potential in rats or rabbits in studies which included maternally-toxic doses.

After reviewing the available genotoxicity data, the meeting concluded that aldicarb, aldicarb sulphoxide and aldicarb sulphone are not genotoxic.

In a range of special studies in animals (involving delayed neurotoxicity, behaviour, antagonistic agents and pesticide interactions) aldicarb displayed no results which gave cause for concern. There was no evidence of immunotoxicity in mice in a number of functional assays of cell-mediated immunity and in host resistance to respiratory infection.

Epidemiological studies provided no convincing evidence that aldicarb could significantly alter immunological function in man.

In addition to the above epidemiological studies, studies conducted in 1982 and 1983 attempted to correlate any potential adverse health effects with the occurrence of aldicarb in drinking-water. Although the authors concluded that further study was needed, there was no clear evidence that aldicarb contamination of drinking water generally at concentrations of about 4-12 mg/l, but at a maximum concentration of 400 mg/l was not related to any health effects.

Table 1: Summary of no-effect levels in repeat-dose toxicity studies which included cholinesterase investigations

Species	Duration	Test Material	Dosages*	NOAEL**	Effects at higher doses
Mouse	7 days	Aldicarb	0,0.1,0.3,0.6,<u>1.2</u>	0.6	Mortality
Mouse	7 days	Aldicarb: Aldicarb sulphone 1:1	0,2,<u>6</u>,18,36	2	Kidney and liver weight reduction, growth depression.
Rat 7 days	Aldicarb		0,4,8,16	Not established	Mortality, growth depression, kidney and liver weight reduction
Rat 7 days	Aldicarb		0,0.8,1.6,3.2	Not established	Growth depression kidney and liver weight reduction
Rat 93 days	Aldicarb		0,0.02,0.1,<u>0.5</u>	0.1	Mortality, growth depression
Rat 2 years	Aldicarb		0,0.005,0.025, 0.05,0.1	>0.1	No effects seen
Rat 7 days	Aldicarb Aldicarb sulphoxide Aldicarb sulphone		0,0.4,0.8,<u>1.6</u>,3.2 0,0.4,<u>0.8</u> 0,0.4,1.0,2.5,<u>5</u>,20	0.8 0.4 2.5	Growth depression RBC cholinesterase depression
Rat 29 days	Aldicarb sulphoxide: Aldicarb sulphone 1:1		0,0.0074,0.03, 0.12,<u>0.47</u>,1.67 in drinking water	0.12	Growth depression brain, plasma and RBC cholinesterase depression
Rat 6 months	Aldicarb sulphoxide		0,0.125,<u>0.25</u>,0.5,1	0.125	Growth depression brain, plasma and RBC cholinesterase depression
Rat 6 months	Aldicarb sulphoxide		0,0.0625,0.125, <u>0.25</u>,0.5,1.0	0.125	Plasma and RBC cholinesterase depression
Rat 6 months	Aldicarb sulphone		0,0.2,0.6,<u>1.8</u>, 5.4,15.2	0.6	Brain, plasma and RBC cholinesterase depression

*: mg/kg bw/day equivalence, by dietary administration, unless otherwise stated. Lowest-effect level is underlined.

**: NOAELs were tabulated without evaluation of methods of sample collection or method of determination of cholinesterase activity.

Table 1: (Continued)

Species	Duration	Test Material	Dosages*	NOAEL**	Effects at higher doses
Rat	7 days	Aldicarb oxime	0,31.25,62.5,<u>125</u>, 250,500,1000	62.5	Growth depression, minor liver and kidney changes
Dog	7 days	Aldicarb	0,0.2,0.3,0.7	>0.7	No effects seen
Dog	100 days	Aldicarb	0,0.2,0.3,<u>0.7</u>	0.3	Minor organ weight changes
Dog	2 years	Aldicarb	0,0.025,0.05 0.1	>0.1	No effects seen
Dog	2 weeks	Aldicarb	0,0.022,0.068, 0.192,0.609, 1.42	Not established	Brain, plasma and RBC cholinesterase depression
Dog	2 weeks	Aldicarb	0,0.003,0.008, 0.027,0.096, <u>0.28</u>	0.096	Brain, plasma and RBC cholinesterase depression
Dog	5 weeks	Aldicarb	0,0.012,0.024, 0.06	>0.06	No effects seen
Dog	52 weeks	Aldicarb	0,0.027,0.054, <u>0.131</u>,0.241	0.054	RBC, plasma and brain cholinesterase depression
Dog	3 months	Aldicarb sulphoxide	0,0.0625,0.125, 0.25,<u>0.5</u>	0.25	Transient growth depression
Dog	3 months	Aldicarb sulphone	0,0.2,0.6, 1.8,5.4	>5.4	No effects seen
Dog	1 year	Aldicarb sulphone	0,0.11,<u>0.59</u>, 2.25	0.11	RBC, plasma and brain cholinesterase depression

*: mg/kg bw/day equivalence, by dietary administration, unless otherwise stated. Lowest-effect level is underlined.

**: NOAELs were tabulated without evaluation of methods of sample collection or method of determination of cholinesterase activity.

The anti-cholinesterase potential of aldicarb has been extensively investigated in humans. These studies revealed the same pattern of rapid cholinesterase inhibition and rapid recovery as was seen in experimental animals. Transient erythrocyte cholinesterase depression was seen at single doses of 0.05 mg/kg bw, and the NOAEL for cholinesterase depression (discounting changes in plasma enzyme activity) was 0.025 mg/kg bw.

A number of poisoning incidents have been reported in the agricultural use of aldicarb, but there has been no indication that the workers exposed were harmed once removed from the source of exposure. Although several deaths have been reported, all of them have been attributed to suicide or gross neglect.

A number of food-borne aldicarb intoxications have been reported in the literature. These have all been associated with misuse, and reliable quantification of the dose of aldicarb involved has always proved difficult, if not impossible.

An ADI was allocated using a 10-fold safety factor applied to the NOAEL for depression of erythrocyte cholinesterase activity in human volunteers.

A toxicological monograph, summarizing the data that were received recently and incorporating the previous monograph and monograph addendum on aldicarb, was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Rat:	0.1 mg/kg bw/day (93 day-dietary study)
Dog:	0.05 mg/kg bw/day (52-week study)
Human:	0.025 mg/kg bw (double-blind, placebo-controlled volunteer study)

Estimate of acceptable daily intake for humans

0-0.003 mg/kg bw

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

Further observations in humans, including information regarding the correlation of blood cholinesterase depression and clinical signs and symptoms.

4.3 ALDRIN, DIELDRIN (001)

RESIDUE AND ANALYTICAL ASPECTS

The 22nd (1990) Session of the CCPR had requested monitoring data for aldrin, dieldrin and endrin so that ERLs could be estimated to replace MRLs. Monitoring data were supplied to the 1990 JMPR and MRLs were converted to temporary ERLs pending the proposed 1992 review.

The 1990 JMPR had recommended conversion of existing MRLs (listed on p 19 of the 1990 Residue Evaluations) to temporary ERLs, but had made no recommendations on the existing ERLs (for carrots, cereal grains (except rice), eggs, lettuce, meat and milks). Part 2 of the Codex Guide to Residue Limits (July 1991 edition) lists temporary ERLs for these commodities, but they should not have been converted to temporary limits.

The Extraneous Residue Limit (ERL) for JMPR purposes refers to a pesticide residue arising from environmental sources (including former agricultural uses) other than the use of a pesticide directly or indirectly on the commodity. It is the maximum concentration of a pesticide residue that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food, agricultural commodity or animal feed (JMPR Report 1990).

Information from Australia, The Netherlands, Thailand and the USA was made available to the Meeting. The new data were evaluated in conjunction with the data supplied in 1990.

Where dieldrin and aldrin have been used and use has been discontinued, traces of dieldrin are likely to be present in the soil for a number of years. Dieldrin in the soil can lead to contamination of plant or animal commodities produced in its vicinity.

Monitoring data demonstrate that for a large range of crop and animal commodities most samples (97-99% plus) do not contain detectable residues of dieldrin, with analytical methods operating usually down to 0.01-0.02 mg/kg. However, this small incidence of detections could cause trade disruptions unless officially recognized as acceptable by the assignment of ERLs.

MRLs are estimated for individual commodities when there are registered uses on those crops or animals, and extrapolation to a commodity group is possible only when there is GAP (registered uses)

on the major crops or animals within the group. ERLs have no such relationship to registered uses, and the possibility of contamination of one commodity in a group is equal to the possibility for other members of the group if produced in similar circumstances. The Meeting agreed that, in general, monitoring data would be interpreted on a commodity group basis for the purpose of estimating ERLs.

Dieldrin has been detected in fruits, vegetables, cereals and animal commodities. Extraneous residues can be particularly troublesome in animal commodities because of the sampling philosophy. For animal commodities every individual unit in a consignment should comply with the MRL or ERL. If any one unit contains a residue exceeding the MRL, the whole consignment is considered to be in violation. For crop commodities the residue level in the final composite sample from the consignment should comply with the MRL or ERL. Under this philosophy a number of samples are taken from the consignment and composited to represent the average. The composite is then analyzed. If the composite contains a residue exceeding the MRL, the consignment is in violation.

Endrin is less persistent in the environment than dieldrin, it was probably less widely used, and its uses were phased out earlier than those of dieldrin or aldrin. Consequently endrin is detected in monitoring programmes less often than dieldrin.

The Meeting recommended ERLs for aldrin, dieldrin and endrin on commodity groups where residues have been detected in recent monitoring programmes. The estimated levels for the ERLs should include residues which inadvertently occur by contamination; direct use of these compounds on an animal or crop would be likely to lead to residues higher than the proposed ERLs. The previously established ERLs for aldrin/dieldrin on eggs, meat and milks should be maintained.

Where no residues have been detected in commodity groups no ERL has been recommended. The monitoring data suggest that in these commodity groups the residues do not exceed 0.01 mg/kg.

It is expected that for environmental contaminants the incidence of detections would increase if analytical methods with lower limits of determination (LODs) were employed. The Meeting noted the comments made at the 24th Session of the CCPR (ALINORM 93/24, para 29) about realistic limits of determination, and agreed that using methods with unjustifiably low LODs was more costly and not the best use of resources. The Meeting concluded that for the general monitoring of aldrin, dieldrin and endrin residues, a suitable LOD would be 0.01 mg/kg.

As production of these compounds ceases, and environmental residues dissipate, extraneous residues in food commodities are also likely to decrease. The Meeting recommended that available monitoring data be evaluated in 1998 with a view to further revision of aldrin, dieldrin and endrin ERLs.

4.4 ANILAZINE (163)

RESIDUE AND ANALYTICAL ASPECTS

Anilazine was evaluated by the 1989 JMPR, which required an analytical method suitable for the determination of the parent anilazine in commodities of animal origin for enforcement purposes.

Further information was considered desirable on (1) residues of anilazine (parent compound) compared with residues of mono- and dihydroxy-anilazine in cereals, celery and tomatoes from trials with approved uses, and (2) residues in other fruits and vegetables.

At the 1990 CCPR reservations were expressed concerning the limits for barley and wheat straw and fodder, dry, because of the large and unexplained variation. The Committee agreed that information on animal products would be necessary, but a suitable method of analysis was not available. The Committee decided to make the proposals for barley and wheat straw and fodder temporary, awaiting a method of analysis for the parent compound in animal tissues.

Some additional use patterns, reports on supervised trials and validated analytical methods were submitted for evaluation.

The results of supervised trials on celery, tomatoes and cereal grains are in line with those considered by the 1989 JMPR and support its recommendations.

The Meeting reconsidered the residue information on barley and wheat forage and straw submitted for the 1989 and 1992 Meetings. The residues in barley straw from supervised trials carried out according to current use patterns support the 10 mg/kg limit recommended by the 1989 JMPR. Residue data on wheat forage and straw were available from 31 trials carried out with 0.96-1.92 kg ai/ha, representing current GAP in several countries. Residues (70 results) in wheat straw were below 10 mg/kg 28 days after the last application and generally decreased further during the observation period of 28-56 days. They amounted to about 1/4 - 1/3 of the 0-day residue in green forage after 35 days, with the exception of two trials in which the following residues (mg/kg) were measured at the given times [days]: 6.6 [27], 13 [35], 7.5 [42] and 31 [28], 30 [35], 31 [42]. The initial residues in green forage were 22 mg/kg and 18 mg/kg respectively.

The Meeting considered the residue ratios in these trials to be atypical and concluded that 10 mg/kg would be sufficient to cover the residues from approved uses.

The validated analytical methods for commodities of animal and plant origin are suitable for regulatory purposes.

The feeding studies reported in the 1989 evaluation indicated that no detectable residue would occur either in the meat and edible offal of cattle, goats and poultry or in the milk of cattle and goats. As validated residue analytical methods have been elaborated, the Meeting was able to estimate maximum residue levels based on the parent compound alone for commodities of animal origin.

4.5 BENALAXYL (155)

RESIDUE AND ANALYTICAL ASPECTS

Benalaxyl was reviewed by the JMPR in 1986, 1987 and 1988. Several items of information were listed as desirable by the 1986 JMPR and other information had been promised at the CCPR. The present Meeting received additional GAP information from Spain and Australia, additional summary data on supervised trials on peppers and, for the first time, summarized supervised trials data on lettuce. The residue data were submitted by the Spanish government, but the trials were conducted in France, Austria and the UK (lettuce) and Italy (peppers). Information on GAP for lettuce was provided only for Spain.

New Australian GAP for cucurbits, onions and grapes does not require revision of previously recommended limits. The additional data on peppers (maximum residue 0.03 mg/kg) do not indicate the need for a revision of the current 0.05 mg/kg limit. Maximum residues in lettuce of 0.2 mg/kg in the Austrian trials at approximately 0.6 times the Spanish GAP rates suggest that a limit of at least 0.2 mg/kg may be required but, because data reflecting GAP were limited and only summary data with no trial details were provided, the Meeting could not recommend a limit for lettuce.

The Meeting was informed that additional residue data would be available for review at a future Meeting.

4.6 BIFENTHRIN (178)

2-methylbiphenyl-3-ylmethyl (*Z*)-(1*RS*,3*RS*)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

Bifenthrin is a synthetic pyrethroid insecticide and acaracide reviewed for the first time by the present Meeting. It is registered on 70 crops in over 30 countries.

TOXICOLOGY

After oral administration of bifenthrin to rats the compound was absorbed and eliminated mainly via the faeces (70-80% within 48 hours). Urinary excretion amounted to 5-10% of the administered doses. Biliary excretion was shown to range from 20 to 30%. Hydrolysis and hydroxylation were the majors steps in the biotransformation.

Bifenthrin has moderate acute toxicity and is classified as moderately hazardous by WHO.

Following dietary administration to rats for 90 days of 0, 12, 50, 100 or 200 ppm bifenthrin tremors were the only treatment-related effect occurring at 200 ppm. The NOAEL was 100 ppm, equivalent to 5 mg/kg bw/day.

In a 13-week oral toxicity study in dogs at doses of 0, 2.5, 5.0, 10 or 20 mg/kg bw/day administered in capsules, the NOAEL of 2.5 mg/kg bw/day was based on the occurrence of tremors at 5.0 mg/kg bw/day and above. In a one-year oral toxicity study in dogs at doses of 0, 0.75, 1.5, 3.0, or 5.0 mg/kg bw/day administered in capsules, the NOAEL of 1.5 mg/kg bw/day was based on the appearance of the same clinical signs.

In a lifetime feeding study with mice at dietary concentrations of 0, 50, 200, 500 or 600 ppm over at least 20 months, the NOAEL (based on tremors at 200 ppm in males and 500 ppm in females) was 50 ppm, equal to 7.6 mg/kg bw/day, in males and 200 ppm, equal to 37 mg/kg bw/day, in females. Treatment at 600 ppm equal to 103 mg/kg bw/day caused an increased incidence of submucosal tumours (haemangiomas) in the urinary bladder in male animals. This finding was of marginal statistical significance, but a tumorigenic potential for bifenthrin in mice cannot be excluded.

In a two-year feeding study with rats at concentrations of 0, 12, 50, 100 or 200 ppm, the NOAEL was 100 ppm, equal to 4 and 7.5 mg/kg bw/day in males and females, respectively. Higher dose levels caused tremors and a reduction in body-weight gain. Bifenthrin was not carcinogenic in rats.

In a multi-generation reproduction study in rats at dietary concentrations of 0, 30, 60 or 100 ppm, the NOAEL was 60 ppm, equivalent to 3 mg/kg bw/day, based on changes in brain weight at 100 ppm. Reproduction was not impaired by treatment.

In a teratogenicity study in rats at gavage dose levels of 0, 0.5, 1 or 2 mg/kg bw/day, the NOAEL was 1 mg/kg bw/day based on the occurrence of tremors at 2 mg/kg bw/day in the dams. There was no evidence of teratogenicity.

In a teratogenicity study in rabbits at gavage doses of 0, 2.7, 4 or 8 mg/kg bw/day, the NOAEL was 2.7 mg/kg bw/day. Doses of 4 and 8 mg/kg bw/day caused tremors and twitching. No teratogenic, fetotoxic or embryotoxic effects were found.

After reviewing the available genotoxicity data, the Meeting concluded that bifenthrin was unlikely to present a genotoxic hazard.

The results of the long-term studies in rats and mice and a series of studies designed to evaluate genotoxicity indicated that bifenthrin is unlikely to pose a carcinogenic hazard to humans.

An ADI was allocated on the basis of the NOAEL of 1.5 mg/kg bw/day in the one-year study in dogs using a 100-fold safety factor. This result was supported by the same NOAEL in the rat teratology study, although in the latter study gavage, rather than dietary administration, was used.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 50 ppm, equal to 7.6 mg/kg bw/day (20-month feeding study)

Rat: 100 ppm, equal to 4 mg/bw/day (two-year feeding study)
1 mg/kg bw/day (teratology study)
60 ppm, equivalent to 3 mg/kg bw/day (multi-generation reproduction study)

Rabbit: 2.7 mg/kg bw/day (teratology study)
Dog: 1.5 mg/kg bw/day (one-year study)

Estimate of acceptable daily intake for humans

0-0.02 mg/kg bw

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

Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Supervised field trials were conducted on numerous food or feed crops.
Only minimal data were available for broccoli, common beans, cucumbers, egg plants, melons, oats, peas, and rye (no GAP was reported for rye). A substantial number of trials was conducted on peaches. However except for the peach trials in the USA, where the use is not GAP, all trials were with only one application instead of the 3-4 generally recommended, so that the only data reflecting GAP application rates and PHI were from the French trials at a 15-day PHI.

Although none of the trials on potatoes were in the countries cited as having GAP, all residues from multiple applications at higher rates than those reported as GAP were below 0.01 mg/kg. A maximum residue level at the limit of determination was therefore estimated.

In the case of rape seed data were available from 3 countries, but only from one in which the use is GAP. Data were available on the seeds from only one country, being described in the other two countries as being on whole plant, plant, cake, pods or oil, without a basis for determining a concentration factor from seeds to oil. Before MRLs can be estimated, additional data reflecting GAP will be needed, as well as additional processing information to permit the estimation of concentration factors.

Although many results were available for strawberries, most of them were from single applications, compared with the 3-4 applications recommended in general. Although not from trials strictly conforming to GAP, maximum residues in dry hops of 8.9 mg/kg indicated a need for a 10 mg/kg limit. This was further supported by applying a concentration factor of approximately 3 to residues in green hops.

Although data indicate that residues of bifenthrin in apples, grapes and tomatoes are unlikely to exceed 0.5, 0.5 and 0.2 mg/kg respectively, the Meeting decided not to recommend limits for these crops until processing studies had been provided. Limits are proposed for other crops for which processing studies are desirable but where estimated maximum residue levels are at the limit of determination.

The fate of bifenthrin has been studied in animals, plants, water and soil, and during storage. Metabolism in animals and plants is similar to the extent that all plant metabolites have been identified in animals and that unchanged parent compound is the predominant residue.

In plants residues are primarily on the surface (e.g. 15.5% of the radioactivity was found in apple pulp) and typically 80-90% (e.g. in cotton seed) is organosoluble, depending on the time after

application. Generally about 60-90% of the organosoluble residue is unchanged bifenthrin. 4′-hydroxy-bifenthrin is the only plant metabolite found at analytically significant levels. For example it amounted to 6-12% of the radioactive residue in maize plants, but was not identified in apples or cotton seed. Other plant metabolites found at low levels include 2-methylbiphenyl-3-ylmethanol and the corresponding aldehyde and acid (BP-alcohol, BP-aldehyde, and BP-acid), and (Z)-(1*RS*,3*RS*)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcycloprop-anecarboxylic acid (TFP acid). The plant metabolism studies indicate that the unchanged parent compound is a suitable indicator of the total residue in plants. All field trials data reported to the Meeting were in fact only for the unchanged compound, except some of the studies on maize. Analyses for 4′-hydroxy-bifenthrin on additional commodities are desirable.

In animals the major routes of elimination of bifenthrin are through the faeces and urine. Although there are some qualitative similarities between metabolism in animals and plants, it appears to be more extensive in animals and additional metabolites have been identified. Metabolism proceeds primarily by oxidation, either at the gem-dimethyl group to form hydroxymethyl metabolites or on the biphenyl ring, and by hydrolysis to TFP-acid and BP-alcohol. Conjugation at the hydroxymethyl group may occur before or after hydrolysis.

In quantitative terms oxidation and conjugation at the gem-dimethyl group appears to dominate in poultry, whereas oxidation of the biphenyl ring appears to be the main route in goats. In goats and poultry, as in plants, a high percentage of the residue is organosoluble, and the predominant residue in eggs, milk, muscle and fat of cattle or poultry is unchanged bifenthrin. In goats, however, the BP-acid metabolite is the predominant residue (35%) in kidney with bifenthrin at 16-22%, while in poultry liver the TFP-acid (25%), fatty acid conjugates of hydroxymethyl-bifenthrin (25%) and unconjugated methyl-bifenthrin (12.1%) are the major residues, with only 2.2% of unchanged bifenthrin.

In cow feeding trials samples were analyzed for bifenthrin, BP acid and BP-alcohol and the parent compound was the predominant residue in tissues. The goat metabolism studies indicate that residues of 4′-hydroxy-bifenthrin may occur in fat at approximately the same level as the BP-alcohol. Although the tissues in the cow feeding trials were not analyzed for the 4′-hydroxy metabolite, the Meeting noted that residues of both metabolites were very low in the goat metabolism studies as was the BP-alcohol in the cow feeding trials.

The greatest potential for meat and milk residues comes from the feeding of pomaces or maize fodder or forage. The Meeting concluded from the estimated maximum residue levels that the dietary intake of bifenthrin by cows is not likely to exceed 2 ppm, and would probably be much lower than that if less exaggerated assumptions about feed residue levels were made. Residues from the 5 ppm feeding level indicate that residues in cattle meat and milk resulting from an intake of 2 ppm are unlikely to exceed the limit of determination on a whole product basis. If proposed uses on maize should become GAP, a more refined estimate of intake may be needed.

Similar estimates for chicken tissues and eggs result in the same conclusion about maximum residues. The maximum residue levels at the limit of determination for both give some support for defining the residue as the parent compound in both plants and animals, even with the recognition that it is not a good indicator of the total residue in chicken liver. The 0.5 mg/kg estimate for cattle fat the limit of determination estimate for chicken fat reflect different dietary intakes.

In keeping with Codex preferences for fat-soluble pesticides, the Meeting estimated maximum residue levels in the meat of cattle and chicken on a fat basis, although residues are not expected to exceed the limit of determination on a whole product basis. The same levels are recommended for use as MRLs in cattle and chicken fats as Codex commodities. In both cases the proposals are based on the meat or chicken fat data.

In aerobic and anaerobic soil studies bifenthrin was the predominant residue, with 4′-hydroxy-bifenthrin or TFP-acid being the major metabolites. The half-life was reported as 75 to 93 days in the aerobic study. In field studies, however, half lives of 150 to 174 days have been observed. A pronounced loss of radioactivity as CO_2 was found under aerobic conditions, but less under anaerobic. Bifenthrin was found to bind strongly to soils, less so in sandy soils where low mobility was observed. In aged soils 95% of the applied radioactivity was in the top 6 cm.

Translocation of radioactivity from treated soils to rotational crops has been observed, with identified residues (in wheat straw) including bifenthrin as the major residue, the TFP-acid the next highest.

Little degradation was observed in aqueous hydrolysis experiments owing to the extremely low solubility of bifenthrin. However, under photolysis conditions some conversion from *cis*- to *trans*-bifenthrin has been observed, more so under artificial lighting.

In maize processing studies concentration was found only in refined oil (2.3 times) from wet milling (there was no concentration in dry milling).

Storage stability studies have been conducted on a variety of plant and animal products with minimal losses in many matrices after 2 years and longer in some. The 4′-hydroxy-bifenthrin metabolite was also relatively stable in plant matrices and cow fat for 12 or more months, and the BP- and TFP-acids in cow liver, muscle and fat for periods up to 2 years (≤23% loss). The BP-alcohol losses however were 55%, 25% and 25% in cow liver, muscle and fat respectively after only 6 months.

Over 24 analytical methods have been developed for bifenthrin and/or its metabolites in various matrices, either individually or as total residues. Although methods vary, most depend on extraction with various solvents, solvent/water partitioning, various combinations of GPC, Florisil, solid phase extraction, or silica column chromatographic clean-up, with determination by GLC. An EC detector is usually used for bifenthrin and 4′-hydroxy- bifenthrin and GC-MS for the BP-acid, BP-alcohol, TFP-acid and total residues where conversion is to the BP-alcohol. Limits of determination are highly variable, depending on the method and matrix, varying from 2.5 ng/l in water to 0.5 mg/kg in corn fodder with one method. Methods used in the field trials were not always provided, although from their description in broad terms they appeared to be similar to those that were provided.

FURTHER WORK OR INFORMATION

Desirable

1. Additional data on strawberries reflecting GAP which allows multiple applications and on tomatoes reflecting outdoor uses.

2. Analyses of additional plant commodities for the major plant metabolite 4′-hydroxy-bifenthrin.

3. Information on residues in food in commerce or at consumption.

4. Information on residue levels of bifenthrin and 4′-hydroxy-bifenthrin in processed fractions from the milling of barley and wheat and the processing of apples, citrus, grapes, potatoes and tomatoes.

4.7 BROMIDE ION (047)

RESIDUE AND ANALYTICAL ASPECTS

Inorganic bromide, resulting from the use of ethylene dibromide and methyl bromide fumigants, has been evaluated several times, most recently in 1989. The 24th (1992) Session of the CCPR (ALINORM 93/24, para 91) was informed that a full residue data package had been submitted for the 1992 JMPR review of residue data. Information was provided from the USA on residues of bromide ion in crops grown in methyl bromide-treated soil, and in commodities fumigated post-harvest with methyl bromide (Methyl Bromide Industry Panel).

The Netherlands provided information on methods of analysis, monitoring data and MRLs.

Bromide ion residues in 24 vegetable crops and 5 spices grown in methyl bromide-treated soils (150-384 kg ai/ha) showed wide variation, from less than 10 mg/kg to 770 mg/kg.

When a crop is planted or sown in treated soil the methyl bromide, which if present would be phytotoxic, has largely dissipated or been degraded to bromide ion. Depending on soil properties and prevailing rainfall and irrigation during crop growth, variable amounts of the bromide will remain in the root zone and be available for uptake by the crop. Levels found at maturity will further depend on the nature of the crop and the part of the plant harvested. Other things being the same, one would expect higher levels of bromide in leaves than in fruits or seeds.

If the soil contains bromide, whether from previous fumigations or from some other source, uptake from the soil will be the same. It follows that residues of bromide ion in crops are not a particularly useful indicator of methyl bromide soil fumigation practices.

However, MRLs for bromide ion are useful indicators of acceptable post-harvest methyl bromide or dibromoethane fumigations. In particular, they restrict multiple fumigations of the same lot or consignment of a commodity.

The Meeting decided that MRLs for bromide ion would be estimated for commodities where sufficient data were available, irrespective of the source of bromide (whether already present in soil, or resulting from soil fumigation or post-harvest fumigation).

Data on peas were limited, but the pea and bean data may be considered to be mutually supportive, and suggest that bromide ion in these vegetables could reach 500 mg/kg. Again, the radish and turnip data are mutually supportive. The Meeting estimated that the maximum residues in these commodities would approach 200 mg/kg.

Methyl bromide at 56 g ai/m^3 was used to fumigate almonds, almond products and walnuts in a series of post-harvest residue trials in the USA in 1983 and 1984. Residues of bromide ion accumulated in approximately equal amounts from repeated treatments. Current post-harvest GAP for methyl bromide was not available, so maximum residue levels for bromide ion in almonds and walnuts could not be estimated.

Monitoring data were provided on brassica vegetables, carrots, cucurbits, egg plant, leafy vegetables, peppers, stalk and stem vegetables, and tomatoes. The range of residues found in a particular crop was frequently very wide, but the mean residue was usually well below half the maximum level reported.

An HPLC method for inorganic bromide relied on aqueous extraction of the crop and direct detection of bromide with a UV detector set at 205 nm. A GLC method measured 2-bromoethanol, formed by reacting the extracted bromide with ethylene oxide.

FURTHER WORK OR INFORMATION

Desirable

Information on current officially authorised or approved post-harvest uses of methyl bromide.

4.8 CADUSAFOS (174)

RESIDUE AND ANALYTICAL ASPECTS

Cadusafos was evaluated in 1991 when the JMPR suggested that a residue analytical method should be published or, ideally, monitoring of cadusafos in a multi-residue method should be demonstrated.

Information was made available to the Meeting that cadusafos residues in crops can be determined by Pesticide Analytical Manual (USFDA) Method 232.4. Cadusafos was recovered quantitatively from bananas at fortification levels of 0.05 and 0.25 mg/kg.

4.9 CHLOROTHALONIL (081)

TOXICOLOGY

In 1990 the Joint Meeting allocated an ADI of 0-0.03 mg/kg bw for chlorothalonil, based upon the results of a two-year feeding study in dogs. A WHO Member State has since requested reconsideration of this ADI and the basis on which it was established. This request and additional information submitted to the Meeting, including a reproduction study in rats, were considered.

The new reproduction study in rats showed a NOAEL of 1500 ppm for maternotoxicity without adverse effects on reproduction, equivalent to 75 mg/kg bw/day.

The ADI allocated in 1990 was based on the NOAEL of 120 ppm first determined by the 1970 Joint Meeting on review of a two-year feeding study in dogs. This NOAEL was revised by the 1987 Joint Meeting to 60 ppm, but it was subsequently restored to its original value of 120 ppm, by the 1990 Meeting after consideration of an independent review of the histopathology which indicated that the renal tubular epithelial vacuolation found in the study was in all probability an artifact of fixation.

Concern has been raised recently over the validity of the 1970 study in dogs. The study was again reviewed by the present Meeting and found to be adequate for evaluation.

Three additional studies in dogs with chlorothalonil at higher doses were considered. None of these showed a no-effect level. In a 30-day study at 0, 50, 150 or 500 mg/kg bw/day, reduced body-weight gain occurred. In a 16-week study at 0, 250, 500 or 750 ppm, protein-bound iodine was increased at all doses. In a two-year study at 0, 1500, 15000 or 30000 ppm, weight loss occurred at all doses. In addition thyroid and kidney weight and liver/body-weight ratios were increased at mid and high doses. Treatment-related histopathological changes occurred in the liver, kidney and stomach of mid and high dose dogs.

A range of genotoxicity studies, *in vivo* and *in vitro*, was considered by the Joint Meeting in 1985 and 1987. The present Meeting confirmed that the data previously reviewed did not show a genotoxic hazard of chlorothalonil for humans.

Feeding chlorothalonil to rats for two years produced gastric and renal toxicity, hyperplasia and neoplasia. Renal epithelial hyperplasia and forestomach hyperplasia/hyperkeratosis occurred with a NOAEL of 1.5 mg/kg bw/day. Renal tumours, adenomas and carcinomas, and non-glandular gastric papillomas and squamous cell carcinomas occurred with a NOAEL for these effects of 3.3 mg/kg bw/day.

Similar findings in a two-year study in mice have increased concern over the carcinogenic potential of chlorothalonil. Mice had demonstrated similar sensitivity to gastric hyperplasia and hyperkeratosis (NOAEL 15 ppm, equal to 1.6 mg/kg bw/day) and papilloma formation (NOAEL 21 mg/kg bw/day) but they were somewhat less susceptible to chlorothalonil renal toxicity (NOAEL for renal epithelial tubular hyperplasia in males, 4.5 mg/kg bw/day) and renal neoplasia (NOAEL for males, 21 mg/kg bw/day).

The 1990 Joint Meeting concluded that the gastric lesions in rats and mice were attributable to the irritancy of chlorothalonil and so had little relevance for humans. The present Meeting confirmed this interpretation and agreed that the gastric lesions occurring in rodents were an inappropriate basis for the

estimation of an ADI.

Previous Joint Meetings considered the results of comparative metabolic studies in rats, germ-free rats, monkeys and dogs. Quantitative differences in the absorption, distribution, metabolism and excretion of chlorothalonil and its metabolites were noted. The urinary metabolites of chlorothalonil differed in each case. Orally-dosed normal rats excreted significantly more urinary thiols than orally-exposed germ-free or dermally-exposed normal rats. Monkeys excreted significantly lower levels of thiols than rats. Thiols were not detected in the urine of treated dogs. This suggested that the intestinal flora of the rat significantly influences the metabolic fate of chlorothalonil in that species and, indirectly, its renal toxicity. Accordingly, the 1990 Joint Meeting considered that these results suggested "that the dog or the monkey may be more suitable models than the rat for predicting the metabolism of chlorothalonil by man".

The present Meeting recalled that the rat is well known to have significantly different gastrointestinal flora from man (1).

Studies reviewed by previous Joint Meetings have shown that chlorothalonil reacts *in vitro* with glutathione (GSH) to produce mono-, di-, tri- and possibly tetra-conjugates with chlorothalonil. Dithiodichloroisophthalonitrile and trithiochloroisophthalonitrile, in both free sulphhydryl and methylated forms, are known to occur as metabolites of chlorothalonil in rat urine. Orally administered monoglutathione conjugates of chlorothalonil are further conjugated with GSH in the gastrointestinal tract of rats prior to absorption. In a 90-day gavage study in rats with the monoglutathione conjugate of chlorothalonil, renal toxicity was induced at 150 mg/kg bw/day. A similar study with equimolar concentrations of chlorothalonil showed renal toxicity at 75 mg/kg bw/day with a similar pattern of urinary metabolites. A mechanism for glutathione conjugation in oncogenesis, and for the causation of nephrotoxicity and renal carcinogenicity by certain chloroalkenes in rats, has been established (2,3). These findings suggest a role for glutathione conjugation in the biotransformation and renal toxicity of chlorothalonil in rats.

Overall, the Meeting considered that there was sufficient concordance between the results of metabolism and toxicity studies to establish that normal rats were sufficiently different from germ-free rats, monkeys and dogs to be discounted as a model for ADI estimation. Accordingly the Meeting used the most sensitive toxicological endpoint that it considered to be appropriate, the NOAEL established in the two-year study in dogs. A safety factor of 100 was applied.

An addendum to the previous toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 15 ppm in the diet, equal to 1.6 mg/kg bw/day (two-year study, reviewed by 1990 JMPR)
Rat: 1.5 mg/kg bw/day (two-year study, reviewed by 1990 JMPR)
Dog: 120 ppm in the diet, equivalent to 3.0 mg/kg bw/day (two-year study)

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

1. Further clarification of the mechanism of nephrotoxicity and renal carcinogenicity in rats and mice.
2. Information on the relevance of findings in animal studies to humans, including results of the metabolism study in dogs known to be in progress.
3. Observations in humans.

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4.10 CHLORPYRIFOS-METHYL (090)

TOXICOLOGY

The Meeting re-evaluated the recently-conducted long-term dietary study in rats on which the ADI of 0-0.001 mg/kg bw was based in 1991. The major interest was the vacuolation of the zona fasciculata of the adrenal gland. The study, which utilized dietary doses of 0, 0.05, 0.1, 1 or 50 mg chlorpyrifos-methyl/kg bw/day, did not show any carcinogenic potential of the compound.

On histopathological examination, no correlation was found between the incidence of vacuolation of the zona fasciculata of the adrenal gland and of other organs. The incidence of vacuolation of the zona fasciculata at all dose levels except the high dose was within the range of occurrence noted in contemporary rat studies performed in the same laboratory. The NOAEL for the study was therefore interpreted as being 1 mg/kg bw/day.

The 1975 Joint Meeting reviewed a human study in which five males/test group were given single doses of 0, 0.03 or 0.1 mg chlorpyrifos-methyl/kg bw/day for four weeks. Test groups were comparable to a control group of four males with respect to plasma and erythrocyte cholinesterase activity, haematology, blood chemistry, blood pressure, pulse rate and ophthalmology. The NOAEL was the highest dose tested, 0.1 mg/kg bw/day.

The ADI allocated by the 1991 Joint Meeting was based on the changes in rat adrenal pathology which were interpreted as showing a NOAEL of 0.1 mg/kg bw/day, to which a 100-fold safety factor was applied. With the revision of the NOAEL with respect to the rat adrenal, the present Meeting allocated an ADI based on the human data (NOAEL 0.1 mg/kg bw/day) using a 10-fold safety factor. This ADI is supported by the NOAEL in studies in rats (1 mg/kg bw/day) using a 100-fold safety factor.

An addendum to the previous toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 50 ppm, equal to 3.9 mg/kg bw/day (78-week study)
Rat: 1 mg/kg bw/day (two-year feeding study)
Human: 0.1 mg/kg bw/day (four-week study)

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

Further observations in humans.

4.11 CLOFENTEZINE (156)

RESIDUE AND ANALYTICAL ASPECTS

At the 23rd (1991) Session of the CCPR, the Committee decided to lower the MRL for citrus fruits from 0.5 to 0.2 mg/kg. The proposal was held at step 7B pending consideration by the JMPR. The 1992 CCPR also requested that the definition of residues as the total clofentezine-derived products be re-examined with respect to commodities of plant origin.

The residue levels in oranges and lemons treated at 0.75 kg ai/ha (0.015% ai) ranged from 0.10 to 0.18 mg/kg (whole fruit) for samples taken at days 30 to 32. Clofentezine residues in mandarin oranges treated at 0.3 kg ai/ha (0.005% ai) and sampled after a minimum PHI of 30 days ranged from 0.15 to 0.43 mg/kg (whole fruit). The residue data for citrus fruits submitted to the JMPR in 1986 and 1990 were also re-examined. Several trials carried out according to GAP resulted in residue levels higher than 0.2 mg/kg but less than 0.5 mg/kg. Taking into account the residue levels in mandarins, together with a re-examination of previous data on citrus fruits, the Meeting concluded that the original MRL of 0.5 mg/kg was appropriate. In general, the higher residue levels appear to be associated with citrus fruit having thinner peel, e.g. tangerines, mandarins etc.

Residue trials carried out in France, Germany and the USA on grapes showed a wide variation in the clofentezine residues. After 23-35 days they ranged from 0.03 to 1.2 mg/kg with an average value of 0.31 mg/kg. The level of 1.2 mg/kg was found in a trial carried out according to GAP in Germany. Although in one trial the residues slightly exceeded 1.0 mg/kg, in estimating an MRL the Meeting took into account the fact that residues were below 1 mg/kg when two applications were made, whereas GAP requires one application. In view of the development of a late-season use for clofentezine and the typical variability in residue levels from GAP trials, the Meeting proposed that the existing MRL for grapes should be increased from 0.2 to 1 mg/kg.

In response to the CCPR request to re-examine the definition of the residues in plant products, the Meeting noted that metabolic studies on apples revealed that clofentezine is degraded very slowly in plants, in contrast to animals where it is degraded extensively. The analytical method of choice for animal products determines the total clofentezine-derived residues as 2-chlorobenzoic acid and the results are expressed as clofentezine. Because degradation in plants is slight, crops are analyzed by an HPLC procedure which determines the parent compound only. After considering the merits of the two analytical procedures, and observing that all the residue data on plants were for the parent compound only, the Meeting decided to revise the proposal made in 1990 that the total residues method should be used for determining clofentezine residues in crops. The HPLC procedure which determines the parent compound can be used for plant material. For animal material, total clofentezine-derived residues should be determined as 2-chlorobenzoic acid and expressed as clofentezine.

The current definition of the residue as the sum of all residues containing the 2-chlorobenzoyl moiety expressed as clofentezine is retained for animal products. The definition is revised to clofentezine (parent compound only) for plant materials.

On the basis of the data on residues from supervised trials, the Meeting concluded that the residue level for grapes shown in Annex 1 is suitable for use as an MRL.

FURTHER WORK OR INFORMATION

Desirable

Information on current GAP for citrus fruits to facilitate re-evaluation of the residue data.

4.12 CYCLOXYDIM (179)

(±)-2-[1-(ethoxyimino)butyl]-3-hydroxy-5-thian-3-ylcyclohex-2-enone

Cycloxydim was reviewed for the first time by the Meeting. It is a systemic cyclohexanedione herbicide registered for use on a variety of crops.

TOXICOLOGY

Cycloxydim was extensively absorbed after oral administration to rats and almost completely excreted within 5 days of dosing. Elimination proceeded predominantly via the urine (74-86% of applied dose) with lower levels in the faeces (12-25% of the applied dose). Less than 1% of an administered dose was retained in the body. Studies confirmed that enterohepatic circulation occurred in rats.

The metabolism of cycloxydim has been investigated in rats and a biotransformation pathway has been proposed. The major metabolite was the sulphoxide, and the pattern of metabolites was similar in urine, bile and tissue residues.

Cycloxydim has low acute oral toxicity. WHO has classified cycloxydim as unlikely to present acute hazard in normal use.

Owing to instability in dietary admixture, the sodium salt of cycloxdim was administered in the drinking water in repeat-dose rodent studies. In dogs, sufficient dietary stability was demonstrated, and dietary administration of cycloxydim was therefore used.

In mice, two 4-week dose range-finding studies were conducted, followed by a 24-month long-term study. In the dose range-finding studies, employing concentration between 30 and 9000 ppm, reduced food and water intake, and reduced body-weight gain were seen at higher doses, together with increased liver weight and hydropic vacuolar hepatocyte degeneration. The NOAEL was equal to 7 mg/kg bw/day in males and 28 mg/kg bw/day in females, the lower NOAEL in males resulting from liver-weight increase in the absence of any histopathological change. In the long-term study, no treatment-related effects were seen up to the highest dose tested of 32 mg/kg bw/day, although liver weights were not measured.

In rats a 4-week dose range-finding study was followed by a 13-week study, an 18-month toxicity study and a 24-month carcinogenicity study. Findings were generally similar to those observed in mice, the liver being identified as the only target organ of note, although no histopathological changes were seen at doses up to 900 mg/kg bw/day. The NOAELs were 100 mg/kg bw/day over 4 weeks, 25 mg/kg bw/day over 13 weeks and 7 mg/kg bw/day over 18/24 months, based on reduced body-weight gain at 25 mg/kg bw/day and above.

Cycloxydim was not carcinogenic in rats and mice.

In dogs, a 4-week dose range-finding study was followed by a 13-week and a 12-month study. In the dose range-finding study (at doses up to 360 mg/kg bw/day) the liver and the red blood cells were identified as target organs and the NOAEL was 40 mg/kg bw/day. In longer-term studies in dogs the NOAELs were 50 mg/kg bw/day over 13 weeks and 20 mg/kg bw/day over 52 weeks. Target organs were the liver and red blood cells. A marginal anaemia was seen, along with a compensatory bone marrow response, but no serious treatment-related histopathological effects were noted at 80 or 300 mg/kg bw/day.

In a multi-generation reproduction study in rats, the NOAELs were about 10 mg/kg bw/day for parental toxicity and 38 mg/kg bw/day for reproductive performance, pup mortality being slightly increased at 150 mg/kg bw/day.

Teratology studies have been carried out with cycloxydim in rats and rabbits. In the rat teratology studies the NOAEL for maternal toxicity was 200 mg/kg bw/day. Fetotoxicity was seen at maternally-toxic doses, together with findings which may be considered indicative of a teratogenic potential (missing/incomplete tail and anal atresia at 600 and 800 mg/kg bw/day and vertebral anomalies at 400 mg/kg bw/day). Although the vertebral anomalies were not completely reversible post natally (up to 21 days after birth), in vitro embryo culture studies demonstrated that cycloxydim did not show any direct embryotoxic effects. In the rabbit teratology study the NOAEL for maternal toxicity was 100 mg/kg bw/day. There was no indication of fetotoxicity in rabbits, even in the presence of maternal toxicity and no indication of any treatment-related vertebral anomalies, even when a special examination was conducted to look specifically for such changes.

After reviewing the available genotoxicity data, the Meeting concluded that cycloxydim and its

sodium salt were not genotoxic.

An ADI was allocated, based upon the NOAEL from the long-term studies in rats, using a safety factor of 100.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: > 240 ppm in the drinking-water, equal to >32 mg/kg bw/day (two-year study)

Rat: 100 ppm in the drinking-water, equal to 7 mg/kg bw/day (18 and 24-month studies)
100 ppm in the drinking-water, equal to 10 mg/kg bw/day (multi-generation study)
200 mg/kg bw/day (teratology study, maternal and fetal toxicity)

Dog: 400 ppm in the diet, equal to 20 mg/kg bw/day (one-year study)

Rabbit: 100 mg/kg bw/day (teratology study, maternal toxicity)

Estimate of acceptable daily intake for humans

0-0.07 mg/kg bw

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

Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Cycloxydim is formulated as an emulsifiable concentrate containing either 200 g/l or 100 g/l cycloxydim. Registered national use patterns have been established in some eighteen countries and national tolerances in food items in another nine. The limits range from 0.05 mg/kg to 5 mg/kg.

Extensive data on residues from supervised trials conducted in 15 countries and with more than 40 crops were supplied but could not be adequately evaluated within the time available. These data will be evaluated at the next Meeting.

In plants cycloxydim is degraded rapidly to a number of metabolites. A residue analytical method was developed for all the metabolites, involving hydrolysis and oxidation, which yields two principal derivatives of glutaric acid, namely the 3-thian-3-yl- (TME) and the 3-hydroxy-3-thian-3-yl (OH-TME). The average recoveries of these from crop matrices were 79.6 and 75.4%, respectively and the LOD was 0.05 mg/kg. The residues are expressed as cycloxydim. A specific method is available for cycloxydim in soil and water, together with one for the main metabolite cycloxydim sulphoxide (TSO).

Plant metabolism was studied in soya beans and sugar beets. Cycloxydim is oxidized to the sulphoxide and sulphone (TSO_2) and the parent, TSO and TSO_2 are de-alkoxylated and hydroxylated. The major metabolites are the sulphoxide and sulphone.

Animal studies in rats were performed with the active ingredient and its sodium salt. These were administered orally and intravenously (salt only). Both forms were readily excreted. Within 5 days, up to 86% of the doses were eliminated via the urine and up to 25% in the faeces. The main metabolites were TSO and desethoxy-cycloxydim sulphoxide (T1SO). No volatile products were detected.

A feeding study with goats showed that no residues occurred in the milk with exaggerated

dose levels.

Laboratory soil column and adsorption/desorption studies indicated that cycloxydim is slightly mobile. The half-life in soil ranged from less than 1 day to approximately 20 days. The products in soil were mainly the desethyl compound, the sulphoxide and sulphone, and the sulphoxide and sulphone of the bicyclic product formed by ring closure between the 3-hydroxy group and the 2-iminobutyl substituent (T2SO and $T2SO_2$). Some 20% of the applied radiolabel remained bound to the soil after 90 days incubation. Owing to the high rate of mineralization, up to 60% after 90 days, and the binding to soil, it is unlikely that cycloxydim would be transported down through the soil to reach the groundwater.

In water at pH 7, the half-life was 234 days and increased with pH, the predominant transformation product being the sulphoxide. Under photolytic conditions the half-life was reduced to 90 min, desethoxy-cycloxydim (T1S) being the main phototransformation product. In water/soil systems the half-life was approximately 5 days, TSO being the major product.

The effects of cycloxydim on the activities of soil microflora in laboratory studies were small in comparison with natural influences such as temperature, soil humidity and soil cultivation. Formulated cycloxydim applied as recommended does not appear to pose a risk to algae, bees or earthworms. In addition, the octanol/water partition coefficient of cycloxydim at pH 6.5 is about 58, indicating that bioconcentration in the food chain is highly unlikely.

4.13 CYFLUTHRIN (157)

RESIDUE AND ANALYTICAL ASPECTS

Cyfluthrin was evaluated in 1986, 1987, 1989 and 1990. The Meeting received additional information on registered uses of cyfluthrin and on residues in food. Reports were received of many supervised trials on crops and commodities for which MRLs or TMRLs are established (apples, plums, tomatoes, peppers, maize, rape seed, cotton seed and cattle milk) and also on pears, berries, onions, cabbage, cauliflower, beans, peas, lupins, cereals other than maize, and animal products other than cattle milk. Additional information was also received on new analytical methods developed for determination in plant materials.

The new results on peppers, maize, rape seed, cotton seed and cattle milk were limited but in agreement with data evaluated at earlier Meetings, and enabled the Meeting to recommend a change from temporary to full MRLs. Residues in some trials on apples and tomatoes were considerably higher than the existing temporary limits, and the Meeting proposes to increase these limits.

In reply to the request of the CCPR to clarify the limit proposed for cattle milk at an earlier Meeting, it was stated that the limit of 0.1 mg/kg proposed at the 1989 JMPR was either a misprint or possibly was based on residues in milk fat. According to the explanation in the text of the 1989 monograph the correct figure is 0.01 mg/kg, which also is confirmed by new data from experiments on cattle in Australia received at the present Meeting.

The 1989 proposal was based on trials with pour-on treatments of cattle with cyfluthrin and was also confirmed by animal feeding studies reported to the JMPR in 1986, where residues in milk from cattle which had been fed for 28 days with a dietary level of cyfluthrin as high as 5 ppm were 0.01-0.02 mg/kg.

Residues in the fat from these cattle were 0.21-0.30 mg/kg, but as the dose level was higher than would be expected in practice no residue limit was proposed for cyfluthrin in fat.

The data received from trials on plums were too scanty and from trials which were not in accord with registered uses. Residues from trials on maize forage were also too limited to confirm the existing temporary limit. The Meeting therefore recommends withdrawal of the temporary limits for plums and maize forage. New trials on maize forage are in progress and results may be expected to be available for the 1994 JMPR. These new data, together with those submitted in 1989 and to the

present Meeting may allow the 1994 Meeting to propose a new residue limit for maize forage.

The data from trials on berries, onions, cabbage, cauliflower, beans, peas, barley, wheat, sorghum and meat from cattle and sheep were too limited and/or not in accordance with registered uses, and the Meeting was unable to propose residue limits for these commodities.

Information was received on a new analytical method developed to determine residues of cyfluthrin in plant material, beer and sugar, and a modification of it to determine also residues in cereal grains. The method is an improvement of an earlier one published by the Deutsche Forschungsgemeinschaft in the Manual of Pesticide Residue Analysis, slightly modified to determine residues of cyfluthrin in plant material.

FURTHER WORK OR INFORMATION

Desirable

1. Supplementary residue data from trials on berries, onions, cabbages, cauliflower, beans, peas, barley, wheat and sorghum.

2. Data on residues in meat from feeding studies with residues in the feed at the 1 ppm level, which may occur in practice.

4.14 CYHEXATIN (067)

RESIDUE AND ANALYTICAL ASPECTS

Cyhexatin was last evaluated by the 1991 Joint Meeting. Information on the current GAP for hops and kiwifruit was considered desirable.

The Meeting was informed that there was currently no GAP on hops.

Results of supervised trials in which 0.3 and 0.6 kg ai/ha were applied once or twice to beans in Italy indicate that the residue in beans without pod is below the limit of determination.

Since no GAP has been reported on beans and the portion of the commodity analyzed was not in accord with the Codex Guide (residues were only reported on seeds without pods), the results cannot be used for estimating maximum residue levels.

FURTHER WORK OR INFORMATION

Desirable

Information on current GAP on kiwifruit and beans.

4.15 CYROMAZINE (169)

RESIDUE AND ANALYTICAL ASPECTS

The 1990 JMPR proposed residue limits for cyromazine in a number of commodities including peppers. New data from trials on peppers supported the existing residue limit of 1 mg/kg. Some residue levels were higher than 1 mg/kg but originated from trials in The Netherlands with an increased application rate of 0.4 kg ai/ha. Registered uses of cyromazine in The Netherlands were not received.

Nearly all the residue data submitted to the JMPR in 1990 were on both cyromazine and its main metabolite melamine. Residues of melamine were in many cases of the same order as those of cyromazine. At the CCPR in 1991 and 1992 some delegations were concerned that melamine was

not included in the residue definition. The 1990 JMPR decided not to include melamine mainly because it is considered to be less toxic than cyromazine. Arguments for including or not including melamine have now been submitted to the Meeting from The Netherlands, the USA, and the manufacturer of cyromazine.

The reasons for including melamine in the residue definition are:

1. It is not clear whether high residues of cyromazine are always connected with high residues of melamine.

2. Residues of melamine can equal or significantly exceed those of cyromazine in plants and animals, and the proportion of melamine in the total residue is highly variable.

3. In mushrooms, cyromazine residues are often undetectable, whereas melamine may be present at levels up to 7 mg/kg.

The reasons for not including melamine are:

1. The available toxicological data base indicates that melamine is of no toxicological concern at the levels present in food or feed.

2. Analytical samples can be contaminated with melamine originating from the production of wet-strength filter paper.

3. Some plastic laboratory utensils and bags may contain melamine as a contaminant.

4. Melamine is also a metabolite of prometryne.

The Meeting has considered these arguments and has decided to maintain the definition established in 1990. The main reasons are that melamine is considered to be less toxic than cyromazine, and that melamine in a sample may have originated from sources other than cyromazine. Nevertheless the Meeting recognizes that the monitoring of good agricultural practice in growing mushrooms under certain conditions is not possible when the metabolite is omitted from the residue definition.

4.16 DELTAMETHRIN (135)

RESIDUE AND ANALYTICAL ASPECTS

Deltamethrin is registered in at least 15 countries for the control of stored product insects in cereals, at 0.5-1 g ai/t when used alone or at 0.25-0.5 g ai/t when synergised by piperonyl butoxide. Information had been previously provided on the fate of deltamethrin residues on wheat during milling and baking, but it was suggested at the 20th (1988) Session of the CCPR that the proposed MRL (2 mg/kg) for unprocessed wheat bran was too low. The proposed MRLs for wheat bran, wheat flour and wheat wholemeal were held at Step 7B pending review of data to be supplied by the manufacturer.

Information on milling and baking studies on deltamethrin-treated wheat in France in 1990 and 1991 was made available to the Meeting. Supervised commercial and pilot milling trials and cooking studies from Australia were also provided.

Residues in the milled and cooked commodities depend first on the level of residues in the wheat. The level applied, established by grain analysis soon after application, can vary from approximately 10 to 100% of the nominal rate. Such values are recorded in the data provided to the present Meeting, which substantially agree with the range 15-85% recorded in the 1980 and 1982 Evaluations. Efficiency of application can be low with a UL formulation applied directly to the grain stream at 80 ml of the formulation (6 g ai/l) per tonne of grain. Much of the deltamethrin is attached to dust which separates from the grain during treatment.

Because much of the residue is in the dust or particulate matter, residues may also be lost during transport (some separation of dust from grain) and during the cleaning process which is the first step in commercial milling. Possibly 10-20% of the residue is removed during cleaning.

From information supplied to the present Meeting, the level of deltamethrin residues in bran was 2.3-4.7 times the level in the cleaned wheat (mean 3.5 times). The mean ratio was 3.6 (residues in bran ÷ residues in wheat) in trials recorded in the 1988 Evaluations.

Residues in the bran depend on the treatment rate, efficiency of application, percentage of residues remaining after cleaning, and ratio of residues in the bran to residues in the wheat. The maximum, most likely and minimum for these four quantities are [1, 1, 0.9, 4.7], [0.5, 0.5, 0.85, 3.5] and [0.25, 0.1, 0.8, 2.3] respectively. The maximum, most likely and minimum residues in bran then become 4.2, 0.74, and 0.05 mg/kg respectively. The figures suggest a maximum residue level of 5 mg/kg for bran, but also suggest that when deltamethrin is used at a lower treatment rate at a typical application efficiency residues in bran are likely to be under 1 mg/kg.

Similar logic applies to residues in flour, although there is an additional complication with the different streams of flour from the mill. Because the residue is associated with the outer portion of the grain those streams containing a higher proportion of the outer grain are likely to have higher residues. Data from Australian milling trials suggest that 0.2 mg/kg would be a suitable maximum residue level for straight-run flour, but residues in last-reduction flour exceeded 0.2 mg/kg. Again, residues in flour are likely to be rather lower if deltamethrin is applied at typical application efficiencies. Generally, residues in flour milled from deltamethrin-treated wheat would be less than 0.1 mg/kg.

Data supplied to the Meeting and to the 1981 and 1988 Meetings show that residues in wholemeal are likely to be 70-100% of the residues in the wheat.

The 1981 JMPR drew some conclusions about the effect of baking on deltamethrin residues. Essentially, there is no degradation during baking, but there is some dilution because of the higher moisture content of the bread. Data provided to the present Meeting would not change that conclusion.

When deltamethrin is used commercially as a grain protectant likely residues in cooked products would be: white bread <0.005-0.05 mg/kg, wholemeal bread and flat bread 0.02-0.2 mg/kg, and noodles 0.02-0.1 mg/kg.

Supervised trials in New Zealand demonstrated that when deltamethrin is used on tamarillos (tree tomatoes) within GAP (0.6-1.25 g ai/hl and 60 days PHI) residues were close to 0.01 mg/kg.

Residue data from Spain showed that, at an application rate of 0.26 kg ai/ha (a greatly exaggerated rate) on artichokes, deltamethrin residues were within the CXL for globe artichoke (0.05 mg/kg) 7 days after application.

At the 24th (1992) Session of the CCPR comments were made (ALINORM 93/24, para 140) about the MRL for meat, particularly with respect to the waiting period before slaughter after veterinary treatments. Data from Australia and France were provided to the Meeting on residues in milk and meat after treatment of cattle with deltamethrin. Residues in milk reached a peak from day 1 to day 3 after treatment, with wide variations between levels in milk from individual animals. Data on deltamethrin residues in fat from treated animals suggest that residues at day 7 after treatment are either the same as or slightly higher than at day 3. Observing 3 or 7 days withholding periods for pour-on treatments would not reduce deltamethrin residues at slaughter.

The Meeting confirmed the previous MRL recommendations for unprocessed wheat bran (5 mg/kg) and wheat wholemeal (1 mg/kg).

4.17 DEMETON-S-METHYL (73)

RESIDUE AND ANALYTICAL ASPECTS

Demeton-S-methyl, originally evaluated by the JMPR in 1973, is included in the CCPR periodic

review programme. The producer informed the Meeting that most national registrations for demeton-S-methyl would be transferred to oxydemeton-methyl during the next few years.

No country reported information on GAP or residue data to the Meeting.

Further information on the metabolites demeton-S-methylsulphon and oxydemeton-methyl is given in the reports on these compounds.

The Meeting proposes to change the definition of the residue because the main uses are now of oxydemeton-methyl and the residue data are largely derived from such uses.

For estimations of maximum residue levels see the oxydemeton-methyl report.

4.18 DEMETON-S-METHYLSULPHON (164)

RESIDUE AND ANALYTICAL ASPECTS

Demeton-S-methylsulphon, together with the other demeton-methyl compounds (demeton-S-methyl and oxydemeton-methyl) is included in the CCPR periodic review programme.

Residue data from supervised trials on pome and stone fruit, together with other information on use patterns, fate of residues, methods of analysis and national MRLs, were provided by the manufacturer. Information on GAP in The Netherlands was also made available.

Demeton-S-methylsulphon is a systemic organophosphorus insecticide. It is effective as a contact and stomach poison against sucking insects such as aphids (Aphidae), thrips (Thysanoptera), leaf hoppers (Cicadidae) and non-organophosphorus-resistant strains of mites (Tetranychidae).

It is used on pome and stone fruits in some European countries and Tunisia as well as on sugar beet in Italy.

The new data on residues from supervised trials together with the information on GAP were evaluated.

Pome fruit. In four trials carried out in Germany 1966 on apples, residues up to 0.3 mg/kg were found 21 - 42 days after application (GAP in France, Belgium, The Netherlands, Italy, Switzerland and Spain). Other available results support the estimation that residues from applications according to GAP are unlikely to exceed 0.5 mg/kg. Results from Germany on pears were used to support GAP in The Netherlands.

Plums. In three trials carried out in Germany in 1975, residues up to 0.15 mg/kg were found 21 - 28 days after application (GAP in Belgium, France and Spain). These results support an MRL of 0.2 mg/kg.

Cherries. On the basis of three trials in Germany where residues were 0.19 - 0.55 mg/kg 21 - 28 days after application, and assuming that these results can be used to support GAP in Belgium, France and Spain, the Meeting estimated a maximum residue level of 1 mg/kg.

Peaches. Results of two trials from Spain were insufficient to estimate a maximum residue level.

The Meeting was not able to re-evaluate the temporary MRLs for Currants, Black, Red and White, Grapes, Plums (including Prunes), Potato, Strawberry or Sugar beet because no current GAP was reported and/or residue data were not made available.

Data were also received on the fate of residues in plants, soil and water/sediment systems, and on methods of residue analysis. Further information on the effects of processing on crop residues, fate in animals, photodegradation and storage stability are given in the oxydemeton-methyl evaluation.

The Meeting proposes to change the definition of the residue because the main uses are now of oxydemeton-methyl and the residue data are largely derived from such uses.

For estimations of maximum residue levels see the oxydemeton-methyl report.

FURTHER WORK OR INFORMATION

Desirable

Additional residue data on apples, pears and peaches, which a producer stated were being developed.

4.19 DICOFOL (026)

Dicofol, originally evaluated by the JMPR in 1968 and re-evaluated for residues in 1970 and 1974, is included in the CCPR periodic review programme

TOXICOLOGY

Dicofol is an acaracide which is structurally similar to DDT. When it was evaluated in 1968 an ADI of 0-0.025 mg/kg bw was allocated, based on a NOAEL of 50 ppm in the diet, equivalent to 2.5 mg/kg bw/day, in the rat.

Dicofol was extensively absorbed from the gastrointestinal tract. At near steady-state conditions, the highest tissue concentrations were found in adipose tissue, followed by the adrenal glands, thyroid, and liver. The *p,p'*-dicofol isomer, the main component of technical dicofol, was more persistent in the body than the *o,p'*-isomer. Females rats tended to retain dicofol to a greater extent than males. Dicofol and DDT showed a similar pattern of distribution and elimination. Dicofol is more polar than DDT and therefore less persistent in the body.

In rats, dicofol was excreted as polar metabolites, primarily in the faeces, but with lesser amounts in the urine. Metabolism involved dechlorination and oxidation of the ethanol moiety and hydroxylation of the aromatic rings. In adipose tissue, the parent compound was predominant. The metabolic profile was similar in mice.

Dicofol had moderate acute oral toxicity. It produces signs of toxicity consistent with CNS depression. WHO has classified dicofol as slightly hazardous.

In a 13-week study in mice using dietary concentrations of 0, 10, 125, 250, 500, or 1000 ppm in the diet, the NOAEL was 10 ppm, equal to 2.1 mg/kg bw/day, based on reduced body weight, liver enlargement, and increased hepatic mixed function oxidase (MFO) activity. In another 13-week study in mice using dietary concentrations of 0, 250, 500, or 750 ppm, liver histopathology, including centrilobular hypertrophy and eosinophilia of heptocytes, was observed at all dose levels.

In a 13-week study in rats at dietary concentrations of 0, 1, 10, 100, 500, or 1500 ppm, the NOAEL was 1 ppm, equal to 0.07 mg/kg bw/day. Although the incidence and severity of thyroid follicular epithelial hypertrophy was increased in males at 10 ppm and above, this thyroid effect was not found in a second 13-week study using dietary concentrations of 0, 50, 200, 1000, or 3000 ppm.

In a 13-week study in dogs using dietary concentrations of 0, 10, 100, 300, or 1000 ppm in the diet, the NOAEL was 10 ppm, equal to 0.29 mg/kg bw/day. At 100 ppm cortisol response to ACTH was reduced. A 1-year dog study using dietary levels of 0, 5, 30, or 180 ppm dicofol was performed to better define the NOAEL. The NOAEL was 30 ppm, equal to 0.82 mg/kg bw/day, based on liver changes and reduced cortisol response to ACTH at 180 ppm.

In a 78-week carcinogenicity study in mice using time-weighted average concentrations of 260 or 530 ppm for males and 120 or 240 ppm for females, dicofol produced an increased incidence of liver adenomas and
adenomas/carcinomas combined in male mice at 260 and 530 ppm, equivalent to 40 and 80 mg/kg bw/day, respectively. Dicofol was not carcinogenic in female mice.

In a two-year study in rats using dietary concentrations of 0, 5, 50, or 250 ppm in the diet, the NOAEL was 5 ppm, equal to 0.22 mg/kg bw/day, based on histopathological changes in the liver and vacuolation of adrenal cortical cells at 50 ppm, equal to 2.2 mg/kg bw/day. No treatment-related changes in the thyroid or in the incidence of neoplasia were observed. There was no evidence of carcinogenicity in a 78-week carcinogenicity study in rats using time-weighted average concentrations of 470 or 940 ppm (24 or 47 mg/kg bw/day) for males and 380 or 760 ppm (19 or 38 mg/kg bw/day) for females. Dicofol was not carcinogenic in rats.

In a two-generation reproduction study in rats using dietary concentrations of 5, 25, 125, or 250 ppm in the diet, the NOAEL was 5 ppm, equal to 0.5 mg/kg bw/day, based on an increased incidence of ovarian stromal cell hypertrophy and hepatocellular changes at 25 ppm. Offspring viability was reduced at 125 and 250 ppm. The NOAEL for reproductive parameters was 25 ppm, equal to 2.1 mg/kg bw/day.

In a teratology study in rats using gavage doses of 0, 0.25, 2.5, or 25 mg/kg bw/day, the NOAEL for maternal toxicity was 0.25 mg/kg bw/day based on clinical signs of toxicity at 2.5 mg/kg bw/day. The NOAEL for embryofoetal toxicity was 25 mg/kg bw/day. In a teratology study in rabbits using gavage doses of 0, 0.4, 4, or 40 mg/kg bw/day, the NOAEL for maternal toxicity was 0.4 mg/kg bw/day based on histopathological changes in the liver at 4 mg/kg bw/day. The NOAEL for embryofoetal toxicity was 4 mg/kg bw/day based on an increased incidence of abortions at 40 mg/kg bw/day. Teratogenic effects were not found in these studies.

After reviewing the available genotoxicity data, the Meeting concluded that dicofol was not genotoxic.

The Meeting concluded, after consideration of the liver tumours in male mice found in the long-term studies together with the genotoxicity data, that dicofol did not present a carcinogenic hazard for humans.

The previous ADI was revised. A new ADI was allocated, based upon the NOAEL in the long-term study in rats, using a safety factor of 100.

A toxicological monograph summarizing the data reviewed at the present Meeting and incorporating the previous monograph on dicofol was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 10 ppm, equal to 2.1 mg/kg bw/day (13-week study)
Rat: 5 ppm, equal to 0.22 mg/kg bw/day (two-year study)
Rat 0.25 mg/kg bw/day (teratology study, maternal toxicity)
Rabbit: 0.4 mg/kg bw/day (teratology study, maternal toxicity)
Dog: 30 ppm, equal to 0.82 mg/kg bw/day (one-year study)

Estimate of acceptable daily intake for humans

0-0.002 mg/kg bw

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

Further observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Extensive residue data from supervised trials and other data were provided by the manufacturer and several countries.

Dicofol is an organochlorine miticide which has been used in agriculture for some thirty years. The product is registered for broad-spectrum contact, non-systemic control of plant-eating mites in citrus, cotton, apples, tea and a wide variety of fruit, vegetable, home, garden and ornamental crops. Dicofol is manufactured from DDT, and as with other members of the DDT class, the mode of action is stimulation of axonal transmission of nervous signals, believed to be related to inhibition of ATPases in the central nervous system.

Manufacturing improvements have recently led to a purified technical grade product with <0.1% DDT-related impurities remaining from the manufacturing process. With the intention of up-dating the information on toxicology, residues, metabolism and environmental fate, this purified product has been subjected to a full battery of modern studies conducted in accordance with OECD and US FIFRA guidelines.

Technical dicofol is an approximately 4:1 to 5:1 mixture of the *p,p'* and *o,p'* isomers, and both isomers produce residues. The Meeting recommends that both isomers should be included in the residue definition.

Apples, pears, citrus, peaches. These large tree fruits have the highest recommended use rates, especially in the USA. This may be because more material is needed to coat the foliage of the trees adequately than is needed for vegetables, for successful protection. Deposits on fruit surfaces from the early applications may be extensively diluted by growth of the fruit, and the final application may be the source of most of the residue.

In supervised residue trials there was little evidence of residue decline in large tree fruits. Commercial washing was seen to reduce residues in some instances (citrus, tomatoes) by as much as 50% of the original level. The extent of the reduction may depend on the nature of the crop surface and how recently the dicofol was applied. A similar reduction in residues would be expected in pome fruits.

Processing trials show that residues are located almost entirely on or in the peel, and are correspondingly low in aqueous products such as apple or citrus juice. Residues concentrate in citrus and apple pomace (peel and pulp left over from commercial processing) and citrus oil, but very little of these processing fractions occur in processed food commodities such as juice, apple sauce, etc. Dicofol is relatively unstable in aqueous solutions at 25°C under neutral to basic conditions. Heating during processing could lead to the degradation of dicofol to dichlorobenzophenone.

On the basis of the use rates and residue data from supervised trials, an MRL of 5 mg/kg is proposed for these crops.

Plums, cherries, figs. Residues are concentrated when fresh plums are dried, and presumably a similar concentration would occur in dried figs. The proposed MRLs are 5 mg/kgfor cherries, 3 for prunes and 1 for plums. Two residue trials on figs were considered insufficient to estimate a maximum residue level.

Walnuts and pecans. The proposed MRL, 0.01* mg/kg, is for the edible nut, free from its shell and husk. Walnut and pecan kernels were devoid of residues as would be expected from the high degree of protection afforded by the shells and husks.

Cotton seed. Shielding from spray is believed to be the cause of the lack of appreciable residues in cotton seed and cotton seed oil. The proposed 30-day pre-harvest interval reduces the likelihood of the cotton boll being open at the time of the final application. Presumably during this period the plant is becoming senescent and protection from mites is no longer needed.

The low MRL of 0.1 mg/kg proposed in this case allows for possible contamination during harvesting or ginning. For cotton seed oil, the Meeting estimated a maximum residue level of 0.5 mg/kg.

Cucumbers, squash, melons. Residues were minimal, as would be expected in large-fruited vegetables such as cucumbers, squash and melons, which grow rapidly and have relatively low ratios of surface area to volume. Japanese data on peeled melons and some of the data on tomatoes showed that residues were in the peel rather than the edible pulp. These factors, coupled with relatively low use rates, combine to result in low residues, even with as short a pre-harvest interval as 2 days. MRLs are proposed for cucumber (0.5 mg/kg), squash (1 mg/kg) and melon (0.2 mg/kg).

Peppers, tomatoes. The proposed MRL for both these crops is 1 mg/kg.

Beans and peas. Both beans and peas have edible-pod varieties (string beans, garden peas, etc.). Both develop rapidly, which precludes a lengthy pre-harvest interval if they are to be harvested at the peak of quality. However, rapid growth also contributes to lower residues by growth dilution. For varieties of beans and peas with edible pods, the proposed MRL is 2 mg/kg.

In dry beans the edible portion is shielded. For dry beans and peas, it is entirely practical to specify a longer PHI (21 days) to avoid application when the pods may have dried and possibly opened, which would allow deposition of the pesticide on the bean itself. The low MRL proposed, 0.1 mg/kg, allows for possible mechanical contamination from pods or vines during harvesting or shelling.

Hops. An MRL of 50 mg/kg is proposed, based on German and US data on dried hops. Hops

are used in the brewing of beer, and trials have shown the absence of dicofol residues in beer brewed with hops containing high residues of dicofol.

Grapes. Grapes are consumed fresh but are also dried to raisins. Grape juice is consumed fresh but is also fermented to wine. Available data suggest an MRL of 5 mg/kg for fresh grapes. The concentration factor for residues in drying grapes to raisins appeared to be about 5. Minimal residues of dicofol are detected in grape juice and wine in processing studies. This is not unusual as the residues are on the surface of the grape skins.

Strawberries. Results from two trials in Brazil within the GAP of other countries are insufficient to estimate a maximum residue level. Because of the long PHIs results from Spain could not be taken into account.

Black currants. Data from France, Germany and the UK could not be used to estimate a maximum residue level because the GAP was unknown.

Tea. On the basis of data available from India on dried leaves (6 results) the Meeting estimated a maximum residue level of 50 mg/kg.

Coffee. In view of the limited data (2 trials) and absence of information on GAP in Brazil (only a PHI of 35 days was reported) the Meeting was unable to estimate a maximum residue level.

MRLs for strawberries and gherkins are recommended to be withdrawn because available residue data are insufficient although GAP is reported.

On the basis of available feeding studies on cattle and hens, the Meeting estimated maximum residue levels for several products of animal origin.

Data were also received on the fate of residues in animals, plants, soil and water.

In plants, dicofol is not metabolized extensively and is recovered intact together with dichlorobenzophenone, which is either a metabolic or chemical degradation product. In some plant studies dichlorobenzhydrol, again either a metabolic or chemical degradation product, has also been detected. In animals dicofol is degraded much more extensively: the major metabolite detected is the dechlorinated analogue of dicofol. Dicofol is not metabolized to DDE or to any other DDT-related compound.

The effects of frozen storage were studied in commodities of plant and animal origin. Residues in citrus and cotton seed were stable for 1-2 years.

Residues in food in commerce or at consumption were reported to the Meeting by the USFDA.

Methods of residue analysis were described for soil and commodities of plant and animal origin.

The octanol/water partition coefficients for *p,p'*-dicofol and *o,p'*-dicofol were reported to be 4.28 and 4.48 respectively. Dicofol was therefore classified as fat-soluble.

FURTHER WORK OR INFORMATION

Desirable

1. Details of rate of application (kg ai/ha or kg ai/hl) for the trials in Thailand on grapes submitted to the JMPR together with information on GAP.

2. Additional data from supervised trials on fruits where limited information is available, namely figs, coffee beans, zucchini, watermelons, tea, strawberries and gherkins.

3. Information on GAP for application to coffee beans.

4. Residue trials on crops where GAP was reported but no residue data were supplied, namely almond, apricot, banana, crab-apple, egg plant, mushrooms, papaya, quince and raspberry.

4.20 DINOCAP (087)

RESIDUE AND ANALYTICAL ASPECTS

Dinocap was evaluated in 1969, 1974 and 1989. Information on GAP was lacking in 1989. The compound is included in the CCPR periodic review programme.

Limited information on GAP, residue data and MRLs from five countries were brought to the attention of the Meeting. The producer informed the Meeting at a very late stage that residue data on several crops (apples, grapes, melons, peaches, squash, strawberries, carrots and black currants) are being developed.

Residue data reported for cucumber, zucchini, pumpkin and squash showed residues well below the temporary MRLs of 0.1* mg/kg, but were not sufficient to recommend revised MRLs.

There are indications that the TMRL of 0.1 mg/kg for apple is to low, but the data submitted by The Netherlands were not sufficient to estimate a revised maximum residue level.

The old data formerly evaluated by the JMPR and the few new data submitted did not enable the Meeting to re-evaluate the pesticide. The Meeting therefore recommended withdrawal of all temporary MRLs.

FURTHER WORK OR INFORMATION

Desirable

Results of supervised trials which the producer stated to be in progress on apples, grapes, melons, peaches, squash, strawberries, carrots and black currants.

4.21 DITHIANON (180)

5,10-dihydro-5,10-dioxonaphtho-[2,3-*b*]-1,4-dithi-in-2,3-dicarbonitrile

Dithianon is used as a multi-site protective fungicide which inhibits spore germination. It is authorized or registered for use in a range of fruits, including apple, pear, medlar, berries, grapes, various stone fruits, citrus and vegetables.

Dithianon was considered for the first time by the present Meeting.

TOXICOLOGY

After oral administration to rats, goats and hens, dithianon was rapidly absorbed, distributed and excreted. Five days after its oral administration to rats almost all of the administered radioactivity had been eliminated, 62-70% via faeces and 30-34% via urine. Only a small proportion of the dose was recovered in tissues, with highest levels in kidneys, gastro intestinal tract and whole blood. Up to 10%

had been excreted in the bile after 48 hours. Dithianon was quickly metabolized to a number of polar metabolites, which have defied identification owing to their lability. Less than 1% unchanged dithianon was found in the faeces.

The acute oral toxicity of dithianon was moderate in mice and rats. WHO has classified dithianon as slightly hazardous.

Short-term studies with mice, rats and dogs indicated that the kidney is the primary target organ. Increased kidney weight, hydropic degeneration of the proximal tubular cells and basophilic tubules were demonstrated in the rat.

In a 90-day study in rats, dithianon was administered at dietary concentrations of 0, 30, 180, or 1080 ppm. At high concentrations effects on red blood cells, an increase in liver and kidney weight and histopathological changes in the kidney were noted. The NOAEL was 30 ppm, equal to 2.5 mg/kg bw/day for males and 3 mg/kg bw/day for females based on increased kidney weight.

Three studies with dogs were reviewed. In a 90-day study, dithianon was fed at dietary concentrations of 0, 40, 200, or 1000 ppm. The NOAEL was 200 ppm, equal to 3 mg/kg bw/day, based on increased organ weights in the high-dose group. In both the 52-week (0, 40, 200 or 1000 ppm) and 2-year (0, 40, 400 or 1000 ppm) studies dithianon caused effects on red blood cells, increased liver and kidney weights, hepatocellular hypertrophy and tubular pigmentation in the kidney. In each study the NOAEL was 40 ppm, equivalent to 1 mg/kg bw/day, based on increased liver weight and histopathological changes at 200 ppm and 400 ppm, respectively.

In an 80-week long-term feeding study in mice at dietary concentrations of 0, 20, 100, or 500 ppm, the NOAEL was 20 ppm, equal to 2.9 mg/kg bw/day, based on increased kidney weight and an increased incidence of chronic nephrosis. Two 2-year studies in rats at dietary concentrations of 0, 20, 200, or 1000 ppm and 0, 20, 120, or 600 ppm were conducted. In the first study, only effects on body weight, red blood cells and liver and kidney weight were observed at 200 ppm, equivalent to 1 mg/kg bw/day, and higher. In the second study these effects were confirmed together with a number of histopathological renal changes, especially in females at 600 ppm. At this level kidney adenomas and adenocarcinomas were also found. The NOAEL was 20 ppm, equivalent to 1 mg/kg bw/day, based on non-neoplastic kidney lesions observed at 120 ppm. The Meeting concluded that dithianon induced kidney tumours in female rats at 600 ppm. It has been hypothesized that tumour induction is secondary to other renal changes seen in rats.

Two reproduction studies in rats were reviewed. In the first study at dietary concentrations of 0, 20, 200, or 500 ppm dithianon, the body-weight gain of parents and pups was decreased, pup mortality was increased, and liver and kidney weights were increased. The NOAEL was 20 ppm, equivalent to 1 mg/kg bw/day, based on decreased body-weight gain and increased kidney weight. In the second study (dietary concentrations of 0, 35, 200, or 600 ppm) the NOAEL was 200 ppm, equivalent to 10 mg/kg bw/day, based on decreased body-weight gain and food consumption at 600 ppm.

Teratogenicity studies were conducted with mice, rats, and rabbits. In mice, maternal toxicity and delayed ossification were observed. The NOAEL for both effects was 3.3 mg/kg bw/day. In rats, maternal toxicity, post-implantation loss and reduced fetal weight were observed at doses of 50-100 mg/kg bw/day. The NOAEL was 20 mg/kg bw/day. In a study in rabbits, 30 mg/kg bw/day caused maternal toxicity, post-implantation loss and retarded ossification. The NOAEL was 10 mg/kg bw/day. In a second study in rabbits, maternal toxicity was observed at 25 and 40 mg/kg bw/day but not at 10 mg kg bw/day. The NOAEL for fetotoxicity was 25 mg/kg bw/day. Teratogenic effects were not observed in any of the studies.

After reviewing the available genotoxicity data, the Meeting concluded that dithianon was not genotoxic.

The Meeting concluded, after consideration of the long-term studies and the genotoxicity data, that dithianon did not pose a carcinogenic hazard for humans.

An ADI was allocated, based on NOAELs in two-year studies in rats and dogs, using a 100-fold safety factor.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 20 ppm equal to 2.9 mg/kg bw/day (80-week study)
Rat: 20 ppm equivalent to 1 mg/kg bw/day (2-year studies)
Dog: 40 ppm equivalent to 1 mg/kg bw/day (one and two-year studies)

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

1. Characterisation of the metabolites of dithianon in mammals and plants.

2. Clarification of the mechanism of nephrotoxicity and induction of kidney tumours.

3. Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Dithianon is marketed as a wettable powder (750 g/kg) and suspension concentrate (750 g/l). Other formulations are less important.

Extensive data were provided on residues from supervised trials carried out around the world and were evaluated in the light of the reported GAP.

MRLs were recommended for pome fruits, grapes, cherries, mandarin, pomelos and hops. A maximum residue level could not be estimated for peaches because the limited residue data submitted did not match GAP.

Results of supervised trials on wheat were available from France, Germany and the UK, but the authorized use on this crop is not yet finalised and GAP is expected to be changed. The Meeting was therefore unable to recommend an MRL for wheat.

The fate of residues in plants was studied in apple, orange, red currant and wheat. Dithianon itself is the major component of residues remaining in crop commodities and an estimate of dithianon will provide a good estimate of the total residues present. No residues were detectable in wine or beer processed from treated grapes and hops.

The Meeting drew attention to the need for critical supporting studies, e.g. studies on the fate of residues in farm animals (metabolism and transfer studies), to be available at the same time as the residue data. Details of animal metabolism and farm animal transfer studies (feeding studies on hens and goats) were not available to the FAO Panel. For summaries of the results see the Toxicology report. It is intended to discuss these studies, together with the results of new studies that the manufacturer stated were in progress, at a future Meeting.

Dithianon is readily hydrolysed in water and the rate of hydrolysis increases with pH. At pH values below 4 the compound is stable for a long period in the absence of irradiation. Decomposition in water at acid pH is accelerated by irradiation by simulated sunlight.

Dithianon is rapidly degraded in soil and available studies have not been short enough to estimate a half-life which is likely to be only a few days.

Degradation, especially in soils, gives rise to a wide range of highly polar and reactive products. It has not been possible to isolate and purify many of these products and their structures in most cases have not been established.

Because of its rapid degradation in soil it has not proved possible to determine such properties as soil adsorption and leachability of intact dithianon. In the studies that have been carried out with labelled material, the whole of the radioactivity has been determined. This has proved to be strongly adsorbed by soil and relatively resistant to leaching in column studies.

With regard to the possible effects on soil microflora, it was reported that dithianon had no inhibiting effect on soil respiration or the mineralisation of horn meal (a substrate for model studies) in a laboratory study. In the case of the nitrogen cycle a slight initial inhibiting effect was found only at the high concentration of 12 µl Delan SC 750/kg of soil, corresponding to 12 times the spray volume. This was reversible within a week.

In terms of crop residues, the rapid degradation of dithianon and the tenacity with which the radiolabel is held by the soil indicate that residues in the soil arising from the treatment of previous crops will not give rise to residues in rotational crops.

The determination of residue levels of dithianon in crops follows the usual pattern of solvent extraction, clean-up and measurement. Dithianon has a relatively low solubility in such solvents as n-hexane, acetonitrile and dichloromethane but these may still be used as extractants. The extracts are cleaned up by gel-permeation chromatography. For determination, high-performance liquid chromatography with UV detection is recommended.

Freezer storage stability studies were submitted for citrus, grapes, apples, and pears. Within the first few months losses up to 30% were measured. There was no analytically significant loss during the next 12 - 24 months.

FURTHER WORK OR INFORMATION

Desirable

1. Additional studies on the fate of residues in farm animals (metabolism and transfer studies), and on plant metabolism and soil degradation.

2. GAP and residue information for uses on cereals in Germany, The Netherlands and the UK.

4.22 ENDRIN (033)

RESIDUE AND ANALYTICAL ASPECTS

Information on endrin is reported in 4.3, aldrin, dieldrin.

4.23 FENBUTATIN OXIDE (109)

TOXICOLOGY

Fenbutatin oxide was previously evaluated by the Joint Meeting in 1977, when an ADI of 0-0.03 mg/kg bw was allocated.

Fenbutatin oxide was poorly absorbed from the gastrointestinal tract. Most (more than 90%) was excreted unchanged in faeces. Less than 1% was excreted in urine.

Fenbutatin oxide has low acute oral toxicity. The World Health Organization has classified fenbutatin oxide as unlikely to present acute hazard in normal use. It is highly irritating to the skin, lungs, and gastrointestinal tract. By the oral route, bolus administration was particularly irritating. Oral administration to dogs resulted in diarrhoea and vomiting. Following gavage administration, rabbits exhibited anorexia and developed gastric mucosal lesions. An increase in serum alkaline phosphatase in a two-year study in rats may also have been related to gastrointestinal tract injury.

A seven-day feeding study in mice gave some indication that fenbutatin oxide possessed less immunotoxic potential than other organotin compounds. However, the data were inadequate to evaluate immunotoxicity.

In a two-generation reproduction study in rats using dietary concentrations of 0, 40, 75, 250, or 500 ppm, the NOAEL was 75 ppm, equal to 6.0 mg/kg bw/day, based on reduced weight of adults and offspring at 250 ppm. Reproductive performance was unaffected.

In a teratology study in rats at doses of 0, 15, 30, or 60 mg/kg bw/day, the NOAEL for maternal toxicity was 15 mg/kg bw/day based on reduced body- weight gain at 30 mg/kg bw/day. The NOAEL for embryofetal toxicity was 30 mg/kg bw/day based on an increase in pre-implantation loss at 60 mg/kg bw/day. In a study in rabbits at doses of 0, 1, 5, or 10 mg/kg bw/day, the NOAEL for maternal and embryofetal toxicity was 1 mg/kg bw/day based on clinical signs of toxicity and gastric lesions in does and an increase in post-implantation loss at 5 mg/kg bw/day. No teratogenic effects were found in rats or rabbits.

After reviewing the available genotoxicity data the Meeting concluded that fenbutatin oxide was not genotoxic.

The 1977 Joint Meeting reviewed two-year studies in rats and dogs in which NOAELs of 50 ppm, equivalent to 2.5 mg/kg bw/day and 15 mg/kg bw/day, respectively, were observed. A multi-generation reproduction study in rats, in which the NOAEL was 100 ppm, equivalent to 5 mg/kg bw/day, was also reviewed at that time.

The ADI of 0-0.03 mg/kg bw that was allocated in 1977 (which was based on the NOAEL of 2.5 mg/kg bw/day (50 ppm) observed in a two-year dietary study in rats in which an increase in serum alkaline phosphatase was observed at higher doses) was retained. A lower NOAEL of 1 mg/kg bw/day from a teratology study in rabbits, in which gastrointestinal tract irritation was observed, was considered less reflective of human exposure because of the high sensitivity of the gastrointestinal tract of the rabbit and the particular physiological characteristics of this species. Therefore, this study was not used as the basis for the ADI.

A toxicological monograph summarizing the data that were reviewed at the present Meeting and incorporating the previous monograph on fenbutatin oxide was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Rat: 50 ppm, equivalent to 2.5 mg/kg bw/day (two-year study reviewed by JMPR in 1977)
75 ppm, equal to 6.0 mg/kg bw/day (two-generation reproduction study)
15 mg/kg bw/day (teratology study, maternal toxicity)

Rabbit: 1 mg/kg bw/day (teratology study, maternal and embryofetal toxicity)

Dog: 15 mg/kg bw/day (two-year study reviewed by JMPR in 1977).

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

1. Adequate information on the immunotoxic potential of fenbutatin oxide.

2. Observations in humans.

4.24 IPRODIONE (111)

TOXICOLOGY

Iprodione was previously evaluated for acceptable daily intake by the Joint Meeting in 1977, when an ADI of 0-0.3 mg/kg bw was allocated.

Iprodione is extensively absorbed from the gastrointestinal tract. It was extensively metabolized and rapidly excreted, primarily in the urine although relative faecal excretion of the parent compound increased at high doses. Higher doses (for example 900 mg/kg bw) appeared to be absorbed to a lesser extent and eliminated at a slower rate than lower doses (for example 50 mg/kg bw). The elimination half-life was 7-9 hours following a single low dose and 13-20 hours following a single high dose. The metabolic pathways elucidated in rats involve dealkylation on the isopropylcarbamoyl chain, hydroxylation of the aromatic ring and rearrangement and opening of the hydantoin ring.

Iprodione had low acute toxicity by all routes of exposure. The oral LD_{50} was greater than 1500 mg/kg in mice, rats, and dogs. The World Health Organization has classified iprodione as unlikely to present acute hazard in normal use.

In three 4-week studies in mice at dietary concentrations of 0, 600, 1900, 6000, 9500, or 15000 ppm, the lowest NOAEL was 600 ppm, equal to 115 mg/kg bw/day, based on macroscopic hepatic changes at 1900 ppm. At 6000 ppm and above, the test material crystallized in the tissues. In a 3-month study in mice at dietary concentrations of 0, 1500, 3000, 6000, or 12000 ppm an increase in liver and adrenal gland weights and hypertrophy and/or vacuolation of hepatocytes and adrenal cortical cells were observed in all treated groups.

In a 3-month study in rats at dietary concentrations of 0, 300, 1000, or 3000 ppm, the NOAEL was 300 ppm, equal to 21 mg/kg bw/day. Higher doses produced swelling in the zona glomerulosa of the adrenal cortex. In another 3-month study in rats at dietary concentrations of 0, 1000, 2000, 3000, or 5000 ppm, the NOAEL was 1000 ppm, equal to 78 mg/kg bw/day, based on reduced body-weight gain and histopathological changes in the adrenal glands, ovaries and uterus at 2000 ppm and higher.

In a one-year study in dogs at dietary concentrations of 0, 100, 600, or 3600 ppm, the NOAEL was 100 ppm, equal to 4.1 mg/kg bw/day, based on the detection of Heinz bodies in erythrocytes and decreased prostate gland weight at 600 ppm and above. In a second one-year study at dietary concentrations of 0, 200, 300, 400, or 600 ppm, the NOAEL was 400 ppm, equal to 18 mg/kg bw/day, based on decreased erythrocyte values at 600 ppm.

In a two-generation reproduction study in rats at dietary concentrations of 0, 300, 1000, or 3000/2000 ppm, the NOAEL was 300 ppm, equal to 21 mg/kg bw/day, based on depressed body weight at 1000 ppm and above. Reproductive performance was unaffected. Offspring survival and growth were reduced at 3000/2000 ppm.

In a teratology study in rats using gavage doses of 0, 40, 90, or 200 mg/kg bw/day, the NOAEL for maternal toxicity and teratogenicity was 200 mg/kg bw/day. The NOAEL for embryofetal toxicity was 90 mg/kg bw/day, based on slightly delayed fetal development at 200 mg/kg bw/day. In rabbits administered 0, 20, 60, or 200 mg iprodione/kg bw/day by gavage the NOAEL for maternal toxicity was 20 mg/kg bw/day based on depressed weight gain at 60 mg/kg bw/day. The NOAEL for embryofetal toxicity was 60 mg/kg bw/day based on increased abortions and post-implantation loss at 200 mg/kg bw/day. No teratogenic effects were found.

After consideration of the available genotoxicity data, the Meeting concluded that iprodione was not genotoxic.

The former ADI, based on a multi-generation reproduction study in rats, was revised. The new ADI was based on the results of several studies, including the reproduction study in rats, the teratology study in rabbits, and the one-year study in dogs. A safety factor of 100 was applied to the NOAELs from

these studies.

A toxicological monograph summarizing the data that were considered at the present Meeting and incorporating the previous monograph on iprodione was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 600 ppm in the diet, equal to 115 mg/kg bw/day (four-week study)

Rat: 300 ppm in the diet, equal to 21 mg/kg bw/day (two-generation reproductions study)
500 ppm in the diet, equivalent to 25 mg/kg bw/day (reproduction study reviewed by the 1977 Joint Meeting)

Rabbit: 20 mg/kg bw/day (teratology study, maternal toxicity)

Dog: 400 ppm in the diet, equal to 18 mg/kg bw/day (one-year study)

Estimate of acceptable daily intake for humans

0-0.2 mg/kg bw/day

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

1. Ongoing toxicological studies.

2. Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

This compound was scheduled for periodic review. Critical GAP information was not available and the evaluation could not be completed at the Meeting. The compound will be evaluated at the next Meeting.

4.25 ISOFENPHOS (131)

RESIDUE AND ANALYTICAL ASPECTS

The expression of MRLs for fat-soluble pesticides in animal commodities was considered by the 1991 JMPR, which noted that isofenphos was an anomalous case because although it is designated fat-soluble in the definition the MRL for meat does not specify the fat portion for analysis.

The residue definition proposed by the 1981 JMPR was: "sum of isofenphos and its oxygen analogue". At the 20th (1988) Session of the CCPR it was agreed (ALINORM 89/24, para 131A) to describe the residue as fat-soluble, but no explanation was recorded.

The octanol-water partition coefficient for isofenphos, log P_{OW} 4.12, suggests that isofenphos is properly described as fat-soluble.

The animal feeding studies previously reviewed in 1981 show that isofenphos is metabolised and excreted quickly, with residues in tissues (also milk and eggs) being very low. The residue is properly defined as fat-soluble as indicated by the relative concentrations in muscle and fat in the hen feeding study.

The MRLs for mammalian fats, meat, poultry fats and poultry meat are all set at 0.02* mg/kg. To harmonise the residue definition (fat-soluble) with the MRLs for meats it is recommended that the fat portion of the sample is specified for analysis.

4.26 METALAXYL (138)

RESIDUE AND ANALYTICAL ASPECTS

The compound has been evaluated several times. The 1990 JMPR required by 1992 current country-specific GAP information for onions and residue data from trials reflecting that GAP, including the dual pre-plant plus multiple foliar treatments at maximum permitted application rates, with residues determined as metalaxyl *per se* and preferably also as the total residue. Information on GAP for leafy vegetables for which residue data had previously been provided to the JMPR was also required.

Detailed information was provided on use patterns in 59 countries for a wide range of crops. The changes in recommended uses reflect the improvement and adaptation of anti-resistance strategies and the development of new formulations. The recommended use for dual pre-plant plus foliar treatment of lettuce has been withdrawn, so questions on this use are no longer relevant.

Spain informed the Meeting that it fully supports the 0.2 mg/kg residue limit for strawberries, as the present GAP allows only pre-planting use of the compound only. Nevertheless, the residue data on strawberries promised at previous CCPR Sessions were submitted for evaluation. The Meeting considered the new information and noted that in the Italian trials the pre-harvest interval was too short to obtain mature fruit, and in the US trials the number of applications was higher than permitted by GAP. It was concluded that the available data do not support changing the current limit of 0.2 mg/kg.

Summaries of residue data from supervised trials in several countries on apples, avocados, grapes, onions, oranges, potatoes, peppers and tomatoes were provided by Spain.

In view of the information from the manufacturer on the submission of new residue data on lettuce and onions in 1993, the Meeting decided that all data should be considered by the next Meeting.

No residue information was provided on broccoli, cabbage, cauliflower, lettuce or spinach.

The Meeting reviewed the residue data reported in the previous evaluations and considered that the maximum residue levels estimated for lettuce, onion, spinach and strawberry correctly reflected the residues likely to result from treatments according to current GAP.

Since US GAP permits pre-planting soil treatment as well as consecutive foliar treatments of onions, the 2 mg/kg limit recommended by the 1989 JMPR (and lowered to a TMRL of 0.2 mg/kg by the 1990 Meeting) is required. It should not be temporary.

FURTHER WORK OR INFORMATION

Desirable

Residue data from supervised trials carried out in accordance with current use patterns on broccoli, cabbages, cauliflower.

4.27 METHACRIFOS (125)

RESIDUE AND ANALYTICAL ASPECTS

Concern has been expressed at the CCPR on several occasions regarding the persistence of methacrifos residues on cereal grains after processing.

Information on the use patterns for stored cereal grains and milling/processing studies on cereals were submitted from Australia and the UK.

At the 1992 CCPR it was noted that animal transfer studies were needed for meats other than poultry in order that MRLs might be recommended by the JMPR. Results of a study on beef cattle fed with wheat treated with methacrifos were submitted by the producer of the compound.

Australian information submitted to the Meeting explained that to control the full range of insect pests in Australia in long-term storage an application rate of 10 g/t was necessary. The application rate for stored cereals in the UK is reported to be 4.75 g/t. The period of protection is about 5 months.

On the basis of the new and previously evaluated data the Meeting proposed not to change the established MRLs for cereal grains, wheat bran, unprocessed, wheat flour and wheat wholemeal. Because methacrifos can be quite stable in some circumstances (e.g. in temperate climates), MRLs should also be based on the approved rate of application.

Beef cattle were given feed prepared from wheat grain containing methacrifos at a level of 15 or 30 ppm and the parent compound and its dealkylated metabolite were determined in the fat and tissues. The treated feed, consisting of 5 parts of wheat to 2 parts of chaff, was made available to the cattle *ad lib* for a maximum period of 14 days. Some calves were killed after 7 days, some after 14 days, and some were allowed a recovery period of 7 days on untreated feed after the 14-day exposure period before slaughter.
Neither methacrifos nor its dealkylated metabolite could be detected in the fat, liver, kidney or muscle. The limit of determination was 0.01 mg/kg in all substrates.

No additional information on GAP and no residue data were submitted for the other commodities held at step 7B of the CCPR procedure (Beans (dry), Cacao beans, Field pea (dry), Peanut, Peanut, whole, Eggs, Milks, and Poultry meat).

4.28 METHIDATHION (051)

Methidathion was first evaluated by the Joint Meeting in 1972, with minor reviews in 1975 and 1979. The present Meeting evaluated the compound within the CCPR periodic review programme.

TOXICOLOGY

Methidathion has been previously evaluated for acceptable intake by the Joint Meeting in 1972 and 1975. An ADI of 0.005 mg/kg bw was allocated in 1975.

Methidathion was extensively absorbed when administered orally to rats. The routes of elimination were via the urine and expired CO_2. There were no significant differences in elimination patterns with regard to dose levels administered, pre-treatment or sex.

In the rat, the predominant urinary metabolites were the sulphide, sulphoxide, sulphone and demonomethyl derivative. Negligible quantities of the parent and oxygen analogue were detected in the urine. The predominant metabolic pathway of methidathion in the goat was via O-demethylation with the demonomethyl derivative as the principal urinary metabolite. Cysteine conjugates were identified in each species.

Methidathion has a high acute oral toxicity. The World Health Organization has classified methidathion as highly hazardous.

Methidathion was administered to dogs for 90 days at dietary concentrations of 0, 0.5, 4, 45 or 140 ppm, or 0.14 mg/kg bw/day by capsule, and for a period of 12 months at 0, 0.5, 2, 4, 40 or 140 ppm in the diet. In both studies the dietary NOAEL was determined to be 4 ppm equal to 0.16 mg/kg bw/day based on liver effects, most notably cholestasis and increased liver enzymic activity in serum at dietary levels of 40 ppm and above.Cholestasis was observed in a single male dog treated by capsule at 0.14 mg/kg bw/day. Erythrocyte and brain cholinesterase activities were affected only at the highest level of 140 ppm.

Long-term dietary treatment of mice with methidathion for 23 months at 0, 3, 10, 50 or 100 ppm revealed an increased incidence of hepatocellular tumours in males at 50 ppm and above, resulting in an NOAEL of 10 ppm equal to 1.4 mg/kg bw/day. Erythrocyte cholinesterase was inhibited at 50 ppm (equal to 6.99 mg/kg bw/day) and above, whereas brain cholinesterase activity was affected at 100 ppm.

A 104-week long-term carcinogenicity study in rats fed methidathion at 0, 4, 40 or 100 ppm indicated a NOAEL of 4 ppm equal to 0.16 mg/kg bw/day, based on inhibition of erythrocyte and brain cholinesterase activity at 40 ppm and above. Methidathion was not carcinogenic in rats.

In a two-generation reproduction study in rats at dietary concentrations of 0, 5, 25 or 50 ppm, an NOAEL of 5 ppm equal to 0.43 mg/kg bw/day was established. At 25 ppm, reduced mating indices in the F_1 generation and decreased progeny body-weights were observed.

There were no teratogenic effects observed when methidathion was administered by gavage to rats at doses of 0, 0.25, 1.0 or 2.5 mg/kg bw/day or to rabbits at doses of 0, 2, 6 or 12 mg/kg bw/day. Maternal effects were demonstrated at the highest doses in both the rat and rabbit as clinical signs of toxicity. In the rat, increased mortality as well as decreased body weights and food consumption were also observed. The NOAELs in the rat and rabbit were determined to be 1 and 6 mg/kg bw/day, respectively.

Treatment of hens with methidathion did not produce any clinical or pathological evidence of delayed neurotoxicity.

In two reported cases of poisoning with methidathion, each of the male subjects exhibited classic clinical and biochemical signs of organophosphorus intoxication. Both subjects recovered, with

no evidence of delayed neurotoxicity uncovered upon follow-up examination. In one of the cases jaundice was reported during the recovery period.

Two human volunteer studies failed to reveal any inhibition of erythrocyte or serum cholinesterase activity at doses up to 0.11 mg/kg bw/day.

After reviewing the available genotoxicity data, the Meeting concluded that methidathion was not genotoxic.

In the dog, the effects on the liver appeared to have occurred at levels lower than the levels causing inhibition of cholinesterase activity giving an NOAEL of 0.1 mg/kg bw/day. Whether or not there was a relationship to the potential induction of liver effects in man could not be ascertained.

The Meeting concluded, after consideration of the hepatocellular tumours found in male mice in the long-term study together with the lack of genotoxicity, that methidathion did not present a carcinogenic hazard for humans.

The previous ADI, based on an NOAEL in man of 0.11 mg/kg bw/day, was revised. The revised ADI is based on the NOAEL in the dog and a 100-fold safety factor.

A toxicological monograph summarizing the data reviewed at the present Meeting and incorporating the previous monograph and monograph addendum on methidathion was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 10 ppm, equal to 1.4 mg/kg bw/day (23-month study)

Rat 4 ppm, equal to 0.16 mg/kg bw/day (104-week study)
5 ppm, equal to 0.43 mg/kg bw/day (reproduction)

Dog: 0.1 mg/kg bw/day (90-day, one-year, and two-year studies)

Human: 0.11 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

During the past eighteen years the use of methidathion has been extended to other crops or the recommendations have been adapted to current needs and in particular cases uses were discontinued. The product has been introduced worldwide in over 90 countries and has been used on more than 40 crop commodities. Major uses are on citrus, cotton, pome and stone fruit, grapes, nuts, olives, forage crops (alfalfa, lucerne) and vegetables.

Since the first evaluation many residue studies have been carried out on a large variety of crops.

In most of the samples the residues of parent methidathion and its main metabolite, the oxygen analogue, were determined. The parent compound accounted for the major part of the residue in every case. Methidathion oxon was undetectable or at relatively low concentration. The results of trials under recommended use conditions are summarized below.

In alfalfa, 0.3-0.8 kg ai/ha rates are recommended with 7 to 30 days pre-harvest intervals. The initial residues ranged between 2.2 and 58 mg/kg in green plants and between 21 and 65 mg/kg in hay. At a pre-harvest interval of 10-14 days, the likely maximum residue level in green plants and hay is 10 mg/kg.

In almond kernels, hulls and shells, residues of the parent compound and the oxon were not detected above the limits of determination (0.05 mg/kg and 0.01 mg/kg, respectively) after a single treatment and >190-day PHI. At sampling intervals of 60-94 days following multiple applications, no residues were detected in the kernels and residues were higher in hulls than in the corresponding shell fractions from the same samples.

In apples the recommended uses vary considerably (PHI from 14 days to pre-blossoming; rates 0.3-3.34 kg ai/ha). Residues of the parent decreased from 0.3-2.4 mg/kg immediately after the last foliar application to <0.02-0.5 mg/kg within approximately 3 weeks. Following the national use recommendations the residue in apples is likely to be below 0.5 mg/kg which is the current MRL.

In artichokes, neither methidathion nor its oxygen analogue was detected above the limits of determination (0.05 mg/kg and 0.02 mg/kg, respectively) in any of the samples treated at normal rates.

In dry beans and peas, the seed contained residues of both compounds below the limits of determination, while in dry bean pods methidathion residues were <0.05-5.9 and <0.05-14 mg/kg at day 14 after treatment with 0.56 and 1.12 kg ai/ha, respectively. The residue ranges for methidathion oxon were <0.02-0.19 for both rates. The results mutually support a maximum residue level of 0.1 mg/kg for dry beans and peas.

In cabbages the residues ranged from non-detectable to 0.04 mg/kg following recommended use patterns.

In cherries the parent residues decreased from a maximum of 2.52 mg/kg immediately after the last application to <0.02 mg/kg within 21 days. Taking into account a 14-day pre-harvest interval the residue data support the current 0.2 mg/kg limit.

In citrus fruit the residue was concentrated in the peel and decreased relatively slowly. Generally residues in the pulp were undetectable or about 20-300 times smaller than in the corresponding peel. The parent compound accounted for the majority of the residue. Residues of methidathion oxon were at or below the limit of determination in all samples. To estimate the residue on a whole fruit basis the following pulp to peel ratios were used: oranges: 63.5/36.5; lemons: 55/45; mandarins: 70/30. In grapefruit, after treatments with recommended rates, the residues in the peel were 1.4-4.8 mg/kg. The residue in whole lemons ranged from 0.78 to 2.7 mg/kg from recommended use patterns. Within 14-21 days after the last application the residues in mandarin pulp and peel ranged from 0.015 to 0.04 and from 4.4 to 5.5 mg/kg, respectively. In whole oranges the residues were below 2 mg/kg at recommended PHI and dosage rates. For lemons, mandarins and oranges the results of the new trials support the present MRLs.

Methidathion residues in cotton seed were <0.05-0.84 mg/kg, <0.05-0.81 mg/kg and <0.05-0.63 mg/kg after pre-harvest intervals of 2, 3 and 4 weeks respectively, with the majority being below the limit of determination. The oxygen analogue was not detected (<0.05 mg/kg) in any of these samples.

In cucumbers initial residues of methidathion (0.18-0.64 mg/kg) decreased rapidly and were <0.02 mg/kg approximately 1 week after the last application.

In grapes, the methidathion residues decreased from 0.84-9.3 mg/kg immediately after the last application to 0.04-0.86 mg/kg within about 5 weeks. The results show residues of methidathion to be rather persistent in grapes.

Residues of methidathion in green hop samples from multiple applications decreased from initially high levels (14-37 mg/kg) to 0.11-2.3 mg/kg within a 14-day pre-harvest interval. Residues in dry cones measured after 5-34 days were between 0.18 and 3.1 mg/kg. The results indicate that 5 mg/kg would be required to accommodate current GAP.

No residues of methidathion in macadamia nuts were detected above 0.003 mg/kg during the observed pre-harvest interval of 0-49 days.

In maize grain, no residues of methidathion or its oxon were detected above 0.05 mg/kg after pre-harvest intervals of 10-41 days. Methidathion residues in the corresponding fodder were <0.05-2.6 mg/kg and residues of the oxon were between <0.05 and 0.1 mg/kg. In many trials, however, the oxon could not be detected. In maize forage methidathion residues were between <0.05 and 2.7 mg/kg after a 7-day PHI and <0.05 mg/kg 4-5 weeks later. Only a few samples contained small amounts of the oxon during a 14-day PHI (0.06-0.27 mg/kg) with most of them having no detectable residues.

In olives the pre-harvest intervals range from 14 to 90 days. The treatments may be carried out by spraying solutions containing 0.02-0.125% ai. The residues in the fruit were <0.04-2.1 and <0.04-0.7 mg/kg 25-30 days and 3 months after the last application. After five months, residues were below the limits of determination.

In onion bulbs the residues of methidathion were <0.01-0.08 mg/kg after a 7-day pre-harvest interval. Residues in whole onion plants were between 0.02 and 0.51 mg/kg after a 14-day interval.

In peaches, residues of methidathion were 0.48-4.6 mg/kg shortly after the last application and decreased to <0.02-0.3 mg/kg during the sampling period of 28 days. Traces of methidathion oxon (0.03-0.06 mg/kg) were found immediately after the last application, but were <0.02 after 7 days. The results support the present 0.2 mg/kg MRL.

In pears, the residues of methidathion were 0.06-2.48 mg/kg shortly after the last application and decreased to <0.02-0.85 and 0.02-0.13 mg/kg within 13-16 and 28-32 days, respectively. Taking into consideration a PHI of 14 days and spray concentrations of 0.04 - 0.08 % ai, as registered in several countries, a maximum residue level of 1 mg/kg is estimated.

In pecan nut kernels, shells and hulls the residues of methidathion and its oxon were not detected above the limits of determination (0.05 mg/kg and 0.02 mg/kg respectively) after pre-harvest intervals ranging between 41 and 72 days.

In whole pineapple fruits the residues were between <0.005 and 0.03 mg/kg approximately two weeks after the last treatment and decreased further to <0.005-0.01 mg/kg within the following 2 or 3 weeks.

In plums following foliar application the residues were 0.4-2.0 mg/kg shortly after the last application and decreased to <0.02-0.05 mg/kg during the sampling interval of 28 or 35 days. Residues of methidathion oxon were not found above 0.02 mg/kg in any of the samples analyzed. The results support the current MRL.

In potatoes, no residues of methidathion were detected above 0.02 mg/kg during the whole sampling period (0-51 days) in most of the samples. In three sets of trials carried out at recommended and double rates the residues were <0.02-0.19 mg/kg 7-13 days after treatment. The samples taken at 21-27 days did not contain detectable residues. The results support the present MRL.

Residues in radish leaves decreased from 0.8-1.3 mg/kg 3 days after the last application to

<0.005-0.1 mg/kg within 2 weeks. Residues in the corresponding root samples were already low initially (<0.005-0.016 mg/kg) and decreased to <0.005 mg/kg within the same period in all samples.

Rape seed was analyzed after a wide range of PHIs (0-129 days) and contained no residues above 0.02 mg/kg except in three samples (0.02, 0.03 and 0.04 mg/kg) from treatments at 0.56-0.6 kg ai/ha.

In safflower seeds neither methidathion nor its oxon was detected above the limits of determination (0.05 and 0.02 mg/kg, respectively) after PHI of 28-63 days. A maximum level of 0.1 mg/kg was estimated.

In sorghum, following multiple applications at the normal rate, high methidathion residues (10 mg/kg) were observed immediately after the last application. The residue was reduced in fodder to <0.05-0.10 mg/kg, in forage to 0.06-0.11 mg/kg and in grain to <0.05-0.19 mg/kg after a PHI of about 5 weeks. The residues in sorghum at the silage stage were <0.05-0.34 mg/kg after a 9-day PHI. Methidathion oxon residues were 0.01-0.06 or <0.05 mg/kg in these samples.

In sugar beet, the residues in whole plants or leaves were 0.24-6.4 mg/kg shortly after the last application and decreased to <0.02-0.05 mg/kg within 3 weeks. Residues in roots (tubers) from these samples and in leaves collected later (28-110 days) were <0.02 mg/kg in all cases.

In sunflower, the residues of methidathion in seeds decreased from 0.50-0.76 mg/kg immediately after the last application to <0.01-0.21 mg/kg, <0.02-0.11 mg/kg and <0.02-0.05 mg/kg within pre-harvest intervals of 2, 11 and approximately 14 weeks, respectively. Residues of methidathion in green heads were 8.3-27 mg/kg on day 0 and 0.01-0.54 mg/kg after a 5-week PHI. Residues of the oxon ranged between 0.01 and 0.10 mg/kg in green heads and were <0.01 mg/kg in seeds during these intervals. The results indicate that sunflower seed would usually contain residues below 0.1 mg/kg and that the maximum residue would not exceed 0.5 mg/kg when methidathion is used according to national GAP.

Residues of methidathion in green tea leaves were 0.08-0.47 mg/kg 6 days after the last application, depending on the rate applied. Residues in processed tea leaves after 3 days were between 0.8 and 32 mg/kg and decreased to 0.10-0.24 mg/kg by day 10.

In tomatoes residues were 0.10-2.75 mg/kg on day 0 and decreased to <0.02 mg/kg within 21 days, except in a single sample (0.13 mg/kg) from an exaggerated treatment. Traces of the oxon (0.03-0.05 mg/kg) were found within 7 days after the last application; they were <0.01 mg/kg thereafter. The present MRL (0.1 mg/kg) is supported by the new residue data.

In most trials with walnuts no residues of either parent or oxon were detected above the limits of determination (methidathion 0.05 mg/kg; oxon 0.05-0.01 mg/kg) in any of the walnut fractions (kernel, shells, hulls) after pre-harvest intervals ranging between 7 and 187 days.

In supervised trials on apricots, kiwifruit, nectarines, soya beans and strawberries, the treatments did not correspond to national GAP (for some plants for foliar applications), so the residue data were not suitable for estimating maximum residue levels.

Since no GAP has been reported, maximum residue levels could not be estimated for barley, dates, mustard seeds or red currants.

The information on avocado, Brussels sprouts, cauliflower, egg plants, grapefruit, peas and peppers (red and chilli), was not sufficient to estimate maximum residue levels.

In the first (1972) evaluation, the metabolism of methidathion in alfalfa and bean plants was described on the basis of available ^{14}C studies. Since then many plant metabolism and crop rotation studies have been carried out in crops such as artichoke, cotton, barley, cabbage, carrot, soya bean and

tomato, and the polar metabolites have been successfully characterized.

The initial metabolism in plants consists in hydrolysis of the ester bond to give the demethyl derivative. Further hydrolysis removes the phosphorothionate group, and the resulting mercaptothiadiazole conjugates with serine to form the alanine conjugate. Other major water-soluble compounds produced include the pyruvic acid, lactic acid and glycolic acid conjugates.

The fate of methidathion in animals was studied in several experiments. A lactating goat given a daily oral dose of ^{14}C-methidathion at a level equivalent to 5 ppm in the feed for 10 consecutive days excreted 20.4% of the administered radioactivity in the urine, less than 5% via the faeces and 66% as CO_2. Methidathion was degraded mainly to polar metabolites. The major metabolite was identified as the demethyl derivative (59.7% of the radioactivity in the urine) indicating that O-demethylation is the predominant pathway. The cysteine conjugate of methidathion accounted for 10.4% of the urinary radioactivity. In the organic fraction, which contained 5.5% of the radioactivity, the sulphoxide, the sulphone, the sulphide derivative, the RH compound and unmetabolized methidathion were detected.

The milk contained 1% of the dose and residues reached a plateau on day 5. Blood contained 0.3%, liver 0.15%, leg muscle 0.35%, omental fat 0.07%, and kidney, tenderloin and perineal fat 0.01% each.

The residue levels of methidathion were studied in the tissues and fat of beef cattle after "pour-on" treatments at rates of 4, 8, and 12 mg ai/kg body weight. The results showed no residues (<0.01 mg/kg) in the liver at 1 and 7 days after any of the treatments. Residues 1 day after treatment at 4 mg/kg were 0.037 - 0.042 mg/kg, 0.04 - 0.11 mg/kg and 0.28 - 0.72 mg/kg in muscle, kidney and fat, respectively, and decreased to <0.01 mg/kg within 7 days. Seven days after treatments at higher rates the residue ranges were 0.01-0.04, <0.01-0.02 and 0.09-0.48 mg/kg. The residues returned to pre-treatment levels within 14 days.

In a feeding study, dairy cows were given daily oral doses (up to 43 days) at rates equivalent to 0, 14.2, and 72 ppm in the feed. No residues of methidathion or its oxygen analogue (<0.01 mg/kg) were found at any feeding level in any of the samples (including milk).

The residues of methidathion in milk and butter were determined after "pour-on" treatment of a large commercial diary herd at rates of 4 - 8 mg ai/kg body weight. The level of methidathion in milk was extremely low, with a maximum of 0.02 mg/kg during the first 24 hours after treatment, and below 0.01 mg/kg thereafter. The residue in butter prepared from the first milking was 0.5 mg/kg, but decreased later.

A white leghorn chicken was dosed orally at a level equivalent to 45.3 ppm in the diet with ^{14}C-methidathion for 16 consecutive days. Ninety per cent of the radioactivity was eliminated in the excreta, while egg yolk and white accounted for 0.2% each. A plateau in egg yolk and white levels was reached between days 9 and 14 at 1.0 and 0.5 mg/kg, respectively. Tissues contained 0.5% of the total radioactivity, with the highest level in the liver (0.17%). The formation of $^{14}CO_2$ was minimal.

The results of these studies indicate that detectable residues are unlikely to arise in eggs and animal tissues except fat from feeding with feed treated with methidathion according to current GAP.

Degradation in soil under aerobic conditions proceeded by cleavage of the thiadiazole ring, resulting in considerable $^{14}CO_2$ production. In non-sterile soil this amounted to 60.9% of the applied radioactivity after one year of incubation. The compounds identified from soil under various conditions include the sulphoxide and sulphone, which were also formed in animals, but these did not exceed 6% of the applied dose. The non-extractable material reached a maximum (about 40%) between 2 and 8 weeks after incubation and decreased to about 23% after one year. Lower amounts of $^{14}CO_2$ were produced from sterile aerobic soil. $^{14}CO_2$ was not evolved under anaerobic conditions.

Methidathion has low mobility in soil, reaching depths of 4, 8 and 16 cm in a sandy loam, silty

loam and silty sand respectively. In the case of aged residues more than 94% of the radioactivity remained in soil columns, mainly in the top 2 cm. This indicates that the soil degradation products of methidathion have similarly low mobilities to the parent compound

In processing studies on cotton seed, maize and sunflower seed the harvested seed was fractionated into grain, hulls and meal as well as crude oil. The oil was then converted into commercial grade edible oil by various processing steps such as refining, bleaching, hydrogenating and deodorizing. The residues were mainly concentrated in hulls (cotton 0.08-0.14, sunflower 0.04-0.09 mg/kg) and crude and partly refined oil fractions (cotton 0.02-0.08, maize <0.05-0.09, sunflower 0.01-0.11 mg/kg). No measurable residues (<0.02-<0.05 mg/kg) were found in the edible grade oil fractions in any experiment.

Whole olives were in some cases processed into crude oil and the corresponding press-cake. The residues remained largely in the oil and the press-cake, and were practically absent from the press-water.

The processing studies indicate that residues in crude oil may be about 2-3 times those in the whole seed or fruit.

Green tea leaves and processed (dried) leaves containing methidathion residues (0.08 - 0.47 and 0.10 - 0.49 mg/kg, respectively), were used to prepare tea beverage by pouring boiling water onto the leaves. Residues were not detected above 0.003 mg/kg in tea made from green leaves, but were 0.08 -0.25 mg/kg in tea made from processed leaves. There was no explanation for this discrepancy.

Analytical methods based on capillary or microbore column GLC and thermionic or flame-photometric detection allow the simultaneous determination of the parent compound and its oxygen analogue, which is the main metabolite. These methods are suitable for regulatory purposes.

The Meeting concluded that methidathion does not belong to the group of fat-soluble pesticides (see Section 3.3, report of 1991 JMPR), taking into consideration the log P_{OW} value of 2.42 and the facts that residues of methidathion decrease rapidly in fat, that they are below the limit of determination 7 days after feeding at exaggerated levels, and that whole meat and milk were analyzed in the trials.

FURTHER WORK OR INFORMATION

Desirable

1. Additional information on national registered use patterns for apricots, kiwifruit, nectarines, soya beans and strawberries, and residue data from supervised trials carried out with approved foliar applications and short PHIs.

2. Additional residue data on avocado, Brussels sprouts, cauliflower, egg plants, grapefruit, peas and peppers from supervised trials representing current GAP.

3. Information on GAP for barley, dates, mustard seeds and red currants, and results of supervised trials carried out according to GAP.

4. Storage stability tests on residues in various commodities.

5. Processing studies on citrus fruits.

4.29 METHYL BROMIDE (052)

RESIDUE AND ANALYTICAL ASPECTS

The 22nd (1990) Session of the CCPR (ALINORM 91/24, para 289) was informed that information on toxicity and residues for methyl bromide was being developed by a panel of producers in the USA, and might be submitted for the 1992 JMPR. The 24th (1992) Session of the CCPR noted that methyl bromide was scheduled for residue evaluation in 1992 and that data were being submitted for review. The Meeting was informed that the US Methyl Bromide Industry Panel is currently working to produce toxicological and residue data for re-registration of methyl bromide post-harvest uses. Information from the Methyl Bromide Industry Panel was made available to the Meeting by the USA.

Information on authorised uses of methyl bromide was provided by Australia, Canada, Germany, The Netherlands, Spain and the USA. Methyl bromide is authorised for post-harvest use on stored grain, cereal products, cocoa beans, nuts, fruits, vegetables, dried fruits, pulses and feeds. It has another use for the control of stored products insects in mills, food storage rooms, railway carriages and the like.

Methyl bromide is registered to control nematodes, insects and weed seeds in soil and compost. Rates of use are usually in the range of 200 to 500 kg ai/ha, and crops are sown or planted 2-3 weeks after the soil treatment. Since January 1992 the use of methyl bromide as a soil fumigant in The Netherlands has not been allowed.

Methyl bromide residue data from an extensive set of supervised trials from a number of locations in the USA from 1987 to 1990 were made available to the Meeting. Crops were grown to first maturity in soils which had been treated with methyl bromide usually at 335-380 kg ai/ha. Crops included in the trials were blueberry, raspberry, strawberry, carrot, potato, radish, sugar beet, taro, onion, asparagus, celery, head lettuce, leaf lettuce, spinach, broccoli, cabbage, cauliflower, bush beans, green beans, peas, soya beans, okra, sweet corn, sweet peppers, tomatoes, cucumber, watermelons, cantaloupe, summer squash, peanut, pineapple, ginger, alfalfa, clover, and peanut hay.

Precautions were taken that methyl bromide residues would not be lost from the samples. The laboratory had generally received and analyzed the samples within one to two days of sampling.

Methyl bromide residues were not detected in any sample from this soil treatment programme. The limit of determination was 0.005 or 0.01 mg/kg.

The Meeting agreed that 0.01 mg/kg would be a suitable limit of determination for methyl bromide in crops for monitoring purposes. Guideline levels of 0.01* mg/kg for all these crops could be introduced to cover the soil treatment use. The Meeting noted that this soil treatment was very unlikely to cause detectable residues of methyl bromide in the commodity of trade, and was reluctant to introduce a number of Guideline Levels which could not become CXLs.

Some further studies in the package supplied could not be evaluated because they lacked field reports. Others lacked vital information such as treatment rate or date of treatment (to permit estimation of the interval between treatment and sampling).

The dissipation of methyl bromide residues from walnuts fumigated post-harvest in-shell was investigated in US trials in 1984. Methyl bromide residues in the kernels were at levels of 30-100 mg/kg 4 hours after fumigation at 56 g/m^3. Aeration at ambient temperature (14.4-24.4°C) was required for 21-24 days to reduce the residues to the <0.01-0.1 mg/kg range.

It was not possible to estimate a guideline level for methyl bromide in walnuts because information on the current US authorised post-harvest use pattern was not available.

No information on methyl bromide residues resulting from supervised trials with post-harvest uses of methyl bromide on other commodities was made available to the Meeting.

Experiments with fruit, vegetable and other samples fumigated with methyl bromide and then stored in plastic bags in a freezer at -13°C showed that 7% to 85% of the methyl bromide residues had dissipated between day 0 and day 7 of the storage.

A further experiment showed that methyl bromide residues in fumigated wheat stored at -50°C were disappearing within a few days.

The Netherlands provided methyl bromide residues monitoring data for raisins (7 samples) and rice (22 samples) for 1987 to 1991.

4.30 MYCLOBUTANIL (181)

2-(4-chlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile

Myclobutanil is a systemic, foliar fungicide which provides good protective activity in pome fruit, stone fruit, vines and other crops. The worldwide trials have defined the systemic, protectant, and eradicant properties of this active ingredient against Ascomyctes, Deuteromycetes (fungi imperfecti), and Basidiomycetes. The compound is used alone or in combination with protectant fungicides such as mancozeb or dinocap.

The compound was considered for the first time by the present Meeting.

TOXICOLOGY

Myclobutanil was rapidly absorbed when administered orally to rats and mice. The principal routes of excretion were via the urine and faeces, with no significant residual tissue accumulation. The toxicokinetic model in the rodent did not differ markedly with respect to species, sex, single versus repeated exposures, or doses.

In both the rat and mouse, myclobutanil was extensively metabolized to more polar compounds. The proposed metabolic pathway of myclobutanil in the rat was through oxidation of the butyl group. The major excretory metabolites were qualitatively similar with respect to sex and dose.

Myclobutanil was only slightly toxic upon acute oral administration to rats and mice. WHO has classified myclobutanil as slightly hazardous.

The primary target organ upon repeated dietary exposure to myclobutanil was the liver. Histomorphological changes, characterized predominantly by centrilobular hepatocytic hypertrophy in association with increased liver weights, were observed in all species investigated. Microscopically, there was accentuated lobular architecture, hepatocytic vacuolation, inflammation, necrosis, and pigmentation of the Kupffer cells. Increased hepatic enzyme activities (ALAT, ASAT, GGT, alkaline phosphatase) in the serum were also observed. Hepatic microsomal MFO activities in rats and mice were increased correspondingly. There were no similar increases in hepatic peroxisomal β-oxidation activity that would have suggested peroxisomal proliferation.

A three-month dietary study with myclobutanil in the mouse at levels of 0, 3, 10, 30, 100, 300, 1000, 3000 or 10000 ppm revealed hepatic alterations at dietary levels of 1000 ppm and higher, resulting in an NOAEL of 300 ppm, equal to 42.1 mg/kg bw/day.

Two 3-month studies in rats fed myclobutanil at levels of 0, 10, 30, 100, 300, 1000, 3000, 10000 or 30000 ppm and 0, 100, 300 or 3000 ppm indicated an NOAEL of 100 ppm, equal to 5.2 mg/kg bw/day, based on treatment-related hepatic effects.

The NOAEL for myclobutanil-related liver effects in dogs treated for 3 months at 0, 10, 200, 800 or 1600 ppm was 10 ppm, equal to 0.3 mg/kg bw/day. Treatment of dogs with myclobutanil for 12 months at dietary levels of 0, 10, 100, 400 or 1600 ppm resulted in an NOAEL for hepatic effects of 100 ppm, equal to 3.1 mg/kg bw/day. Myclobutanil administered to two dogs per sex at dietary levels up to 1000 ppm, equal to 39 mg/kg bw/day, did not produce any hepatic changes after a period of 4 weeks.

Long-term dietary treatment of mice with myclobutanil for two years at 0, 20, 100 or 500 ppm revealed a NOAEL of 20 ppm, equal to 2.7 mg/kg bw/day, based on increased MFO activity at 100 ppm as well as more pronounced liver toxicity at 500 ppm and above. Myclobutanil was not carcinogenic in mice.

A 24-month long-term/carcinogenicity study in rats at dietary concentrations of 0, 50, 200 or 800

ppm revealed an NOAEL of 50 ppm, equal to 2.5 mg/kg bw/day, based on findings of testicular atrophy and increased MFO activity at 200 ppm and above. Myclobutanil was not carcinogenic in rats.

A two-generation reproduction study in rats at dietary concentrations of 0, 50, 200 or 1000 ppm revealed a NOAEL of 50 ppm, equal to 3.6 mg/kg bw/day, based on increased liver weights and an increase in numbers of stillborn pups at 200 ppm and above. At 1000 ppm atrophy of the testes and prostate were observed.

An oral teratogenicity study in rats at gavage doses of 0, 31, 94, 310, or 470 mg/kg bw/day demonstrated clinical signs of toxicity at 310 mg/kg bw/day and above indicating an NOAEL of 94 mg/kg bw/day. The NOAEL for embryofetal toxicity was 31 mg/kg bw/day. There was no evidence of teratogenicity at doses up to 470 mg/kg bw/day.

Myclobutanil was not teratogenic when administered to the rabbit at gavage doses of 20, 60 or 200 mg/kg bw/day. An NOAEL for maternal toxicity was 20 mg/kg bw/day, based on decreased body weight at 60 mg/kg bw/day and above. Embryofetal toxicity was evident at 200 mg/kg bw/day.

After reviewing the available genotoxicity data, the Meeting concluded that myclobutanil was not genotoxic.

An ADI was allocated on the basis of NOAELs in two-year feeding studies in mice and rats, a reproduction study in rats and a one-year study in dogs, using a 100-fold safety factor.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 20 ppm, equal to 2.7 mg/kg bw/day (two-year study)
Rat: 50 ppm, equal to 2.5 mg/kg bw/day (two-year study)
Dog: 50 ppm, equal to 3.6 mg/kg bw/day (two-generation reproduction study)
100 ppm, equal to 3.1 mg/kg bw/day (one-year study)

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.

1. Results of ongoing long-term studies in mice and rats known to be in progress.

2. If the results of (1) show a carcinogenic response, studies (a) to determine whether myclobutanil acts as a tumour promoter in the two-stage rat liver bioassay and (b) whether it causes inhibition of intercellular communications.

3. Observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

The range of use rates among all the countries in which myclobutanil is registered is 20 to 140 g ai/hectare, and the interval between sprays required to provide effective disease control may vary from 7

to 14 days. In general, use rates are higher in the USA than in Europe and the resultant residues are correspondingly higher.

Myclobutanil is extensively degraded in plants, animals, and soil. It is rapidly excreted by animals.

The main metabolites which occur in both animals and plants are the keto derivative α-(3-oxobutyl)-α-(4-chlorophenyl)-1*H*-1,2,4-triazole-1-propanenitrile, RH-9089, and the hydroxy derivative α-(3-hydroxybutyl)-α-(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile, RH-9090.

Metabolism and translocation studies in apples and grapes have demonstrated that myclobutanil can readily move from the root zone to the plant, but the translocation following foliar treatment is negligible.

Supervised field trials were conducted on grapes and pome and stone fruits in several States of the USA, France, Germany, Italy, Spain and the UK.

Grapes. When the total amount of myclobutanil applied was 0.56 kg/ha, close to the permitted maximum of 0.67 kg/ha, and samples were taken 13 to 15 days after the last application, residues of the parent compound ranged from 0.05 to 0.64 mg/kg, while the total residues were between 0.19 and 0.67 mg/kg. The ratio of parent compound to its metabolites varied, depending on the residue level. When the residue was at or above 0.4 mg/kg the proportion of metabolites was <20%. In European trials the maximum amount applied was 0.33 kg ai/ha, which led to residues below 0.09 mg/kg at the registered 7-14-day PHIs. It appears that a maximum residue limit of 1 mg/kg, expressed as myclobutanil, is not likely to be exceeded if recommended use patterns are followed. As the metabolites account for less than 20%, the limit would be the same for the total residue.

Apples and pears. In samples taken at about 14 days after treatment from apple orchards treated at or below the maximum prescribed total use rate of 2.24 kg/ha, the ranges of parent and total residues were from non-detected (<0.01 mg/kg) to 0.2 and from <0.01 to 0.24 mg/kg, respectively. Trials in Germany and the UK at about 1 kg ai/ha resulted in parent residues of 0.04-0.3 mg/kg at 14-day pre-harvest interval. The proportion of metabolites was below 30% of the parent compound. In pears the residues were slightly lower. When myclobutanil is used according to GAP, the parent or total residue is unlikely to exceed 0.5 mg/kg in apples and pears.

Stone fruits. In the trials submitted to the Meeting for evaluation the residues were measured in the edible portion of the fruits, not in the whole fruits including stones. The proportional weights of the stones were not given. The residues found in the edible portion of the fruits are reported in the evaluation and the appraisal. In order to express the residue levels in accordance with the Codex commodity description, the average percentage weights of the stones indicated for the individual commodities were taken into account to estimate maximum residue levels for the whole fruits.

Trials on apricots were carried out in France and Italy with maximum rates of 0.45 kg ai/ha, which is 36% of the maximum registered in the USA. The parent myclobutanil was determined except in two trials in which the metabolites were below the limit of determination (<0.01 mg/kg). The residues in apricots were in the same range as in plums and the results are mutually supportive. Taking into account an average weight of stones of 25%, the results indicate that the maximum residue level in apricots would be below 0.2 mg/kg for European uses. There were no data on residues from US uses.

In cherry trials in the USA where a total of 1.05 - 1.26 kg ai/ha was applied and samples were taken at seven or fourteen days, the parent and total residues ranged from 0.02 to 1 and 0.81 to 2.4 mg/kg respectively. In German cherry trials, where a total of 0.315 kg/ha was applied, total residues declined to 0.02-0.2 mg/kg at 7 days and 0.007-0.08 mg/kg at 14 days. In two trials after 14 days the parent residues were 0.02-0.17 and 0.007-0.06 mg/kg. When the compound is used according to current use patterns in cherries a maximum residue limit for the parent compound of 1 mg/kg would be required (the weight of the stone is about 30%). The maximum limit for the total residue would be 2 mg/kg under the same conditions.

In peaches treated with approximately the maximum permitted US rate and sampled at the shortest PHI, residues of the parent compound ranged from 0.15 to 0.45 mg/kg, while the total residue varied from 0.34 to 0.60 mg/kg. In other trials with slightly lower rates (1.26 - 1.47 kg/ha) where samples were taken after 14 days, the parent and total residues ranged from 0.07 to 0.61 and 0.11 to 1.34 mg/kg respectively. In the trials in France and Spain the total amounts of myclobutanil applied ranged from 0.075 to 0.75 kg/ha. The residues of myclobutanil alone in peaches were similar to those in the US trials. It appears that a residue level of 0.5 mg/kg (weight of stone about 30%), expressed as parent compound, is not likely to be exceeded in peaches if label directions are followed.

In plum and prune residue trials, run in the USA at 1.26 to 1.28 kg/ha, the fresh plums contained the parent and total residues in the range from 0.05 to 0.41 and from 0.05 to 0.48 mg/kg, respectively, at 14 days after the final application. In five trials where the fresh fruit was dried, the parent and total residues in the prunes varied from 0.22 to 0.74 and 0.24 to 0.96 mg/kg, respectively. Residue trials on plums reported from France and Italy were carried out with much lower rates (total dose 0.028-0.5 kg ai/ha). The parent residue was below 0.15 mg/kg in all samples taken from 0 to 28 days. Taking into account average weights of stones of 25% and 50% in fresh and dried fruits respectively, the maximum residues of the parent compound from recommended uses would be 0.2 mg/kg in plums and 0.5 mg/kg in prunes. The total residue is expected to be somewhat higher.

Metabolism studies in rats, cows, and hens have demonstrated that oral doses of myclobutanil are absorbed, rapidly metabolized, and excreted. The major metabolites are RH-9090, RH-9089, and other oxidation or conjugation products.

Animal metabolism and residue studies indicated that myclobutanil and its crop metabolites are rapidly metabolized and all residues rapidly eliminated. More than 95% of the dose is eliminated via the excreta in poultry and cows. Steady-state egg residues ranged from 0.003 mg/kg to 0.11 mg/kg, representing at the most 0.4% of the dose, at exaggerated feeding levels. Steady-state milk residue levels at exaggerated feeding levels ranged from 0.007 to 0.12 mg/kg, representing 0.5% of the dose or less. No accumulation of myclobutanil in meat, milk, or eggs occurred. Feeding crops treated according to current national GAP does not lead to detectable residues in any edible tissues or milk.

Myclobutanil is metabolized by apples and grapes to RH-9090 and RH-9089 and a glucoside conjugation product. The half-life of the total ^{14}C residue on foliage was 15-28 days. The field residue studies indicated that myclobutanil residues decline with a half-life in the range of 7-30 days with typical values of 10-15 days. These analytical data correlate well with the residual efficacy against fungal diseases in crops.

Myclobutanil has a very low vapour pressure and relatively low solubility in water but may be absorbed and retained in waxy surfaces or in the oily components of crops. It has been shown to be susceptible to degradation by ultraviolet light in water in the presence of an activator. It is stable to hydrolysis and photolysis in sterile water and soil in the laboratory.

Laboratory and field studies with myclobutanil have demonstrated that it is moderately stable in the environment with a half-life of 65 days in the laboratory and 20 to 280 days under field conditions. It has a K_{OC} of 518 and low mobility potential.

Based on half-lives measured under field conditions, the model calculations indicated that residues would reach a plateau concentration in soil in one to four years following regular yearly applications of myclobutanil, and no further accumulation or downward movement below 50 cm would occur. The residue data from ongoing field studies confirmed the predictions made by the models during the first year.

Separate analytical methods using GLC with electron capture and nitrogen/phosphorous detection were developed to measure residues of the parent compound and those of the combined residues of the main metabolites independently in apples, grapes, processed fractions, soil and animal

by-products. The limits of determination range from 0.005 mg/kg to 0.01 mg/kg, depending on the substrate.

Results of supervised field trials indicated that the parent compound is the major part of the residue. Although it would be desirable to have analytical data for metabolites in all samples, it is evident from the available data that residues of the main metabolites, RH-9089 and RH-9090, are low compared with those of the parent compound and their proportion is below 30% of the total residue except in cherries where it is about 50%. In residue decline studies where metabolites have been determined, the metabolites decline below the detectable level at about the same time as myclobutanil itself.

As the parent compound and the combined residues of RH-9089 and RH-9090 are determined separately in two different procedures, and the results are added together to obtain the "total" residue, the Meeting concluded that compliance with GAP can be reliably and conveniently controlled by determining the residues of the parent compound alone, which would save time and reduce the cost of enforcement analyses.

FURTHER WORK OR INFORMATION

Desirable

1. Storage stability tests on various commodities.

2. Results of ongoing multi-year field studies on dissipation and downward movement of myclobutanil in soil.

4.31 OXYDEMETON-METHYL (166)

RESIDUE AND ANALYTICAL ASPECTS

Oxydemeton-methyl has been proposed for review, together with the other demeton-methyl compounds (demeton-S-methyl and demeton-S-methylsulphon), largely because of toxicological concerns and potential dietary exposure. As most of the proposed MRLs of the group date from 1973 it was considered appropriate to re-evaluate the residue information in view of probable changes in GAP.

Extensive residue data from supervised trials on all important crops together with other data on use patterns, storage stability, processing, methods of residue analysis and national MRLs were provided to the Meeting by the manufacturer. Additional data were also made available from Canada, The Netherlands and Germany. In view of the extent of the new data, the Meeting undertook a complete re-evaluation of the compound.

Oxydemeton-methyl is a systemic organophosphorus insecticide. It is effective as a contact and stomach poison against sucking insects such as aphids, thrips, leaf hoppers and non-organophosphorus-resistant strains of mites. It is authorized or registered for use in many countries on all important crops, and is marketed in several formulations mainly as EC or SL or as mixtures with parathion or beta-cyfluthrin.

Extensive data were provided on residues from supervised trials and were evaluated together with the information on GAP.

Grapefruit. On the basis of limited residue results from the USA and GAP in Mexico (PHI 7 days) the Meeting estimated a maximum residue level of 0.1 mg/kg.

Lemons. US residue results and GAP indicate that an MRL of 1 mg/kg (PHI 7 days) is necessary.

Oranges. Residues up to 0.4 mg/kg were found 7 days after application. The Meeting estimated a maximum residue level of 0.5 mg/kg.

Mandarins. 14 - 28 days after application residues did not exceed 0.5 mg/kg.

Apples. Available residue data from Germany supported the established MRL of 1 mg/kg.

Pears. Available residue data from Germany supported the established MRL of 0.5 mg/kg.

Currants, Black, Red and White. Results of 12 German residue trials were reported to the Meeting, but without the corresponding GAP. The Meeting therefore proposed withdrawal of the temporary maximum residue limit.

Grapes. The worst-case GAP from countries from which residue data were available was reported for Germany. On the basis of this GAP (1 application) the Meeting estimated a maximum residue level of 0.5 mg/kg.

Raspberries. Results of two residue trials available from Germany were insufficient to estimate a maximum residue level. The Meeting proposed withdrawal of the temporary maximum residue limit.

Blackberries. There are registered uses in The Netherlands and Canada but no residue results were available. The Meeting therefore recommended withdrawal of the TMRL.

Gooseberries. Neither GAP nor residue data were submitted. The Meeting proposed withdrawal of the TMRL.

Strawberries. Residue data from Germany, Canada and the USA supported the established temporary MRL of 0.5 mg/kg.

Cherries. Only 3 residue trials were brought to the attention of the Meeting. The number of applications (4) was higher than in the reported GAP. On the basis of these results and additional data available for demeton-S-methylsulphon the Meeting estimated a maximum residue level of 1 mg/kg.

Peaches. Taking into account results from German trials and a PHI of 21 - 28 days the Meeting estimated a maximum residue level of 1 mg/kg and thus confirmed the established temporary MRL.

Plums. On the basis of 3 German trials and a GAP range of 21 - 28 days for the PHI, the Meeting estimated a maximum residue level of 0.5 mg/kg.

Onions. Results of 13 supervised trials from the USA were brought to the attention of the Meeting. Residues were up to 0.02 mg/kg except in 1 trial where 0.13 mg/kg was found. The Meeting estimated a maximum residue level of 0.05 mg/kg and proposed withdrawal of the TMRL for bulb vegetables.

Broccoli. The results of 9 supervised trials were reported from the USA. Except in one trial (highest residue 1.25 mg/kg) all residues were below 1 mg/kg (PHI 7 days).

Brussels sprouts. Several results of supervised trials were available from the USA, Canada and The Netherlands. Taking into account application rates up to 0.58 kg ai/ha and a PHI range of 7 - 10 days, the Meeting estimated a maximum residue level of 1 mg/kg.

Head Cabbages. On the basis of US trials, reported GAP and a PHI of 7 days, the Meeting estimated a maximum residue level of 1 mg/kg.

Savoy Cabbage. Several residue trials were reported, mainly from Germany. No residues were found 21 - 28 days after the last application (limit of determination 0.01 mg/kg).

Cauliflower. Several German trials carried out in accordance with GAP showed no residues 14 - 21 days after the last application. Canadian and US data could not be taken into account because application rates exceeded GAP.

Kohlrabi. German residue trials showed no detectable residues (limit of determination 0.01 - 0.06 mg/kg) after a PHI range of 7 - 28 days. US trial data could not be taken into account because information on GAP was lacking.

Cucumbers. Taking into account a PHI of 4 days, US GAP and residue results from the USA, the Meeting estimated a maximum residue level of 0.5 mg/kg.

Pumpkins. 13 - 15 days after application (the US PHI is 14 days) residues were all below the limit of determination (<0.1 mg/kg).

Summer and winter squash. 14 days after the last application (the assumed GAP PHI in the USA) residues were all below the limit of determination (<0.1 mg/kg).

Watermelons. Residues in the whole fruit were below 0.2 mg/kg 7 days after the last application (US PHI).

Cantaloupe melons. The Meeting was unable to estimate a maximum residue level because available residue data from the USA did not match GAP (the PHI was 7 days instead of 14 days). The Meeting recommended withdrawal of the TMRL of 0.2 mg/kg for melons, except watermelons.

Egg plants. Except in one trial with a maximum residue of 1 mg/kg after 7 days, residues in 7 US trials never exceeded 0.2 mg/kg 1 - 21 days after application.

Peppers. Results of 15 trials on sweet peppers were available from the USA and Canada. Taking into account Mexican GAP (PHI 0 days) the Meeting confirmed the estimated maximum residue level of 1 mg/kg. One result of 4.9 mg/kg was assumed to be an outlier.

Tomatoes. On the basis of German residue results and a PHI of 4 days the Meeting estimated a maximum residue level of 0.5 mg/kg.

Kale. Taking into account German residue results and GAP, and assuming a PHI of 28 days (the PHI in The Netherlands) the Meeting estimated a maximum residue level of 0.05 mg/kg.

Lettuce. On the basis of US data and taking into account 1 - 3 applications at a PHI of 14 - 28

days, the Meeting estimated a maximum residue level of 2 mg/kg for leaf lettuce.

Common beans. On the basis of German trials which included the worst-case GAP (PHI 7 days), the Meeting estimated a maximum residue level of 0.2 mg/kg. Most of the US data could not be taken into account because application rates exceeded GAP.

Lima beans. Three results from US trials within GAP indicated that a maximum residue level of 0.2 mg/kg (PHI 21 days) is sufficient. Results from other trials with higher application rates could not be taken into account.

Garden peas (young pods). Five results from Germany were available. Although only 2 of these were at the recommended PHI in Germany (7 days), the Meeting concluded that residues in young pods were unlikely to exceed 0.1 mg/kg. The Meeting recommended withdrawal of the temporary MRL for peas.

Dry peas and beans. Residue results for dried peas and beans were available from the USA. In one trial 0.32 mg/kg was found in dried peas. Residues in all other trials (12) were undetectable (limit of determination 0.01 mg/kg).

Carrots. Six trials in Germany showed no residues (limit of determination 0.05 mg/kg). The Meeting was not able to estimate a maximum residue level because no GAP was reported.

Potatoes. Data from Germany, The Netherlands and the USA showed residues up to 0.17 mg/kg 24 days after the last application. The distribution of the other results indicated that this high value was not an outlier. The Meeting estimated a maximum residue level of 0.2 mg/kg (PHI 7 - 21 days).

Sugar beet. Trials with application rates within GAP were carried out in Germany, the USA and France. Except in one trial where 0.07 mg/kg was found 30 days after application, residues were undetectable (limit of determination 0.01 - 0.05 mg/kg). Two results from Germany were not taken into account because residues in the beet were significantly higher than in the leaves. Thirty days after application residues in leaves and tops were well below 0.5 mg/kg.

Barley, oats, wheat, maize. Residue results available for these crops (most of them from Germany and the USA) support the established temporary MRL of 0.2 mg/kg for cereal grains. The Meeting however estimated maximum residue levels for the individual crops.

Sweet corn (kernels and corn-on-the-cob). The Meeting concluded from US residue data that residues were unlikely to exceed 0.05 mg/kg.

Maize fodder. The data available support the present TMRL.

Sorghum. On the basis of various available residue results and US GAP, the Meeting estimated a maximum residue level of 0.5 mg/kg (PHI 45 days).

Sorghum forage (green). Twenty-one days after application (the PHI for grazing and cutting forage), residues in green forage did not exceed 1 mg/kg.

Sorghum straw and fodder, dry. On the basis of the residues in green sorghum forage, and assuming a drying factor of 3 - 5, the Meeting estimated a maximum residue level of 3 mg/kg.

Tree nuts. Residue data were available for hazelnuts, walnuts and pecans. Because no residues were detectable in the edible part the Meeting estimated a maximum residue level at the limit of determination.

Cotton seed. The Meeting estimated a maximum residue level of 0.05 mg/kg (PHI 14 days), based on data from Brazil and the USA.

Safflower seed. In four trials in the USA, residues were up to 0.9 mg/kg. The Meeting recommended a maximum residue level of 1 mg/kg (PHI 7 days).

Sunflower seed. Two residue trials available from France were insufficient to estimate a maximum residue level.

Mints. In five trials in accordance with GAP in the USA, residues 2 weeks after application ranged from 1.09 to 12.35 mg/kg (mean 3.9 mg/kg). The Meeting estimated a maximum residue level of 20 mg/kg.

Alfalfa fodder, clover hay or fodder. The USA recommends that only chaff from seed crops may be used for feed or forage (PHI 21 days). Limited residue results did not exceed the present TMRLs of 5 mg/kg for alfalfa fodder and clover hay or fodder.

Turnips. Seven trials in the USA and Canada showed no residues at the recommended PHI (14 - 21 days). A limit of determination of 0.1 mg/kg was reported.

Turnip leaves or tops. Residue data from USA trials supported the TMRL of 5 mg/kg.

Commodities of animal origin. Additional results available from feeding studies on dairy cows and chickens or hens confirmed that no detectable residues were likely to occur in commodities of animal origin if contaminated plant material is fed. The limit of determination was reported to be 0.005 - 0.05 mg/kg.

Data were also received on the fate of residues in animals, plants, soil and water.

The effect of frozen storage on oxydemeton-methyl and demeton-S-methylsulphon residues was studied in frozen cabbage and soil. The results indicated stability of these two compounds for 3 - 24 months.

Results of processing studies on several crops (orange, apple, peach, grape, cabbage, tomato, potato, sugar beet, maize, sorghum, wheat, cotton, safflower and mints) were examined by the Meeting.

Additional information on methods of residue analysis (special methods and methods for enforcement purposes) was brought to the attention of the Meeting. The limits of determination were 0.005 - 0.2 mg/kg.

The Meeting proposes to change the definition of the residue because the main uses are now of oxydemeton-methyl and the residue data are largely derived from such uses. In the previous definition the name demeton-S-methyl sulphoxide was used for oxydemeton-methyl. The names are synonymous.

The recommendations listed in Annex I are based on all new data available for demeton-S-methyl, demeton-S-methylsulphon and oxydemeton-methyl. Further information on demeton-S-methyl and demeton-S-methylsulphon is given in the evaluations of those compounds.

FURTHER WORK OR INFORMATION

Desirable

Results of supervised trials on grapes, sunflower, sugar beet, potato, barley and wheat and processing studies on grapes and rape seed, all of which the producer stated were in progress.

4.32 PARATHION-METHYL (059)

RESIDUE AND ANALYTICAL ASPECTS

Parathion-methyl, originally evaluated by the JMPR in 1965 and re-evaluated for residues several times up to 1984, is included in the CCPR periodic review programme.

Information on current world-wide GAP and limited residue data were provided by one manufacturer. Information was also provided by The Netherlands and the USA. It had been anticipated

that data from an extensive set of residue studies recently completed in the USA might have become available for evaluation, but they did not arrive in time for review. The Meeting was provided with a list of studies which had been completed, which included supervised residues trials on 29 crops, and processing studies on six commodities.

Because parathion-methyl is being evaluated in the periodic review programme, the Meeting drew attention to the need for critical supporting studies to be available at the same time as the residue data. Critical supporting studies are on metabolism, animal transfer, processing, analytical methods and freezer storage stability. A detailed index of the available critical supporting studies should be prepared by the manufacturer and studies not previously reviewed by the JMPR should be included in the submitted data. The range of critical supporting studies required depends on the proposed uses and the list of commodities likely to contain residues of parathion-methyl. (See report item 2.4 for an outline of FAO Panel procedures for the periodic review programme).

Parathion-methyl is registered as an insecticide in many countries for use on apple, avocado, banana, bean, beet, blackberry, cereals, cherry, citrus, currant, fruit, gooseberry, grape, guava, maize, mandarin, mango, nuts, onion, orange, peach, pear, peas, persimmon, pineapple, plum, pome fruit, pomelo, potato, rape seed, raspberry, stone fruit, strawberry, tropical fruit and vegetables. Application rates for fruits fall in the range 0.12 - 3 kg ai/ha, for vegetables 0.015 - 0.57 kg ai/ha, and for cereals 0.13 - 0.26 mg/kg. Spray concentrations for fruits are in the range 0.008 - 0.3 kg ai/hl, for vegetables 0.013 - 0.13 kg ai/hl, and for cereals 0.022 - 0.13 kg ai/hl.

Residue data from supervised residue trials in Germany in the 1970s were received for apple, blackberry, cherry, gooseberry, grape, plum and raspberry. On blackberry, cherry, gooseberry, plum and raspberry the spray concentration according to GAP in Germany is 0.02 kg ai/hl, and the authorised PHI is 28 days. Spray concentration and pre-harvest interval primarily determine whether trial conditions fall within GAP for these fruit crops. Under these conditions residues were not detected (<0.01 mg/kg) in cherry, gooseberry, plum and raspberry, while a residue of 0.02 mg/kg was reported for blackberry.

The data for each crop are limited, but the pattern of residues was similar in each except blackberry, so the data may be used for mutual support. Also, residues were not detectable (<0.01 mg/kg) in any of the fruits 21 days after the final spray application as well as after the official 28 days. The Meeting agreed to recommend parathion-methyl maximum residue limits for cherries, gooseberry, plums and raspberries at 0.01* mg/kg. The Meeting noted that the limit of determination for parathion-methyl on the crops in these trials was 0.01 mg/kg and considered that this would be a suitable limit for general crop commodity monitoring.

Data on other fruits were either not available or were not from supervised trials conditions matching current GAP. Consequently, no other individual or group fruit MRLs are recommended to replace the fruits MRL, which is recommended for withdrawal.

Neither residue data nor current GAP were available for brassica vegetables, cotton, cucumber, hops, melons, tea or tomato. Residue data were not available for sugar beet. Consequently, the Meeting recommended withdrawal of the MRLs for brassica vegetables, crude cotton seed oil, edible cotton seed oil, cucumber, dry hops, melons except watermelon, sugar beet, green or black tea, and tomato.

The USA provided information on parathion-methyl detections in its surveillance and compliance monitoring programmes for 1988-1990. Parathion-methyl was detected in a wide variety of feed and food crop commodities.

4.33 PENCONAZOLE (182)

1-(2,4-dichloro-β-propylphenethyl)-1*H*-1,2,4-triazole

Penconazole is a systemic triazole fungicide with preventive and curative properties for the control of powdery mildew. It stops the development of fungi by interfering with the biosynthesis of sterols in cell membranes. It is used on fruit, especially apples and grapes, and vegetables.

The compound was considered for the first time by the present Meeting.

TOXICOLOGY

Penconazole administered orally to mice and rats was rapidly absorbed and excreted, predominantly in the urine. Female rats eliminated more in the urine and less in the faeces than male rats. Very low residues were found in organs and tissues in both males and females.

Numerous metabolites were identified in the urine and faeces. The major metabolic pathways involved oxidation of the pentyl side chain to alcohols and acids with sequential cleavage of the terminal carbon. As the oxidation products were conjugated, the resulting metabolic patterns were complex. More polar and conjugated products were found in female rats. Cleavage of the alkyl bridge between the two rings led to the formation of 1,2,4-triazole, which was a major metabolic route in male rats.

Penconazole showed low acute oral toxicity to mice, rats and hamsters, but was slightly more toxic to rabbits. The World Health Organization has classified penconazole as unlikely to present acute hazard in normal use.

Short-term studies with mice, rats and dogs indicated that the liver was the primary target organ. In a special study with male rats, induction of microsomal liver enzymes was demonstrated. In a 13-week study in mice, increased liver weight and liver hypertrophy were observed at 500, 1000 or 2400 ppm. The NOAEL was 300 ppm, equivalent to 43 mg/kg bw/day.

In three 90-day studies with rats, liver weight and liver histopathology were the main effects, except for the second study. In the first study these effects were observed at all dietary levels (30, 300 or 3000 ppm), while in the third study (dietary levels of 10, 100, 300, 500, 1000 or 2400 ppm) the NOAEL was 300 ppm, equivalent to 15 mg/kg bw/day. In the second study (dietary levels 10, 30 or 100 ppm) some biochemical parameters were affected at 30 and 100 ppm. The NOAEL was 10 ppm, equal to 0.8 mg/kg bw/day.

In a one-year study in dogs, increased liver weights and histopathological liver effects were observed at dietary concentrations of 500 and 2500/5000 ppm At the highest level reduced testis weight and atrophic changes were also observed. The NOAEL was 100 ppm, equal to 3.0 and 3.3 mg/kg bw/day for males and females, respectively.

In a two-year feeding study in mice (dietary concentrations of 0, 5, 75, 150 or 300 ppm), increased liver weight at interim kill was seen at 300 ppm. The NOAEL in this study was 150 ppm, equal to 19.3 mg/kg bw/day for males and 17.2 mg/kg bw/day for females. In a long-term study in rats (dietary concentrations of 0, 5, 75, 150 or 300 ppm) liver weight was increased at 150 and 300 ppm. The NOAEL was 75 ppm, equal to 3.8 and 4.0 mg/kg bw/day for males and females respectively. Penconazole was not carcinogenic in mice or rats.

Two two-generation reproduction studies in rats were reviewed. In the first (dietary concentrations of 0, 80, 400 or 2000 ppm), mortality and delayed parturition were observed, as well as decreased body-weight gain of parents and pups and increased relative liver weights in parents and pups at 2000 ppm. Hypertrophy of liver cells was found at 400 and 2000 ppm. The NOAEL was 80 ppm, equal to 5.5 - 6.5 mg/kg bw/day for males and 7.5 - 8.5 mg/kg bw/day for females. In the second

study (dietary concentrations of 0, 25, 250 or 2500 ppm), liver weights were not determined. The main effect at 2500 ppm was reduced body-weight gain of parents and pups and mortality of pups during lactation. The NOAEL was 250 ppm, equivalent to 12.5 mg/kg bw/day.

Embryotoxicity/fetotoxicity was observed in three teratology studies with rats. In two studies (gavage doses of 0, 30, 100 or 300 mg/kg bw/day in one study and 0, 300 or 450 mg/kg bw/day in the other) maternal toxicity, an increased number of resorptions, decreased pup weight and delayed ossification were observed at the high doses. No maternal toxicity or embryotoxicity was observed at 30 mg/kg bw/day. In the third study (gavage doses of 0, 5, 100 or 500 mg/kg bw/day) the NOAEL was 100 mg/kg bw/day. In two teratogenicity studies with rabbits (doses of 0, 25, 75 or 150 mg/kg bw/day in one study and 0, 10, 50 or 200 mg/kg bw/day in the other) maternal body weight and food consumption were reduced and the number of early resorptions was increased at the highest doses. Overall, the NOAEL was 75 mg/kg bw/day for both maternal toxicity and embryotoxicity.

After reviewing the available *in vitro* and *in vivo* genotoxicity data, the Meeting concluded that penconazole was not genotoxic.

An ADI was allocated on the basis of the NOAEL determined from the one-year study in dogs, which was supported by the NOAEL from the long-term study in rats. A safety factor of 100 was applied.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 150 ppm, equal to 17 mg/kg bw/day (two-year study)

Rat: 75 ppm, equal to 3.8 mg/kg bw/day (two-year study)
80 ppm, equal to 5.5 mg/kg bw/day (two-generation reproduction study)
30 mg/kg bw/day (teratology study)

Rabbit: 75 mg/kg bw/day (teratology study)

Dog: 100 ppm, equal to 3 mg/kg bw/day (one-year study)

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

Observation in humans

RESIDUE AND ANALYTICAL ASPECTS

Penconazole is formulated as wettable powders, emulsifiable concentrates or tablets, and is often used in mixtures with other fungicides. Usually several applications are made.

Supervised trials were carried out on fruit and vegetables in European countries, Canada, South Africa, Australia, New Zealand, Brazil and India. In all experiments the residues were determined as the parent compound only.

On apples residues after 2 weeks, which is the recommended pre-harvest interval in many countries, were generally below 0.1 mg/kg, but also occurred up to 0.17 mg/kg. On grapes the pre-harvest interval in many countries is 4 weeks but for some only 2 weeks. Residues were below 0.2 mg/kg after 4 weeks and below 0.4 mg/kg after 2 weeks, except after applications at very high rates. In wine produced from grapes treated with penconazole, residues were mostly undetectable but in some cases 0.02-0.06 mg/kg.

In trials with other fruits and vegetables residues were of the same order as in apples and grapes: normally low but in some trials up to 0.2-0.5 mg/kg. In hops residues were somewhat higher, and trace residues were detectable in beer brewed from hops treated with penconazole, but at a maximum of 0.007 mg/kg.

Metabolic studies were carried out on apples and grapes with triazole-[3,5-^{14}C]-penconazole, and in some studies on grapes also with ^{14}C-phenyl-labelled penconazole. In all studies the propyl side chain was oxidized to monohydroxy and dihydroxy metabolites, which were present in the free state or as glucoside conjugates. There was some cleavage of the bridge between the phenyl and triazole rings and triazolylalanine, triazolyllactic acid and triazolylacetic acid were formed. In apples triazolylglycolic acid was also observed. Levels of the triazole metabolites were highest in pulp and juice, whereas the free and conjugated hydroxy metabolites were highest in the peel.

Residues of penconazol parent compound were present in grapes and apples at only 10-15% of the total residue levels. The toxicity of the metabolites containing the triazole ring has been investigated in combination with an investigation of other members of the group of triazole fungicides, and the presence of these metabolites in crops is considered to be of no toxicological importance (JMPR, 1987 report, item 3.2). For this reason the residue definition is limited to the parent compound only, and all residues in the supervised trials were determined as the parent compound.

Although penconazole is not normally applied to crops used as animal feed, by-products of crops such as apples and grapes may be used as feed, and investigations were made to follow the fate of residues of penconazole after intake via feed by goats, cows and hens.

In goats and cows the major part of the penconazole ingested was eliminated via the urine, and hens given penconazole in the feed excreted 99% within 24 hours after the dose. The same metabolic patterns were observed as in plants except for the presence in animal tissues of hydroxytriazole derivatives. After intake of ^{14}C-labelled penconazole radioactive residues were present in the kidney and liver of goats, but none were observed in muscles or fat. In milk from goats and cows given high doses of ^{14}C-labelled penconazole the highest value of the total radioactive residue was 0.01 mg/kg penconazole equivalents which reached a plateau by day four. Residues of the parent compound were all below the limit of determination in animal tissues, eggs and milk except where doses were 10 to 100 times the levels that would occur in practice. Residues of penconzole were found in samples of liver from a cow at the level of 0.23-0.26 mg/kg, but only after an intake of 100 mg penconazol/kg in the feed.

The degradation of penconazole in soil was mainly by aerobic soil micro-organisms. The half-life of penconazole in a laboratory experiment was between 20 and 49 weeks under aerobic conditions. The compound was degraded in soil to 1,2,4-triazole and to unextractable compounds. From the results of leaching experiments with several soil types penconazole can be classified as having low mobility in soil.

Residues of penconazole in plants are determined by gas chromatography with a nitrogen-specific detector. The compound is extracted with methanol, cleaned up by partitioning with water/methanol/dichloromethane and by gel chromatography or preparative HPLC. The limit of determination is 0.02 mg/kg. The same method with minor modifications can be used for soil and water. A separate method has been developed to determine penconazole in hops and beer.

In animal products residues of penconazole are determined after extraction with acetonitrile. Fat is removed by partitioning with hexane, and further clean-up is by partitioning into dichloromethane and by column chromatography. The final determination is by GLC using a nitrogen-specific detector. The

limit of determination is 0.05 mg/kg for animal tissues and 0.01 mg/kg for milk. A method has also been developed to determine the sum of penconazole and its metabolites containing the 2,4-dichlorophenyl moiety in milk, eggs and animal tissues.

Maximum residue limits are proposed for a number of commodities. Although residues in pears were generally lower than in apples, the use patterns for the two crops are similar and residue limits for them are proposed at the same level. For strawberries, the treatments were exactly in agreement with registered uses in only a few trials but the data were adequate, with residue data on blackberries also taken in consideration, to propose an MRL for strawberries. For currants, gooseberries, onions, leeks, peppers, watermelons, artichokes, beans and peas, the residue data were too limited to recommend residue limits.

FURTHER WORK OR INFORMATION

Desirable

1. Processing studies on apples and tomatoes.

2. Determination of residues of penconazole and its metabolites containing the 2,4-dichlorophenyl moiety in field-grown apples and grapes.

4.34 PHORATE (112)

RESIDUE AND ANALYTICAL ASPECTS

The 1990 JMPR, on the basis of residue data from supervised trials, recommended an MRL of 0.2 mg/kg for potato, and requested information on the fate of phorate residues during peeling and cooking. Several delegations at the 23rd (1991) and 24th (1992) Sessions of the CCPR also requested more information on the fate of phorate during the processing and cooking of potatoes.

The 1991 JMPR had also listed as desirable, studies on the stability of phorate residues in potatoes stored in a freezer, and details of the analytical method used on potatoes and its validation.

Information on the fate of phorate residues in potatoes in commercial processing and in stored analytical samples in freezer storage, and the residue analytical method and its validation were made available to the Meeting.

In processing studies in the USA potatoes were treated at sowing with phorate at 5 times the maximum label rate and grown to maturity in two separate processing studies. At least 11 kg of potatoes in each trial were processed, in one study after washing and peeling to produce potato granules, microwave-cooked potatoes and potato chips. In the other study washing, peeling, boiling, baking and frying were investigated.

The data suggested that washing removed some residues, perhaps 50% or more. However, the very large variation in residue levels between samples did not permit a definite conclusion.

Residues were higher in the peel than in the body of the tuber. Peeling of washed potatoes reduced residue levels by a further 25-50%.

Cooking in granule production, in the drying of peels and by microwave eliminated approximately 50-75% of phorate residues. Very vigorous cooking, as in the oil-frying of chips, eliminated all detectable residues.

Boiling and baking eliminated 50-60% of the phorate residues in potatoes. Frying, to produce French fries, eliminated somewhat more. It should be noted that in some cases the levels in the cooked products increased because of weight loss during cooking even though phorate residues were lost.

Phorate residues were shown to be stable in ground potato tuber samples fortified with analytical grade phorate, phorate sulphone and phorate sulphoxide equivalent to a total phorate concentration of 0.15 mg/kg and stored in a freezer at -23° to -29°C for 706 days.

In the methods of residue analysis phorate and its metabolites are oxidised to phorate oxygen analogue sulphone prior to GLC analysis with detection by a flame-photometric detector. Potato tubers are extracted with dichloromethane, while potato flakes, chips and granules are extracted with aqueous methanol prior to the oxidation step.

The validated limit of determination was 0.05 mg/kg with recoveries generally in the range 70-110% in the concentration range tested (0.05 - 5 mg/kg).

4.35 PIPERONYL BUTOXIDE (062)

Piperonyl butoxide was evaluated by the JMPR in the period 1965-1972 and is included in the CCPR periodic review programme. The existing maximum residue limits on fruits and vegetables were deleted by the CCPR in 1991.

TOXICOLOGY

Toxicological aspects of piperonyl butoxide were previously evaluated by the Joint Meeting in 1965, 1966, and 1972. An ADI of 0-0.03 mg/kg bw/day was allocated in 1972.

Pharmacokinetic studies performed on male rats with single oral doses of approximately 500 mg/kg bw of [^{14}C]piperonyl butoxide showed that peak blood radioactivity was reached between 3 and 12 hours after dosing and that peak values dropped to about 50% within 24 hours. Most of the radioactivity was eliminated via urine and faeces between 12 and 24 hours after dosing. At 168 hours after dosing the proportion of radioactivity recovered was approximately 38% in urine and 62% in faeces. Tissue distribution studies showed that the highest levels of radioactivity were persistently in the gastrointestinal tract and its contents, which suggested that enterohepatic circulation occurs after piperonyl butoxide administration. High levels of radioactivity were also found in lungs, liver, kidneys, fat, prostate and seminal vesicles. The excretion pattern was unchanged after 14 repeated doses of piperonyl butoxide.

A number of studies served to elucidate the mechanism of action as an inhibitor and inducer of MFOs in rodents.

In a two-year study in rats at dietary concentrations adjusted to achieve doses of 0, 30, 100 or 500 mg/kg bw/day, an NOAEL was not determined owing to an increased incidence of bilateral atrophy of the testes in all dose groups. Other effects were increased liver weights with corresponding hyperplasia and hypertrophy of hepatocytes at 100 and 500 mg/kg bw/day and widespread morphological changes and lesions in the endocrine and hormone-sensitive organs. These effects were considered to be secondary to the ability of piperonyl butoxide to induce hepatic MFOs. Piperonyl butoxide was not carcinogenic in rats.

In a two-litter, two-generation reproduction study in rats at dietary levels of 0, 300, 1000 or 5000 ppm, the NOAEL for reproductive toxicity was 5000 ppm, equal to 350 mg/kg bw/day and 480 mg/kg bw/day in males and females, respectively. The NOAEL for parental toxicity and pup development was 1000 ppm, equal to 68 and 94 mg/kg bw/day for males and females respectively, based on lower body weight at 5000 ppm in comparison with controls.

In a teratogenicity study in rabbits at 0, 50, 100 or 200 mg piperonyl butoxide/kg bw given by gavage on days 7-19 of gestation, the incidence of common developmental variations such as a greater number of full ribs and more than 27 presacral vertebrae was increased in all dosed groups. A clear dose-effect relationship was lacking and the relationship of this finding to treatment was considered dubious. The NOAEL for maternal toxicity was 50 mg/kg bw/day and the NOAEL for embryofetal toxicity was 100 mg/kg bw/day.

Toxicological data reviewed by the present Meeting did not give rise to particular concern. The Meeting was informed that additional toxicological data on piperonyl butoxide existed, that more were being generated and that these data will be provided to the Joint Meeting for evaluation. Accordingly, the previously determined ADI of 0-0.03 mg/kg bw was maintained, pending future review.

The Meeting recommended that piperonyl butoxide should be reviewed again in 1995 following submission of the following studies to WHO by 1994.

1) Acute toxicity studies.

2) Teratology studies in rats.
3) Appropriate genotoxicity studies.
4) Ongoing one-year study in dogs.
5) Ongoing carcinogenicity study in mice.
6) Carcinogenicity studies in rats and mice performed by the US National Toxicology Program (1979).
7) Observations in humans.

An addendum to the previous toxicological monograph was prepared.

RESIDUE AND ANALYTICAL ASPECTS

Information on registered uses was received from Australia, Germany and The Netherlands. The compound is mainly used on stored cereals and other stored commodities and in empty storage rooms. Information was also received on pre-harvest uses on fruit.

Trials with pre-harvest uses of piperonyl butoxide on vegetables were carried out in The Netherlands, but the Meeting was informed only of non-professional pre-harvest uses of the compound on vegetables in The Netherlands. A number of commercial milling trials on stored wheat with known application rates was carried out in Australia. The rates were from 9 to 16 mg/kg, and samples of grain, flour, wholemeal, bran and germ were analyzed from 7 to 26 weeks after treatment. Residues in grain and wholemeal were normally at the level of 5-10 mg/kg: they were lower in flour and considerably higher in bran and germ. The application rates at 9 and 10 mg/kg are approximately equal to the registered use rate in Australia. Residues in grain in a survey carried out in five regions of Australia, where samples of grain were analyzed every month during 1½ years, were somewhat lower at levels of 1.5-3 mg/kg.

The compound is very persistent when used on stored wheat, which was confirmed in further experiments in Australia.

Information was received from The Netherlands on a gas-chromatographic method with flame-ionization detection for the determination of residues of piperonyl butoxide.

The Meeting could not carry out a complete re-evaluation of the compound as planned. A full data package was not submitted, in particular no information was received on metabolism studies on plants and animals, and stability and processing studies were received only in connection with commercially stored wheat and wheat products. For this reason all maximum residue limits were withdrawn, but a maximum residue limit of 10 mg/kg was proposed for wheat to replace the previous MRL of 20 mg/kg for cereal grains (see Report item 2.4 for an outline of FAO Panel procedures for the periodic review programme).

4.36 PIRIMIPHOS-METHYL (086)

TOXICOLOGY

Pirimiphos-methyl was previously evaluated for acceptable daily intake in 1974 and 1976. An ADI of 0-0.01 mg/kg bw was allocated in 1976.

Following oral administration of pirimiphos-methyl to male rats, 80.7% and 7.3% of the administered dose was excreted via urine and faeces, respectively, within 24 hours. In the dog, 48 hours after dosing with either 18.4 or 16.7 mg pirimiphos-methyl/kg bw, urinary excretion was 64.4% or 82.5% and faecal excretion 17.3% or 13.3%.

Metabolic data indicated that the PO-C bond of pirimiphos-methyl was readily cleaved and that *N*-de-ethylation and/or conjugation were further steps in the metabolism of the pyrimidine leaving group. Although the oxygen analogue of pirimiphos-methyl was not detected as a urinary metabolite, the fact that cholinesterase inhibition occurred *in vivo* suggests that the oxygen analogue was also formed and may be an intermediate step leading to the identified urinary products.

In rats and dogs 2-ethylamino-4-hydroxy-6-methylpyrimidine was the major metabolite (30% of the administered dose).

The oral toxicity of pirimiphos-methyl is low. WHO has classified the compound as slightly hazardous.

The only biochemical effect consistently observed with pirimiphos-methyl in acute, short-term or long-term studies was cholinesterase inhibition.

In a series of short-term rat studies at dose levels of 0, 8, 80 or 360 ppm for three months, 0, 10, 250, 500 or 1000 ppm for 28 days, 200 mg/kg bw five times weekly for 14 days, and 0, 5, 8, 10 or 50 ppm for 28 days (young rats) the overall NOAEL was 10 ppm (equivalent to 0.5 mg/kg bw/day), with effects on erythrocyte cholinesterase and brain acetylcholinesterase at 80 ppm. At high dose levels (200 mg/kg bw five times weekly for two weeks) erythrocyte morphology was affected. The NOAEL in young rats was also 10 ppm, with brain (but not erythrocyte) acetylcholinesterase depressed at 50 ppm after 28 days.

In two studies in dogs (13 weeks at dose levels of 0, 2, 10 or 25 mg/kg bw/day via capsule and 0, 0.5, 2 or 10 mg/kg bw/day for two years by capsule) the NOAEL was 10 mg/kg bw/day, based on brain acetylacetylcholinesterase inhibition.

In an 80-week study in mice at dietary concentrations of 0, 5, 250 or 500 ppm, the NOAEL based on blood cholinesterase depression was 5 ppm (equal to 0.5 mg/kg bw/day) (blood cholinesterase was not measured at 250 ppm, only at 5 and 500 ppm). Pirimiphos-methyl was not carcinogenic in mice.

In a two-year study in rats at dietary concentrations of 0, 10, 50 or 300 ppm, tumour incidence was comparable to controls. The NOAEL was 10 ppm (equivalent to 0.5 mg/kg bw/day) with brain acetylcholinesterase inhibition occurring at higher levels. Pirimiphos-methyl was not carcinogenic in rats.

In a four-generation reproduction study in rats at nominal dietary concentrations of 0, 20 or 200 ppm, dose-related reduction of pregnancy rates and reduced mating performance at 200 ppm were noted. Dietary analyses indicated that the 20 ppm diet contained only 9 ppm pirimiphos-methyl. No NOAEL was demonstrated in this study.

A repeat study at dietary concentrations of 0, 5, 10 or 100 ppm for three generations (1 litter/generation) did not show any adverse effects on reproductive parameters at any dose level. The NOAEL was 100 ppm (equivalent to 5 mg/kg bw/day) for reproductive effects.

In two rat teratology studies, one at dietary concentrations of 0, 10, or 200 ppm and the other at dose levels of 0, 1.5, 15, or 150 mg/kg bw/day, dosing extending over or beyond the period of embryogenesis did not demonstrate any evidence of teratogenicity. Fetotoxicity was observed at 200 ppm (equivalent to 10 mg/kg bw/day) and 150 mg/kg bw/day. NOAELs for maternal toxicity (15 mg/kg bw/day), embryotoxicity (15 mg/kg bw/day) and teratogenicity ($\leq$ 150 mg/kg bw/day) were identified.

A rabbit teratology study at doses of 0, 1 or 16 mg/kg bw/day administered from days 1-28 of gestation did not show any evidence of teratogenic effects. The NOAEL for fetotoxicity and teratogenicity was 16 mg/kg bw/day.

Four studies indicated that pirimiphos-methyl does not cause delayed neurotoxicity.

After considering the available *in vitro* and *in vivo* genotoxicity data, the Meeting concluded that pirimiphos-methyl was not genotoxic.

In two experimental studies with human volunteers of 28 and 56 days, the highest dose tested in both studies (0.25 mg/kg bw/day) failed to induce erythrocyte cholinesterase inhibition in either study.

In determining the ADI the first multi-generation study in rats was discarded because the dietary concentrations were uncertain, and the adverse effects noted (decreased pregnancy rate and mating performance) were atypical of those normally seen in reproduction studies with organophosphorus esters (decreased pup weight gain and pup mortality during early lactation). A clear NOAEL of 100 ppm (equal to 5 mg/kg bw/day) (the highest dose tested) was demonstrated in the repeat study.

Studies with mice, rats and dogs showed NOAELs of 0.5 mg/kg bw/day or above. In human studies, no cholinesterase inhibition was seen at 0.25 mg/kg bw/day (the highest dose tested). On this basis, the Meeting revised the previous ADI to 0.03 mg/kg bw/day by applying a 10-fold safety factor to the NOEL in the human studies.

A toxicological monograph summarizing the data reviewed at the present Meeting and relevant data from the previous monograph on pirimiphos-methyl was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 5 ppm, equal to 0.5 mg/kg bw/day (80-week study)

Rat: 10 ppm, equivalent to 0.5 mg/kg bw/day (two-year study)
100 ppm, equivalent to 5 mg/kg bw/day (three-generation reproduction study)

Dog: 10 mg/kg bw/day (two-year study)

Man: 0.25 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.

4.37 PROCHLORAZ (142)

RESIDUE AND ANALYTICAL ASPECTS

A reappraisal of the data on which the MRLs for cattle fat, cattle meat, cattle edible offal and milks were recommended at the 1990 JMPR was requested at the 24th Session of the CCPR (Alinorm 93/24, para 148).

Residues in animal produce originate from animal feed, principally from cereal straw and fodder.

The MRL for prochloraz in straw from all cereals (dry) was recommended as 15 mg/kg by the 1985 JMPR, but a large number of residue studies have shown that this level is seldom seen and nearly all the residues found were present at 5 mg/kg or lower. Assuming a value of 5 mg/kg and that a cow eats 20 kg of straw/day, the anticipated intake for cows would be 100 mg/day. In the feeding studies reported, the levels of prochloraz used gave from 2 to 7 times this daily intake.

In one metabolic study involving a cow dosed with 733 mg prochloraz/day for 3 days, that is about 7 times the anticipated daily intake, the total ^{14}C residues in milk reached 0.014 mg/kg. Hence it is unlikely that any residues containing 2,4,6-trichlorophenol would be found above the 0.05 mg/kg limit of determination either in monitoring milk or in commercial production from the anticipated daily intake.

The analytical procedure of Godfrey *et al.*, 1990, does not determine the two main (hydroxyphenyl) metabolites found in milk, since on hydrolysis they produce 2,4,6-trichlororesorcinol. However, it will determine the formylurea metabolite (BTS 44596) which represents approximately 25% of the prochloraz-derived residues found in milk. Since the residues in milk are at or about the limit of determination and the two hydroxylated metabolites are not of toxicological concern, the Meeting concluded that this method was adequate for monitoring purposes.

An animal feeding study was conducted in which cattle were dosed twice daily with prochloraz at rates equivalent to 10, 30 and 100 ppm in the feed for 28 days. At the lowest dose level, residues of 2.8, <0.05, 0.5 and 0.1-0.2 mg/kg were found in liver, muscle, kidney and fat respectively. On the basis of these data, the JMPR in 1990 recommended maximum residue levels of 0.5 and 5 mg/kg for cattle fat and edible offal respectively. The feeding level of 10 ppm has been estimated to be at least twice the anticipated level of prochloraz in cereal straw. The Meeting considered that this factor was not significant enough to warrant changing the MRLs recommended in 1990.

From a re-examination of previously evaluated data the Meeting concluded that the maximum residue levels estimated at the 1990 JMPR for edible offal of cattle and cattle fat of 5 and 0.5 mg/kg, respectively, were adequate. Since no residues were found in muscle and milk above the limit of determination, the Meeting proposed that the MRLs in cattle meat and milk be retained at 0.1* mg/kg.

4.38 PROFENOFOS (171)

RESIDUE AND ANALYTICAL ASPECTS

Profenofos was first reviewed by the 1990 JMPR, which estimated maximum residue levels for numerous crops and other commodities which were designated as temporary pending the submission of information on nationally approved uses. The Meeting received information on current GAP, re-examined previously estimated levels in its context, and reviewed additional supervised trials data.

New summarized information on artichokes was insufficient to estimate a maximum residue level.

The 1990 JMPR estimated a 1 mg/kg maximum level for oranges. Citrus data summarized in the 1990 monograph, when reviewed in the context of current GAP, suggest that residues could approach 2 mg/kg at the current 14- to 21-day GAP PHIs: the 1990 estimate was based on a PHI of 49 days. However, no GAP information was received for the countries where the trials were conducted, nor for neighbouring geographical areas. The Meeting concluded that it could not esimate a maximum residue level for a crop as important as oranges without such information, and therefore recommended that the previous 1 mg/kg TMRL should be withdrawn.

No relevant information on GAP was received for broccoli, Brussels sprouts, cucumber or

peaches as required by the 1990 JMPR. Accordingly, the Meeting recommended that previously recommended temporary maximum residue limits for these commodities should be withdrawn. Although some information on GAP for "brassicas" that might apply to cauliflower was available, it could not be translated to the geographical areas of the trials. The Meeting therefore recommended that this limit should also be withdrawn.

The required GAP information for head cabbages was provided. While the rates were generally comparable to those used in field trials on which the 1990 JMPR based its 0.5 mg/kg TMRL recommendation linked to a 14-day PHI, the GAP provided (from Asia and South America) was not from the geographical areas of the trials (Australia, Canada, Germany, South Africa and Switzerland). It also reported 7-day GAP PHIs in addition to the 14 days used by the 1990 JMPR.

While the GAP is not truly representative of the areas of the supervised trials, because the rates are generally comparable and because wide geographical representation is provided by the trials, the Meeting concluded that it would not be unreasonable to use it as a basis for evaluation. It concluded that the shorter PHIs need to be accommodated however, noted that residues up to 1.7 mg/kg were reported after 5 days and observed, as did the 1990 JMPR, that one sample had residues up to 0.7 mg/kg after 14 days. The Meeting recommended an increase in the previous estimate.

Because the required information on GAP for "spring onions" was not provided and only limited data from one country on whole onion plants were available, the Meeting recommended that the 2 mg/kg TMRL should be withdrawn. No information was provided on GAP for sweet peppers, and although GAP for "vegetables" or "fruiting vegetables" was available, a good match could not be made with the data on sweet peppers. The Meeting therefore recommended that the 1 mg/kg TMRL for sweet peppers be withdrawn.

The GAP reported for bulb onions did not closely match the data provided. Although not an ideal situation, an evaluation of the South African data in the light of the Indonesian GAP suggests that 0.05 mg/kg may not be exceeded at a 14-day GAP PHI as opposed to the 7 days used by the 1990 JMPR for its 0.2 mg/kg estimate. However, assuming that residues are roughly halved between 7 and 14 days (generally supported by the data), the 7-day Indonesian residues suggest that residues of 0.1 to 0.15 mg/kg may occur after 14 days. Because the data are relatively limited and do not closely match GAP, the Meeting concluded that it would not be prudent to lower the 0.2 mg/kg 1990 JMPR estimate unless more data closely reflecting GAP become available. It concluded that sufficient information was available to change the TMRL to an MRL. Additional data reflecting GAP would be desirable.

Information on GAP for tomatoes was provided as required by the 1990 JMPR, but not for the countries in which the trials supporting the 0.5 mg/kg TMRL were carried out. Nevertheless, because substantial data with a broad geographical representation were provided and because the trials were at rates generally comparable to the GAP reported to the present Meeting, the Meeting concluded that it is reasonable to link the new GAP information to the available data base.

However, since the PHI is 4 days in South Africa where the bulk of the data were generated, and 7 days in the Philippines, the Meeting concluded that the 14-day basis for the 1990 estimate may be too long to accommodate GAP. The Meeting observed that after applications at GAP rates, residues were 0.53, 0.9, 0.73, 0.7, 1.8, 0.6 and 0.53 mg/kg after 7 to 8 days, up to 1.8 and 1.9 mg/kg after 4 days, and 0.8 mg/kg after 3 days. Taking into account the shorter PHIs, the Meeting recommended that the 0.5 mg/kg limit should be increased and the temporary status removed.

The Meeting received the required information on GAP for potatoes. Although this applied mostly only in Asia and South or Central America, it was available for 11 countries. Generally the GAP rates were consistent with those at which supervised trials were conducted and the PHIs are 7 to 14 days compared to the 14-day PHI basis for the 1990 JMPR estimate. Because the GAP application rates are consistent with those in the trials and because residues after 7 days or more were still below the 0.05 mg/kg resulting from maximum application rates, the Meeting confirmed the 1990 estimate and recommended that the temporary status be removed.

The GAP information for sugar beet required by the 1990 JMPR was provided for Chile, Greece and Japan, whereas the supervised trials were carried out in France, the UK, Italy and Switzerland. Nevertheless, because application rates are similar, the PHIs generally comparable, and the residues $\underline{\leq}$0.02 mg/kg, the Meeting confirmed the 1990 estimate and recommended that the temporary status be removed.

GAP information for "beans" was provided in response to the 1990 JMPR requirement for GAP for dry beans. However, the GAP for El Salvador, the Philippines and Thailand cannot well be applied to the dry bean trials in Brazil and Switzerland, nor were the GAP rates comparable to those in the trials. The 7-day PHI of one of the two countries for which the PHI was provided is not represented by data. Even though the 1990 TMRL proposal was at the limit of determination, the Meeting concluded that insufficient information was available to determine whether the supervised trials adequately reflected GAP and recommended withdrawal of the TMRL.

GAP information for soya beans required by the 1990 JMPR was provided, but was for Brazil, Egypt, Mozambique and Paraguay (and for Mung bean for Indonesia) while the soya bean trials were in Brazil, Indonesia, Mexico and the USA. Generally the supervised trials were at application rates comparable to the GAP rates, but PHIs of 14 days appear to be common, whereas the 1990 JMPR estimate of 0.05 mg/kg was based on 21 days. The Meeting noted that the 1990 JMPR had concluded that residues at GAP rates did not exceed 0.02 mg/kg in "all samples". Although additional data produced according to GAP would be desirable, because a substantial number of trials reflecting most GAP showed residues below the limit of determination, the Meeting confirmed the 1990 estimate and recommended that the MRL should no longer be temporary.

The Meeting noted that residues were below 0.05 mg/kg in refined, bleached, deodorized and hydrogenated soya bean oil and confirmed the 1990 estimate for oil so defined. However, because processing data reviewed by the 1990 JMPR were not adequate to determine a concentration factor, some concentration of residues in the crude oil was observed, and no analyses of refined oil without all processing steps were available, the Meeting requested (as desirable) an additional processing study with finite seed residues so that concentration factors could be determined in all the processing fractions, including refined oil that had not received all of the refining treatments.

The required GAP information on maize was provided but most of it was for Central and South America while the supervised trials were in France, Mexico, Spain and Switzerland. Application rates were generally comparable between the trials and the GAP, but PHIs were usually 14 or 15 days, whereas none were specified in 1990. While the 1990 JMPR estimate of 0.05 mg/kg was at the limit of determination, the Meeting concluded that it was unsatisfactory to apply Central and South American GAP to European trials data for such a major crop. The Meeting recommended that the TMRL be withdrawn until sufficient residue trials data reflecting approved uses can be evaluated.

The GAP information on cotton seed required by the 1990 JMPR was provided. This was for 21 countries, including the two countries for which supervised trials data were evaluated in 1990. The Meeting noted that the usual national PHI is now approximately 14 days instead of 21 as in 1990, and therefore re-examined the 1990 monograph. This showed that residues in one trial from rates approximating GAP reached 2.8 mg/kg in one of the two replicates after 14 days, 2.6 mg/kg after 21 days and 2.3 mg/kg after 30 days. The highest residue in the other trials after 14 days was 1.2 mg/kg (mean of 4 analyses). The Meeting concluded that the 1990 estimate may be exceeded at the shorter PHI and recommended a new (non-temporary) limit to replace the 1 mg/kg TMRL. The Meeting confirmed the 1990 estimate for refined, bleached, deodorized, hydrogenated (RBDH) cotton seed oil.

The GAP information for sunflower seed was only for Pakistan, while trials were in Argentina and Brazil. The GAP rate is 1 kg ai/ha and the PHI 14 days, while in the trials the highest rate was 0.6 mg ai/ha with PHIs of 34 to 53 days. The Meeting concluded that insufficient information was available to support a limit for sunflower seed and recommended withdrawal of the MRL.

GAP information for profenofos on tea was provided for the country in which the trials were

conducted, but the Meeting could not compare the GAP 40 g ai/hl application rate with the 1 kg ai/ha applied in the supervised trials. No GAP PHI was specified, although 21 days was reported to the 1990 JMPR as the national PHI of the country concerned. The Meeting recommended that the 0.5 mg/kg TMRL be retained until information is provided on the supervised trial rates in terms of g ai/hl.

The Meeting confirmed the 1990 estimates for meat, milks and eggs and recommended them as full MRLs.

FURTHER WORK OR INFORMATION

Required (by 1993)

Information on the application rates in terms of g ai/hl used in the supervised trials on tea reviewed by the 1990 JMPR.

Desirable

1. Additional data reflecting GAP for bulb onions in countries in which the trials were conducted and/or additional GAP information for the countries for which data have already been provided.

2. Additional soya bean processing study conducted with beans with finite residues to permit determination of concentration factors in all processed fractions.

3. Additional soya bean data reflecting GAP in countries in which the trials were conducted and/or additional GAP information for the countries for which data have already been provided.

4.39 PROPHAM

isopropyl carbanilate

TOXICOLOGY

Propham, isopropyl carbanilate, was previously evaluated by the JMPR in 1965. The data eview available at that time were considered inadequate for allocating an ADI.

Following oral administration to rats, propham was eliminated via the urine (80-96%), faeces (5%) and expired air (5%). Metabolism proceeds by hydrolysis and oxidation.

Propham had a low acute oral toxicity in rats. The World Health Organization has classified propham as unlikely to present acute hazard in normal use.

In short-term toxicity studies in rats at dietary concentrations of 0, 200, 1000 or 5000 ppm for 13 weeks or of 0, 10, 30 or 100 ppm for 12 months, effects were observed on haematological parameters, ASAT, and relative weights of the adrenals, liver and spleen. Increases in haemosiderin content in the spleen were seen. On the basis of the haematological effects a NOAEL of 100 ppm equal to 5.8 and 7.8 mg/kg bw/day in males and females, respectively, was determined.

In a 2-year long-term/carcinogenicity study in rats at dietary concentrations of 0, 100, 500 or 2500 ppm propham, effects on haematological parameters and spleen weight were observed. Increased haemopoiesis was seen in the spleen and liver. On the basis of the effects on the haematological effects, an NOAEL of 100 ppm, equal to 5.7 and 7.6 mg/kg bw/day in males and females respectively, was determined. There was no evidence of carcinogenicity.

A 33-month study in hamsters was inadequate for evaluation.

In a two-generation reproduction study in rats at dietary concentrations of 0, 200, 1000 or 5000 ppm propham, an NOAEL of 1000 ppm, equal to 80 mg/kg bw/day, was determined on the basis of effects on lactation index, food intake, and body-weight gain.

An oral teratogenicity study in rats was inadequate for evaluation.

Although the data were not fully adequate, the Meeting concluded that propham was not likely to be genotoxic.

The available toxicological data on propham were not adequate to allocate an ADI.

A toxicological monograph was prepared.

Studies without which the determination of an ADI is impracticable

1. A biotransformation study in rats.
2. Short-term toxicity study in a non-rodent species.
3. A test specifically for aneuploidy.
4. Teratogenicity studies in two species.
5. Available observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Limited information on GAP and residue data were submitted by a single manufacturer. Critical supporting study data were lacking. Data were inadequate for the estimation of MRLs. It was noted that an industry task-force had been formed. A new compound, propham will be rescheduled for residue evaluation according to the availability of adequate data.

4.40 PYRAZOPHOS (153)

TOXICOLOGY

Pyrazophos is an organophosphorus systemic fungicide used in the control of powdery mildews on a wide range of crops and cereals. It was scheduled for evaluation at the 1985 Joint Meeting but the data base available at that time was not sufficient for the estimation of an ADI.

In rats after a single or 14 daily (with only the last dose radio-labelled) oral administrations of ^{14}C-pyrazophos, blood radioactivity peaked within six hours after administration. The half-life was approximately five hours. Radioactivity was eliminated mainly via urine (71-78%) and faeces (16-24%). The parent compound accounted for most of the radioactivity detected in faeces, indicating incomplete absorption from the gastrointestinal tract. Intact pyrazophos was not found in urine, where the radioactivity mostly corresponded to its hydrolysis products.

Pyrazophos was moderately toxic after single oral doses to mice, rats and dogs. No significant differences between sexes or routes of administration were detected. WHO has classified pyrazophos as moderately hazardous.

In two 28-day studies in mice at dietary concentrations of 0, 1, 5, 25 or 125 ppm (the highest dose in only one study) the NOAEL was 25 ppm, equal to 4.7 and 5.0 mg/kg bw/day for males and females respectively. The NOAEL was based on 20% inhibition of brain cholinesterase observed at 125 ppm.

In a 13-week study in rats at dietary concentrations of 0, 2.5, 50 or 1000 ppm the NOAEL was 2.5 ppm, equal to 0.21 mg/kg bw/day, in both sexes, based on brain cholinesterase inhibition at the end of the study at 50 ppm.

In a 52-week study in rats at dietary concentrations of 0, 2, 20 or 200 ppm the NOAEL was 20 ppm, equal to 1.0 and 1.4 mg/kg bw/day in males and females respectively. The NOAEL was based on 30% inhibition of brain cholinesterase activity in females at 200 ppm.

In a 92-day (moist semi-solid diet) study in dogs at dietary concentrations of 0, 0.5, 2.0, 5.0 or 10/125/320 ppm the NOAEL was 5 ppm, equivalent to 0.4 mg/kg bw/day, based on inhibition of erythrocyte cholinesterase activity at the next to highest dose (brain acetyl cholinesterase activity was not determined). Clinical signs of the cholinergic type were observed when the dietary concentration was raised to 320 ppm.

In a 6-month study in dogs at dietary levels of 0, 1.2, 18 or 320 ppm pyrazophos (moist semi-solid diet), the NOAEL was 1.2 ppm equivalent to 0.09 mg/kg bw/day, based on marginal brain acetyl cholinesterase inhibition observed at 18 ppm.

In a two-year study in dogs at dietary concentrations of 0, 2, 5 or 320 pm (moist semi-solid diet), the NOAEL was 5 ppm, equivalent to 0.4 mg/kg bw/day based on erythrocyte cholinesterase inhibition, reduced body-weight gain and histopathological abnormalities observed in the kidneys of dogs fed 320 ppm.

In a 92/96 (female/male) week study in mice at dietary concentrations of 0, 1, 5 or 25 ppm, pyrazophos did not cause adverse effects up to the highest nominal concentration of 25 ppm, equal to 3.5 and 4.1 mg/kg bw/day in males and females, respectively. Inhibition of serum and erythrocyte cholinesterase activities but not of brain acetyl cholinesterase activity was observed at 5 ppm and above. The poor correspondence between actual and nominal concentrations of pyrazophos in diets hampered definitive evaluation of this study.

In a two-year study in rats at dietary levels of 0, 2, 80 or 320 ppm, the NOAEL was 2 ppm, equal

to 0.1 mg/kg bw/day, based on a higher incidence of hemangiomas in mesenteric lymph nodes detected in males at the higher doses. Marginal brain acetyl cholinesterase inhibition was noted at 320 ppm only.

In a two-year study in rats at dietary concentrations of 0, 5, 8, 10 or 50 ppm the NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw/day, based on the absence of adverse effects including brain acetyl cholinesterase inhibition at this dose level. No compound-related abnormalities were detected in mesenteric lymph nodes.

In a two-litter, three-generation study in rats (a 90-day toxicity study was also conducted on the F_{3b} generation) at dietary levels of 0, 5, 10 or 50 ppm the NOAEL was 5 ppm, equal to 0.45 and 0.42 mg/kg bw/day for males and females respectively, based on increased thymus weight observed at 10 and 50 ppm and increased lymphocyte counts observed at 50 ppm in both sexes in the 90-day toxicity study.

In a two-generation reproduction study in rats at dietary concentrations of 0, 2, 20 or 200 ppm of pyrazophos the NOAEL was 20 ppm, equivalent to 1 mg/kg bw/day, based on retardation of body-weight gain of pups of both generations, reduced lactation index of the F_1 generation and slight inhibition of brain acetyl cholinesterase activity in parental females and in pups of the F_2 generation.

Pyrazophos did not cause delayed neuropathy in hens.

Pyrazophos was not teratogenic in rats or rabbits. The NOAELs for maternal and embryofetal toxicity in rats were 5 mg/kg bw/day and in rabbits was 100 mg/kg bw/day, the highest doses tested. Maternotoxicity was not observed. However, cholinesterase activity was not measured.

Male and female human volunteers received pyrazophos orally at 0.07, 0.15/0.07 or 0.15 mg/kg bw/day for 10 days. At the highest dose level only plasma cholinesterase activity was inhibited (20-40%), with marginal inhibition of erythrocyte cholinesterase activity. Symptoms which could be attributed to cholinergic toxicity were observed in all groups. The study was considered inadequate because of deficiencies in its design and conduct.

After reviewing the available genotoxicity data, it was concluded that pyrazophos was not genotoxic.

The Meeting concluded after consideration of the long-term studies and the genotoxicity data that pyrazophos was unlikely to pose a carcinogenic hazard for humans.

An ADI was allocated on the basis of the NOAELs in the two-year study in dogs and the three-generation study in rats, using a 100-fold safety factor.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 25 ppm, equal to 4.7 mg/kg bw/day (28-day study)
Rat: 5 ppm, equal to 0.4 mg/kg bw/day (three-generation repro-duction study)
Dog: 5 ppm, equivalent to 0.4 mg/kg bw/day (two-year study)

Estimate of acceptable daily intake for humans

0-0.004 mg/kg bw

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

Further observations in humans.

RESIDUE AND ANALYTICAL ASPECTS

Limited residue data were available, but the late submission of relevant information on GAP did not allow enough time to complete the evaluation.

4.41 THIRAM (105 - dithiocarbamates)

TOXICOLOGY

Thiram, a dimethyldithiocarbamate fungicide, was evaluated by the Joint Meeting several times between 1963 and 1987. A temporary ADI of 0-0.005 mg/kg bw, allocated in 1974, was extended in 1977 and 1980. The temporary ADI was withdrawn in 1985 because of the inadequacy of the total data base. The studies available to the 1987 Joint Meeting were not adequate for estimating an ADI. A complete data base on thiram has been generated since the previous evaluation, and was evaluated at the present Meeting.

Following oral administration to rats, thiram was well-absorbed (>83%) and eliminated via the expired air (41-48%), urine (25-40%), and faeces (2-5%). About 3% was recovered in various organs. The majority of the dose (84-90%) was eliminated within four days after dosing.

The metabolism of thiram was studied in rats. During the first five hours after administration a dose-dependent formation of carbon disulphide was demonstrated in the expired air. Metabolites detected in urine included polar oxidation products and conjugates.

The acute oral toxicity of thiram is low in mice and rats. The World Health Organization has classified thiram as slightly hazardous.

A 13-week dietary study in rats at levels of 0, 50, 500 or 1000 ppm resulted in changes in haematological and serum biochemical parameters and gastric irritation at 500 and 1000 ppm. The NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw/day.

Dogs received thiram as a dietary admixture at levels of 0, 75, 250 or 500 ppm for 13 weeks or at levels of 0, 30, 90 or 250 ppm for 52 weeks. The NOAELs were 75 ppm (equal to 2.2 and 2.3 mg/kg bw/day in males and females respectively, for the 13-week study) and 30 ppm (equal to 0.84 mg/kg bw/day) in males and 90 ppm (equal to 2.5 mg/kg bw/day) in females in the 52-week study on the basis of changes in body-weight, increased absolute and relative liver weights and changes in haematological and serum biochemical parameters. In another study, dogs received thiram in gelatin capsules at doses of 0, 0.4, 4.0 or 40 mg/kg bw/day 7 days/week for 104 weeks. Nausea, vomiting and salivation, ophthalmological effects, convulsions, changes in haematological parameters, and renal changes were observed at 4 and 40 mg/kg bw/day. On the basis of the described effects, the NOAEL was 0.4 mg/kg bw/day. Since thiram was administered in capsules in this experiment and significantly less information was available on the study conditions than in those in the former two experiments with dietary administrations of thiram this NOAEL was not used as the basis for the estimation of an ADI.

In a 97-week oncogenicity study in mice using dietary concentrations of thiram of 0, 15, 150 and 300/600 ppm, the effects included dose-dependent decreases of food consumption and body-weight gain and changes in haematological parameters. Non-neoplastic findings included retinal atrophy, changes in the urinary bladder and in the skin, hyperkeratosis in the non-glandular stomach, and increased pigmentation in the spleen. Thiram was not carcinogenic in mice. The NOAEL for long-term toxicity in male and female mice was 15 ppm, equal to 3 mg/kg bw/day.

In a two-year toxicity study in rats at dietary concentrations of 0, 3, 30 or 300 ppm a NOAEL of 30 ppm, equal to 1.2 and 1.4 mg/kg bw/day in males and females respectively, was determined. It was based on lower red blood cell counts, haemoglobin levels and haematocrit levels and degenerative changes of the sciatic nerve accompanied by atrophy of the gastrocnemius muscle at 300 ppm. Thiram was not carcinogenic in rats.

In a second two-year long-term/carcinogenicity study in rats at dietary concentrations of 0, 30, 150 or 300 ppm, dose-dependent lower erythrocyte counts, haemoglobin levels and haematocrit values

were observed. Based on these haematological changes a NOAEL of 30 ppm, equal to 1.5 and 1.8 mg/kg bw/day in males and females respectively, was determined.

In a 2-year carcinogenicity study in rats at dietary concentrations of 0, 500, or 1000 ppm (equal to 39 and 42 mg/kg bw/day in males and females respectively) there was no evidence of carcinogenicity. The Meeting concluded that thiram was not carcinogenic in rats.

In a two-generation reproduction study in rats at dietary concentrations of 0, 30, 60 or 180 ppm, no adverse effects on reproduction were observed. The NOAEL for reproductive effects was >180 ppm (equal to >8.9 and >14 mg/kg bw/day in males and females, respectively). The NOAEL for systemic toxicity was 30 ppm (equal to 1.5 and 2.3 mg/kg bw/day in males and females respectively). It was based upon reduction in body-weights and/or food consumption in both parental and offspring animals.

An oral teratogenicity study was performed in rats at gavage dose levels of 0, 7.5, 15 and 30 mg/kg bw/day. An NOAEL for maternal toxicity was not determined owing to a dose-dependent decrease in body weight gain and placental weight at all dose levels. Teratogenicity was not observed.

In an oral teratogenicity study in rabbits at gavage doses of 0, 1.0, 2.5 or 5.0 mg/kg bw/day, an NOAEL of 2.5 mg/kg bw/day for maternal toxicity was based on a dose-dependent reduction of body-weight gain. Teratogenicity was not observed.

An oral teratogenicity study was carried out in rabbits at gavage dose levels of 0, 1.0, 5.0 or 10 mg/kg bw/day. The NOAEL for maternal toxicity was higher than 10 mg/kg bw/day. Teratogenicity was not observed.

Thiram was mutagenic in the Ames test but not in mammalian cells *in vitro*. Since thiram was not mutagenic *in vivo*, the Meeting concluded that it did not present a genotoxic hazard for humans.

The central and peripheral nervous systems have been recognized as a possible targets for thiram toxicity. Neurotoxicity may be related to the thiram metabolite carbon disulphide.

An ADI was allocated, on the basis of the 1-year study in dogs and the 2-year studies in rats, using a 100-fold safety factor.

An addendum to the previous toxicological monographs on thiram and the dithiocarbamates was prepared.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse: 15 ppm, equal to 3.0 mg/kg bw/day (97-week study)

Rat: 30 ppm, equal to 1.2 mg/kg bw/day (two-year study)
30 ppm, equal to 1.5 mg/kg bw/day (two-generation reproduction study)

Rabbit: 2.5 mg/kg bw/day (teratology study, maternal toxicity)

Dog: 30 ppm, equal to 0.84 mg/kg bw/day (one-year study)

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

1. Clarification of the potential for neurotoxicity of thiram.

2. Observations in humans.

4.42 TRIADIMEFON (133)

RESIDUE AND ANALYTICAL ASPECTS

Residue aspects of triadimefon have been reviewed 9 times since its first evaluation in 1979 and an ADI was estimated in 1985. The most recent residue review was in 1989, at which the JMPR evaluated additional data and addressed questions raised at the CCPR. The 1989 JMPR also estimated separate limits and an ADI for triadimenol, the primary metabolite of triadimefon, which is also itself a pesticide. Current limits for triadimefon are expressed as the sum of triadimefon and triadimenol and those for triadimenol as triadimenol. This has resulted in separate limits for some commodities, one for triadimefon plus triadimenol and another for triadimenol only, depending on the use.

The 1989 JMPR drew attention to the need for a future Meeting to consider estimating separate limits for triadimefon and triadimenol in accordance with the principle outlined in the 1989 JMPR report (para 2.10). This was a recommendation that, where possible, separate limits should be established for a parent pesticide and a metabolite that is also registered for use as a pesticide. Triadimefon/triadimenol was cited as an example.

The 1991 CCPR noted that a complete review of the data would be required for the JMPR to estimate separate limits. The manufacturer provided new data for a scheduled 1991 review, but the compounds could not be evaluated that year. The 1992 CCPR discussed specific MRLs for triadimenol in certain commodities, on which opinions varied.

The 1992 JMPR re-examined the old monograph data summaries and additional data provided to the Meeting on triadimefon and triadimenol in the context of current GAP with a view to recommending separate limits where possible and considering the question of triadimenol on grapes discussed at the 1992 CCPR. Triadimenol is discussed in Section 4.43.

Several new data submissions could not be used for estimating maximum residue levels, because only summary data were provided. The Meeting was informed that the detailed studies could be provided for review at a future Meeting.

Trials on the following commodities were evaluated.

Bananas. Supervised trials data on bananas were provided to the Meeting for the first time, from three countries. Information on GAP was available for only one country and most of the data could not be related to the GAP. In the one trial which approximated the GAP rate (but with a different formulation), data were only for the pulp, not the whole fruit. The Meeting concluded that residues and GAP information was insufficient to estimate limits.

Cereals

Barley. The current 1 mg/kg proposal is based on maximum residues for the sum of triadimefon and triadimenol at 0.7 mg/kg and was necessary to accommodate North American GAP. Lower levels were generally sufficient elsewhere. The available data from separate analyses of the two compounds are variable, but maximum residues of 0.3 mg/kg of each have been recorded. As a generalization residues of triadimefon and triadimend are comparable at shorter GAP PHIs, where they are high enough to be compared, but triadimenol becomes relatively more pronounced as PHIs increase. A

reasonable estimate for each compound would be 0.3 mg/kg.

Oats, rye and wheat. The current 0.5 mg/kg MRL at step 7B for triadimefon plus triadimenol was recommended by the 1983 JMPR for barley, oats, rye and wheat, primarily to accommodate barley uses. Previously the limit for the three had been 0.2 mg/kg. While the barley limit was later revised to 1 mg/kg, the 0.5 mg/kg limit was retained for oats, rye and wheat. The Meeting concluded that it was appropriate to examine wheat, rye and oats data independently of those for barley. The wheat data have previously been mostly from separate analyses of the two compounds, with maximum residues from trials approximating GAP of 0.06 mg/kg triadimefon and 0.09 mg/kg triadimenol. Residues reported to the present Meeting from approximately half the GAP rates were 0.05 mg/kg triadimefon and 0.12 mg/kg triadimenol at the 60-day PHI of the country where trials were conducted and up to 0.17 mg/kg triadimenol after 33 days, which is GAP in some countries. Corresponding maximum residues in rye were <0.04 mg/kg triadimefon and 0.11 mg/kg triadimenol. Residues of both compounds in oats were reported as n.d. Reasonable estimates for wheat, rye and oats would be 0.1 mg/kg for triadimefon and 0.2 mg/kg for triadimenol, not at the limit of determination.

Dry straw and fodder of barley oats, rye and wheat. The current MRL (at step 7B) is 5 mg/kg for the dry straw and fodder of barley, oats, rye and wheat. While it is clear that barley grain is appropriately considered separately from the other cereals, there is no compelling reason to treat the dry straws and fodders separately. Data on total residues and on the separate compounds are available. The highest total residues from trials approximating GAP for the dry straw and fodder were barley 3.7 mg/kg, wheat 8.7 mg/kg, and oats 0.4 mg/kg. The highest residues of triadimefon were barley 1.4, oats <0.05, rye 0.74, wheat 1.2 mg/kg, while the maximum triadimenol levels were barley 3 mg/kg, oats 0.6 mg/kg, rye 2.1, and wheat 3.3 mg/kg. A reasonable maximum estimate for the dry straws and fodders of these cereals would be 2 mg/kg for triadimefon and 4 mg/kg for triadimenol.

Chick-pea (dry). The current CXL for the sum of triadimefon and triadimenol in chick peas (0.1 mg/kg, limit of determination) was based on separate analyses for the two compounds, with maximum residues of 0.02 mg/kg triadimefon and 0.01 mg/kg triadimenol. Additional summary data submitted to the 1992 JMPR reflecting Mexican GAP (125 g ai/ha, 21-day PHI) resulted in maximum residues of <0.01 and 0.02 mg/kg for the two compounds respectively. A reasonable estimate of the maximum residue levels would be 0.05 mg/kg (limit of determination) for each compound.

Coffee beans. The current 0.1 mg/kg limit of determination CXL for the sum of triadimefon and triadimenol in coffee beans was again based on separate analyses of the two compounds. Maximum residues from trials approximating GAP in the original and subsequently submitted data were triadimefon $\leq$0.02 or <0.05 mg/kg, depending on the method, and triadimenol 0.08 mg/kg in green coffee beans (no triadimefon detected in this sample). More often than not, most of the residue is the triadimenol, with <0.01 mg/kg triadimefon. Methods were validated down to 0.05 mg/kg for both compounds in at least one study. A reasonable estimate is a limit of determination maximum level of 0.05 mg/kg for triadimefon and 0.1 mg/kg for triadimenol.

Cotton seed. No limit has been recommended for cotton seed. Summary information on trials reflecting the GAP of one country were provided to the Meeting, with maximum residues of 0.06 mg/kg triadimefon and 0.05 mg/kg triadimenol. Because the data were limited, with no details of the trials, analytical methods etc., the Meeting could not estimate a maximum residue level.

Currants, Black, Red, White. The present CXL of 1 mg/kg for the sum of triadimefon and triadimenol in currants was at first for red currants only, and was based on total residue data with a maximum residue of 0.65 mg/kg (the next highest being 0.35 mg/kg). It was later extended to include black currants. Separate analyses of red and black currants have also been available, but appear not to have been the determining factor in the estimates. The highest residues in trials approximating GAP were 0.07 mg/kg of triademefon and 0.16 mg/kg of triadimenol. The triadimefon residue is usually about half or less of the triadimenol residue at GAP PHIs. Reasonable estimates of maximum residue levels would be 0.2 mg/kg for triadimefon and 0.5 mg/kg for triadimenol, giving a total for the two compounds approaching 1 mg/kg.

Eggs. The current 0.1 mg/kg limit of determination CXL for the sum of triadimefon and triadimenol was based on separate analyses with residues of triadimefon below 0.1 mg/kg and undetectable residues of triadimenol from the feeding of triadimefon. Subsequently reviewed studies showed maximum "total" residues of 0.07 and 0.22 mg/kg at 25 and 75 ppm feeding levels respectively. On the basis of analytical methods used in animal studies reviewed by the 1981 JMPR, it is reasonable to conclude that triadimefon and triadimenol may be determined at 0.05 mg/kg levels. Given that the feeding levels were exaggerated, a reasonable estimate of maximum residues in eggs would be 0.05 mg/kg (limit of determination) for each compound.

Egg plant. Supervised trials data from one country were available for the first time and reflected GAP rates (but not a GAP PHI). The data were insufficient to estimate a limit.

Fodder beet. The current 0.1 mg/kg limit of determination CXL for the sum of triadimefon and triadimenol in fodder beet was based on undefined "undetectable" residues of both compounds. A reasonable estimate would be at a 0.05 mg/kg limit of determination level for both compounds.

Fodder beet leaves or tops. The current 0.1 mg/kg limit of determination CXL for the sum of triadimefon and triadimenol on fodder beet leaves or tops was estimated in 1983 on the basis of separate analyses for the two compounds. The maximum residues reflecting current GAP are 0.04 mg/kg of triadimefon and 0.16 mg/kg of triadimenol (German data, UK GAP). Reasonable maximum levels would be 0.05 mg/kg (limit of determination) for triadimefon and 0.2 mg/kg for triadimenol.

Fruiting vegetables, cucurbits. The current 0.2 mg/kg CXL for the sum of triadimefon and triadimenol in cucurbits replaced separate limits for individual members of the group. The data base includes both total residues and separate analyses for the two compounds in various members of the group, depending on the study and year. The highest total residue from trials approximating current GAP was 0.2 mg/kg. The highest individual residues were 0.13 mg/kg of triadimefon and 0.05 mg/kg of triadimenol. Reasonable estimates of maximum expected residues from triadimefon uses would be triadimefon 0.1 mg/kg and triadimenol 0.05* mg/kg, but uses of triadimenol could lead to residues approaching 2 mg/kg (see also "Cucumber" in triadimenol report).

Grapes. The current 2 mg/kg MRL (step 7B) for the sum of triadimefon and triadimenol in grapes is based on analyses for the sum of the two compounds and on separate analyses. The estimate has been confirmed by six Joint Meetings. The maximum total residue from trials approximating GAP was 0.95 mg/kg in a country with a 35-day PHI. The same trials showed residues of 1.3-1.7 mg/kg, however, at the 14-day PHI common in other countries, some with higher GAP application rates. Maximum residues from separate analyses were 0.15 mg/kg of triadimefon at the 35- day PHI and 0.55 mg/kg after 14 days and for triadimenol 1.2 to a reported 2.9 mg/kg. Reasonable estimates would be 0.5 mg/kg for triadimefon and 2 mg/kg for triadimenol.

Hops, dry. The current 15 mg/kg CXL for the sum of triadimefon and triadimenol in hops is based both on separate analyses for the two compounds and on data on total residues. The maximum total residue from trials approximating GAP was 12.9 mg/kg, and the highest separate residues were 8.1 mg/kg of triadimefon and 4.1 mg/kg of triadimenol. Reasonable maximum estimates would be 10 mg/kg for triadimefon and 5 mg/kg for triadimenol.

Mango. The CXL of 0.1 mg/kg at the limit of determination for the sum of triadimefon and triadimenol is based on separate analyses, with maximum residues of <0.02 mg/kg triadimefon and 0.05 mg/kg of triadimenol from trials approximating GAP. Reasonable estimates of maximum residues would be 0.05 mg/kg at the limit of determination for both compounds.

Meats. The 0.1 mg/kg limit of determination CXL for the sum of triadimefon and triadimenol in meat was estimated by the 1981 JMPR, although relevant studies were also available in 1979 and 1983. Data were available on total residues and on separate analyses. Feeding trials were with triadimefon and triadimenol separately or combined in equal proportions. Total residues from exaggerated feeding

levels give confidence that residues are likely to be <0.05 mg/kg in meat. The difficulty in estimating limits has lain largely in uncertainty of the limits of determination of triadimefon and triadimenol separately in meat tissues, with limits for combined residues in cattle tissues reported as 0.05 to 0.1 mg/kg. Despite these uncertainties, the Meeting concluded that the validation of the analytical method for triadimenol (q.v.) justified a level of 0.05 mg/kg at the limit of determination for both compounds.

Milks. The 0.1 mg/kg CXL at the limit of determination for the sum of triadimefon and triadimenol in milk was estimated by the 1979 JMPR on the basis of feeding studies at exaggerated rates. The limit of determination appears to have been 0.1 mg/kg for both compounds. Later data on total residues indicate that residues are likely to be substantially lower than 0.1 mg/kg. As in the case of meat, the Meeting concluded that 0.05 mg/kg (limit of determination) maximum residue levels would be appropriate for both compounds. See also triadimenol.

Onion, Welsh. The current 0.1 mg/kg limit of determination CXL for the sum of triadimefon and triadimenol in Welsh onions was based on maximum residues of <0.01 mg/kg triadimefon and <0.02 mg/kg triadimenol. A limit of determination level of 0.05 mg/kg would be reasonable for both compounds.

Peaches. No MRL is currently proposed for triadimefon on peaches. Limited data show maximum residues of 0.02 mg/kg triadimefon and 0.05 mg/kg for triadimenol, although methods were validated only down to 0.04 mg/kg. The Meeting concluded that data reflecting GAP were insufficient to estimate maximum residue levels.

Peas. The current limit of determination CXL for the sum of triadimefon and triadimenol on peas is 0.1 mg/kg. Data have included maximum total residues of <0.1 mg/kg in "peas without pods", ≤0.1 mg/kg of triadimefon in "peas" and 0.05 mg/kg in "pods". Summary data provided to the Meeting reported <0.01 mg/kg triadimefon and 0.06 mg/kg triadimenol in "peas in pod" from applications according to GAP. The reported limits of determination for the method used were 0.01 and 0.05 mg/kg for triadimefon and triadimenol respectively, but details were not provided. Although reluctant to use the summary data, the Meeting concluded that when combined with other data, reasonable estimates for peas would be 0.05 mg/kg at the limit of determination for triadimefon and 0.1 mg/kg for triadimenol, the latter not at the limit of determination.

Peppers, Sweet. The current 0.5 mg/kg CXL for triadimefon plus triadimenol was estimated by the 1979 JMPR from Italian data, and confirmed by the 1988 Meeting. No data were provided separately for triadimefon and triadimenol to permit an estimate of separate limits resulting from triadimefon uses. The 1979 data (showing a maximum residue of 0.25 mg/kg at the current GAP PHI, but at an exaggerated application rate) and additional data on triadimefon *per se* (maximum residue 0.03 mg/kg from trials according to current GAP) suggest that 0.2 mg/kg for triadimefon plus triadimenol would probably be more than adequate for the current GAP of the two countries for which there were data.

The only obvious way to estimate separate limits on the basis of current information is to assume that residues of triadimefon and triadimenol may occur at approximately the same levels (as observed by the 1979 JMPR for fruits and vegetables). With this assumption and a recognition that a 0.2 mg/kg total residue limit is probably liberal, it might be reasonable to estimate 0.1 mg/kg each for triadimefon and triadimenol from the use of triadimefon on sweet peppers. Separate data on triadimefon and triadimenol residues from trials with triadimefon in accordance with current GAP are desirable.

Pineapple. The CXL of 3 mg/kg for triadimefon plus triadimenol in pineapples is based on total residues up to 2.2 mg/kg. Additional data showing maximum residues of triadimefon and triadimenol of 0.25 and 0.33 mg/kg have been reported. With emphasis on the total residue data but taking into account the results of separate analyses, and observing that residues of triadimenol tend to be equal to or less than those of triadimefon from dip uses, the Meeting concluded that 1 mg/kg each for triadimefon and triadimenol would be reasonable estimates of maximum residues. Additional data reflecting GAP with separate analyses would be desirable.

Pome fruits. The current 0.5 mg/kg CXL for triadimefon plus triadimenol in pome fruit appears to be based on both total residue data and separate analyses. Maximum total residues from trials approximating GAP were 0.7 mg/kg at PHIs of 0-1 day. Maximum individual residues were 0.35 mg/kg of triadimefon and 0.07 mg/kg of triadimenol. Overall data suggest a tendency for triadimenol residues to be a little higher than those of triadimefon. A reasonable estimate of maximum residues on pome fruit would be 0.3 mg/kg each for triadimefon and triadimenol.

Poultry meat. The CXL for the sum of triadimefon and triadimenol in poultry meat is 0.1 mg/kg at the limit of determination. As in the case of meat, the data indicate that total residues are likely to be <0.05 mg/kg, and the Meeting concluded that a 0.05 mg/kg limit of determination estimate for both compounds would be appropriate. See also triadimenol.

Raspberries. The current 2 mg/kg MRL (step 7B) for the sum of triadimefon and triadimenol in raspberries is based on maximum residues of 1.1 mg/kg triadimefon and 0.5 mg/kg triadimenol. A reasonable estimate of maximum residues for the separate compounds would be 1 mg/kg for triadimefon and 0.5 mg/kg for triadimenol.

Spring onion. The CXL of 0.1 mg/kg (limit of determination) for the sum of triadimefon and triadimenol in spring onions was based on maximum residues of <0.02 mg/kg triadimefon and <0.04 mg/kg triadimenol. A reasonable estimate of maximum residues would be 0.05 mg/kg at the limit of determination for both compounds.

Strawberry. The 0.2 mg/kg CXL for the sum of triadimefon and triadimenol on strawberries is based on maximum residues of 0.12 mg/kg for each compound. A reasonable maximum residue estimate for the two compounds is 0.1 mg/kg.

Sugar beet. The CXL of 0.1 mg/kg (limit of determination) for the sum of triadimefon and triadimenol in sugar beet was based on residues of each referred to as "n.d." (undefined). Analytical methods described at the time reported limits of determination of 0.03 mg/kg for triadimefon and 0.06 mg/kg for triadimenol in plants in general, except cereals and their straws. Subsequently submitted data reported maximum residues of 0.07 mg/kg for triadimefon and (except for one value of 0.15 mg/kg), for triadimenol. Reasonable estimates of maximum residues for each compound would be 0.1 mg/kg, near the limit of determination, but actual residues.

Sugar beet leaves or tops. The data bases for the current 2 mg/kg CXL for the sum of triadimefon and triadimenol in sugar beet leaves or tops includes maximum residues of 1.4 mg/kg each for triadimefon and triadimenol (not on the same sample). A reasonable estimate ofmaximum residues would be 2 mg/kg for triadimefon and 1 mg/kg for triadimenol.

Sugar cane. No maximum level has been estimated for sugar cane. Summary data provided previously and to the present Meeting suggest that residues from current GAP (seed piece treatments or soil applications) are unlikely to exceed 0.05 mg/kg triadimefon or 0.1 mg/kg triadimenol. Because data were relatively limited for each use, and reported only as summaries without trial and analytical details, the Meeting could not estimate maximum residue levels.

Tea. No limit has been proposed for manufactured tea. Data from one country submitted to the Meeting indicate that residues of triadimefon and triadimenol are unlikely to exceed 2 and 20 mg/kg respectively from GAP. Because the summary analytical reports were available from only one country and did not include important details of sample handling, storage conditions, or other important trial or analytical details, or information such as the interval from sampling to analysis, the Meeting could not estimate a maximum residue level.

Tomato. The data base for the current 0.5 mg/kg CXL for tomatoes includes both total residue data and separate analyses for triadimefon and triadimenol. Maximum residues from trials approximating current GAP were 0.25 mg/kg total, 0.2 mg/kg triadimefon and 0.5 mg/kg triadimenol at a 7 day PHI which is GAP in some countries (the original estimate was based on a 3 day PHI). Maximum

residues at 5 days were 0.3 and 0.6 mg/kg for triadimefon and triadimenol respectively. A good match between data and current GAP could not be made but overall reasonable estimates of maximum residues would be 0.2 mg/kg triadimefon and 0.5 mg/kg triadimenol, based on a 7 day PHI.

The Meeting was informed that the multi-residue analytical method DFG S 19, validated for triadimenol in animal products, is also suitable for determining triadimefon. The Meeting considered it desirable that the method should also be validated for triadimefon in cattle and poultry meat and offal and in milk and eggs.

FURTHER WORK OR INFORMATION

Desirable

1. Separate analyses for residues of triadimefon and triadimenol in sweet peppers resulting from the use of triadimefon in accordance with GAP.

2. Additional data (separate analyses) for triadimefon and triadimenol residues in pineapple reflecting current GAP.

3. Validation of the analytical method DFG S 19 (Specht, W. and Thier, T.H., 1987. Multi-residue method S19: Manual of Pesticide Residue Analysis: DFG/Deutsche Forschungsgemeinschaft Weinheim, N.Y., Vol.1, 1987, 3830400) for cattle and poultry meats and offal, and milk and eggs.

4.43 TRIADIMENOL (168)

RESIDUE AND ANALYTICAL ASPECTS

Triadimenol was reviewed by the 1989 JMPR at which an ADI was allocated and maximum residue levels based on the uses of triadimenol as a pesticide were estimated for several commodities. The further work or information required included validation of the method of analysis DFG S 19 for products of animal origin to permit conversion of the TMRLs for these commodities to MRLs.

Triadimenol residues may also result from the use of triadimefon, of which triadimenol is a metabolite. Current limits for triadimefon are expressed as the sum of triadimefon and triadimenol and limits for triadimenol as triadimenol *per se*. This has resulted in the estimation of separate maximum residue levels in some commodities, one for triadimefon plus triadimenol and another for triadimenol alone, depending on which pesticide was used in the trials concerned. The Meeting also evaluated triadimefon and estimated separate maximum levels for triadimefon and triadimenol residues that might occur from current uses of triadimefon.

As recommended by the 1989 JMPR, the Meeting re-examined the old monograph data summaries and additional data on triadimefon and triadimenol in the context of current GAP with a view to recommending separate limits where possible and considering the question of triadimenol on grapes discussed at the 1992 CCPR. Several new data submissions could not be used for estimating maximum residue levels because only summaries were provided. The Meeting was informed that the detailed studies could be provided for review in the future.

Trials on the following commodities were evaluated.

Artichokes. Although data reflecting current GAP were relatively limited, a need for a 1 mg/kg

limit is indicated (maximum residues 0.55 mg/kg). If proposed EC uses at higher rates become GAP, the substantially more extensive data from trials at those rates show that 2 mg/kg might be required.

Bananas. Data from trials with triadimenol were reviewed for the first time, as were those from trials with triadimefon. Most of the available information on GAP was not for the 7 countries from which substantial trials data were provided. Triadimenol residues on whole bananas would not be expected to exceed 0.2 mg/kg from triadimenol applications (calculated maximum residues of approximately 0.14 mg/kg). Residues of the butane-2,4-diol metabolite (KWG 1342) may equal or exceed those of triadimenol.

Cereals

Barley. All residues from GAP applications of triadimenol in new trials were <0.05 mg/kg and would not require a change in the 0.1 mg/kg estimate of the 1989 JMPR, which was based on residues of 0.1 mg/kg, except in one sample containing 0.14 mg/kg. However, data from trials with triadimefon indicate that residues of triadimenol may exceed 0.1 mg/kg from triadimefon applications in some countries. The Meeting concluded that the 0.1 mg/kg estimate should be increased to accommodate triadimefon uses.

Oats, rye and wheat. No maximum residue level was estimated for triadimenol in oats by the 1989 JMPR, although a level of 0.1 mg/kg was estimated for barley, rye and wheat. Additional data provided to the Meeting for the seed treatment of oats, rye and wheat would not require a limit higher than this, but data from triadimefon trials on oats, rye and wheat indicate that a triadimenol limit above 0.1 mg/kg would be needed to accommodate triadimefon uses in some countries.

Maize and Sorghum. The Meeting received several summary reports of seed treatment uses on maize and sorghum, but preferred not to propose MRLs on the basis of such information. The reported levels of <0.01 mg/kg in maize and its green and dry plant parts and in sorghum grain and plant parts, except in one sample of green forage of 0.02 mg/kg, indicate that there may be no compelling need for a limit.

Cereal straws and fodders, dry. The 1989 JMPR estimated maximum residue levels of 5 mg/kg for the dry straws and fodders of barley, rye and wheat to accommodate triadimenol uses showing residues up to 2.2 mg/kg on straw. No maximum level was estimated for oats. Additional data from seed treatments showed no residues in straws although residues up to 1.7 mg/kg were reported in green forage. These results do not require a revision of the 1989 JMPR estimates. Triadimenol residues in the straw of barley, oats, rye and wheat arising from triadimefon uses also show the need for the 5 mg/kg limit in these feeds to accommodate triadimefon applications.

Coffee. The 1989 JMPR estimated a 0.1 mg/kg (limit of determination) level for coffee beans from the use of triadimenol according to GAP. Additional data provided to the Meeting do not require a change in that estimate, and the Meeting concluded that it would also accommodate triadimefon uses. No revision is required.

Cucumber. The 1989 JMPR estimated a 0.1 mg/kg triadimenol level to accommodate German GAP for triadimenol. Data reflecting Israeli GAP were provided to the Meeting. While the national PHIs are the same, Israeli GAP allows only 2 applications compared with 8-10 in Germany, but Israeli application rates are 3-4 times the German rates. This not unexpectedly caused the Meeting to increase the estimated maximum residue in cucumbers to accommodate the new data which showed residues exceeding 1.0 mg/kg from applications approximately GAP.

A 0.2 mg/kg CXL is currently established for the sum of triadimefon and triadimenol in cucurbit vegetables to accommodate triadimefon uses. Although no triadimenol limits have been recommended for curcurbits other than cucumbers, there is a need for a limit to cover triadimefon uses since a separate limit for triadimefon on cucurbits has been requested. The new level for cucumbers would more than meet that need. In order to avoid separate limits for triadimenol in cucumbers and in other cucurbits, the

Meeting concluded that the triadimenol MRL recommended for cucumbers should apply to the group.

In addition to the data on cucumbers summarized in this monograph, data on melons from 5 French and 2 Australian supervised trials were also provided during the Meeting. However, only two of the French trials were reflective of maximum GAP (residues <0.05 mg/kg) and no information was available on Australian GAP. The Meeting considered that additional supervised trials data on triademenol reflecting GAP for cucurbits other than cucumbers were desirable to confirm the proposed level.

Grapes. A maximum residue level of 2 mg/kg was estimated for triadimenol by the 1989 JMPR to accommodate triadimenol uses. The CCPR discussed whether the limit should be 1 or 2 mg/kg. The Meeting re-examined the 1989 data base and additional data. The original estimate was based on maximum residues of 1.9 mg/kg resulting from application rates of 1.4 times the maximum GAP rates. Additional data report maximum residues of 1.4 mg/kg from applications at 1.3 times GAP rates. While the overall data indicate that 1 mg/kg would usually be adequate, there is reason to expect that this level may be exceeded on occasion from triadimenol uses. Furthermore, the Meeting estimated that residues of the order of 2 mg/kg may result from applications of triadimefon. The Meeting confirmed the 1989 estimate.

Cattle meat, poultry meat, eggs and cattle milk. The 1989 Meeting recommended 0.05 mg/kg (limit of determination) TMRLs for cattle meat, poultry meat and eggs and 0.01 mg/kg for cattle milk, pending validation of a proposed enforcement method. It was validated with acceptable recoveries at 0.01 mg/kg in each of these matrices, although the data were insufficient for the Meeting to confirm 0.01 mg/kg as a reasonable routine limit of determination. However, the Meeting was reasonably confident that residues could be confirmed at 0.05 mg/kg for all these commodities and recommended full MRLs. However, because a triadimenol limit is needed to accommodate triadimefon uses, for which a 0.1 mg/kg CXL is established on "meat" and "milk" for the sum of triadimefon and triadimenol, the Meeting recommended that the levels for cattle meat and cattle milk be applied to "meat" and "milks", to accommodate uses of triadimefon and triadimenol.

Onions. No triadimenol MRL has previously been recommended for onions. Data provided from one country reflecting "envisaged" uses indicate that an MRL of 1 mg/kg may be required. However, because the use is only proposed at present and data are available for only one country, the Meeting concluded that a limit should not be recommended. When the GAP is confirmed and additional data are available further consideration should be given to a recommendation.

A 0.1 mg/kg CXL for the sum of triadimefon and triadimenol is established for Welsh onions to accommodate the use of triadimefon. The Meeting recommended that a separate triadimenol limit should be recommended to accommodate that use. It would not be adequate to accommodate the proposed triadimenol use.

Pome fruit. The 1989 JMPR estimated a 0.2 mg/kg maximum residue level for apples to accommodate triadimenol uses, but no limit was recommended for pome fruit although there is a 0.5 mg/kg CXL for the sum of triadimefon and triadimenol in pome fruit. New triadimenol supervised trials data did not require a change in the 0.2 mg/kg estimate for apples, but triadimenol residues resulting from the use of triadimefon may approach 0.3 mg/kg. The Meeting concluded that a higher limit would be required to accommodate both triadimefon and triadimefon uses and for conssistency proposed that it should apply to pome fruit so that the triadimefon uses would be accommodated. Accordingly, the Meeting recommended that the separate triadimenol proposal for apples be withdrawn.

The Meeting considered it desirable that supervised trials data be provided from the use of triadimenol on other pome fruit if such uses become GAP.

Sugar beet leaves and tops. No triadimenol limit has previously been proposed for triadimenol in sugar beets. Data derived from "envisaged" GAP (to be considered by the European Community) indicate that residues would not be likely to exceed 0.05 mg/kg in roots from the proposed use and

would not exceed 0.5 mg/kg in leaves after 14 days (the proposed UK PHI) or 0.1 mg/kg after 28 days (the proposed German PHI).

The Meeting was reluctant to recommend triadimenol limits on the basis of proposed GAP and data from only one country, but estimated that maximum triadimenol levels of 0.1 mg/kg (near limit of determination, but unambiguous residues) in beet roots and 1 mg/kg in the tops could be expected from triadimefon uses. It recommended limits accordingly.

The Meeting reviewed a triadimefon apple processing study in which residues of both triadimefon and triadimenol were determined. It revealed that residues of triadimenol concentrate only in wet and dry pomace, with a concentration factor of about 6.

Validation data for analytical method DFG S19 (Specht and Thier, 1987) were provided as required by the 1989 JMPR in order to confirm the temporary MRLs recommended for animal products. The method had been considered suitable for enforcement. The Meeting noted that the method had been validated in various animal matrices at 0.01 mg/kg with reasonable recoveries, but information was insufficient to confirm this level as a routine limit of determination. However, the Meeting was confident that 0.05 mg/kg would be reasonable.

FURTHER WORK OR INFORMATION

Desirable

Results of supervised trials with triadimenol applied according to GAP on cucurbits other than cucumbers.

4.44 TRIAZOPHOS (143)

RESIDUE AND ANALYTICAL ASPECTS

Triazophos was evaluated by the JMPR in 1982, 1983, 1984, 1986 and 1990. At the request of the 1991 and 1992 Sessions of the CCPR the proposed TMRLs for Banana, Brussels sprouts, Cabbages, Head, Carrot, Citrus fruits, Common bean and Cauliflower were referred to the JMPR for reconsideration. The proposed MRLs (at the limit of determination) for cereal grains, Onion, Bulb, Potato and Sugar beets were at Step 7B, awaiting review by the Joint Meeting.

Written comments were received from France, Germany and The Netherlands on bananas, Brussels sprouts, head cabbages and citrus. The manufacturer submitted limited new residue data on carrots. There was insufficient time to complete the review of the data.

4.45 VAMIDOTHION (078)

RESIDUE AND ANALYTICAL ASPECTS

At the 22nd and 23rd Sessions of the CCPR (1991 and 1992) the opinion was expressed that residue levels in pome fruit should be re-evaluated by the JMPR, and it was stated that more data would be made available.

The Meeting received information on registered uses of vamidothion on pome fruit and other crops in a number of countries, and reports were submitted from supervised trials on apples in France, Italy and South Africa. Residues in apples from applications according to registered use rates and PHIs in France and Italy were approximately 0.1 mg/kg, while residues in apples from South Africa from registered GAP were from 0.10 to 0.83 mg/kg, supporting the existing MRL of 1 mg/kg.

4.46 VINCLOZOLIN (159)

RESIDUE AND ANALYTICAL ASPECTS

At several Sessions of the CCPR, most recently at the 23nd Session in 1992, the opinion was expressed that a review of the proposed limits for apricots and lettuce was needed.

New residue data were received from trials in the USA on stone fruit including apricots and leafy vegetables including lettuce.

The 1990 JMPR reviewed residue data on apricots received by earlier Meetings and confirmed the proposed maximum residue limit for apricot of 5 mg/kg. No data from the trials reported to the present Meeting were from samples taken 3 days after treatment, which is the registered pre-harvest interval in the USA, but all residues in the trials were considerably lower than 5 mg/kg, includingg those in samples taken 6-7 days after treatment. For this reason the Meeting felt no need to propose an increase of the limit previously recommended. Residues in nectarines and fresh prunes were with a few exceptions at about the same level as those in apricots resulting from the same application rate, but the number of trials was too limited to propose residue limits for those crops.

It has been suggested at the CCPR that residue data from trials on lettuce already provided to earlier Meetings would support a residue limit higher than the proposed 5 mg/kg. The Meeting reviewed the data submitted to earlier Meetings, and observed that residue levels higher than 5 mg/kg were reported only in trials where the required experimental conditons were not met. All residues in the trials submitted to the present Meeting were well below 5 mg/kg, including those at a 10-12 days pre harvest interval. Residues in endive and chicory leaves were similar to those in lettuce, but the number of trials was too limited to propose residue limits for endive and chicory.

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 2.3) that for compounds in the Periodic Review Programme, in addition to copies of the full studies, a detailed index of the available critical supporting studies (metabolism, animal transfer, processing, analytical methods, and storage stability of analytical samples) be prepared by the manufacturer and be included in the submission.

5.3 The Meeting recommends for periodic review compounds (Section 2.4): (1) that the JMPR recommend withdrawal of relevant MRLs if there is no information on GAP or no residue data from trials conducted in accordance with GAP, (2) that the FAO Joint Secretary indicate which are the periodic review compounds in the list of reviewer-assigned compounds given to JMPR members.

5.4 The Meeting recommends (Section 2.10) that information on national approaches to requiring animal transfer studies be considered in the development of the FAO Guide.

5.5 The Meeting reiterates the 1990 JMPR recommendation (Section 3.2) that future FAO Guidelines provide guidance on conducting analytical sample storage stability studies.

5.6 The Meeting recommends (Section 4.3) that available aldrin/dieldrim and endrin monitoring data be evaluated in 1998 with a view to further revision of aldrin, dieldrim and endrin ERLs.

5.7 The Meeting recommends (Section 4.35) that piperonyl butoxide should be reviewed again in 1995 following submission of various toxicology studies to WHO.

6. FUTURE WORK

The following items should be considered at the 1993 or 1994 Meeting. Compounds recommended for priority attention by the 24th 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 1993 Meeting (tentative)

Toxicological Evaluation

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

Residue Evaluation

Aldicarb
Amitrole
Azinphos-methyl
Benalaxyl
Bendiocarb
Benomyl
Bromopropylate
Captan
Carbendazim
Carbofuran
Carbosulfan
Chlorothalonil
*Chlorpropham
Chlorpyrifos-methyl
Cycloxydim
Cyfluthrin
DDT
Diazinon
Dichlorvos
Dimethoate
Endosulfan
Ethephon
Ethion
Ethylenethiourea (ETU)
*Etofenprox
Fenbutatin oxide
*Fenpropathrin
Ferbam
Flucythrinate
Flusilazole
Folpet
Formothion
Heptachlor
Hexaconazole
Iprodione
Mancozeb
Maneb

6.1 1993 Meeting (tentative) (contd.)

Residue Evaluation

*Metiram
Omethoate
Parathion-methyl
Phosalone
Procymidone
Profenofos
Propham
Propineb
Propiconazole
Propylenethiourea (PTU)
Pyrazophos
Quintozene
Thiophanate-methyl
Thiram
Triazophos
Zineb
Ziram

6.2 1994 Meeting (tentative)

Toxicological Evaluation

Azocyclotin
Carbofuran
Chlorfenvinphos
Chlormequat
*Clethodim
Cyhexatin
2,4-D
Dicloran
Ethoxyquin
*Fenpropimorph
Parathion
Parathion-methyl
Phorate
Phosmet
Pyrethrins
*Tebuconazole
Tecnazene
*Teflubenzuron
*Tolclofos-methyl
Triforine

Residue Evaluation

Acephate
Chlorfenvinphos
*Clethodim
Dicloran
Ethoxyquin
*Fenpropimorph
Methamidophos
Phosmet
Pyrethrins
*Tebuconazole
Tecnazene
*Teflubenzuron
*Tolclofos-methyl
Triforine

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CORRIGENDA TO REPORT OF 1991 MEETING

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

REPORT

Section	Page	Para	Line	
4.2	22	2	6	**Delete VS 0624 Celery** (the Meeting recommended withdrawal of the MRL)
4.10	44	1	4	Change 'temporary estimates' to **'the temporary estimate'**

ANNEX I

Page 106, AZINPHOS-METHYL: Change Alfalfa hay to **Alfalfa fodder**

Change Clover hay to **Clover hay or fodder**

Page 108, BENTAZONE: Change VD 0561 to VD 05**23**

Page 112, DISULFOTON: Change GC 0081 Cereal grain to GC 008**0** Cereal grain**s**

Add **and fodder, dry** after AS 0640 Barley straw

Page 113, DISULFOTON: Add **(green)** after Forage crops

Add **and fodder, dry** after AS 0647 Oat straw and after AS 0654 Wheat straw

Page 114, GLUFOSINATE-AMMONIUM: Correct the ADI to **0.02** mg/kg bw

Correct the recommended MRL for VD 0541 Soya beans to **2** mg/kg

Correct the recommended MRL for SO 0702 Sunfolwer seed to **2** mg/kg

Page 114, HEPTACHLOR: Change VR 0527 to VR 05**7**7

ANNEX II

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

ANNEX III

Page 130: Delete azocyclotin from the list of compounds for which the TMDI did not exceed the ADI or TADI.

ANNEX I

ACCEPTABLE DAILY INTAKES AND RESIDUE LIMITS PROPOSED AT THE 1992 Meeting

These figures are additional to, or amend, those recorded in Annexes of the reports of earlier Meetings[1]. 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 may be temporary. 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 the meat.
Po (following (T)MRLs)	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 animal origin)	The (T)MRL accommodates veterinary uses.
W (in place of an MRL)	The previous recommendation is withdrawn.

[1]In the case of compounds evaluated in the CCPR periodic review programme all limits, including previous recommendations which are unchanged, are recorded.

If a recommended MRL is an amendment the previous value is also recorded. 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 (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
ABAMECTIN (177)	0.0001	FC 0001 Citrus fruits	0.01*	-
		FP 0230 Pear	0.01*	-
		VC 0424 Cucumber	0.05	-
		VO 0445 Peppers, Sweet	0.02	-
		VO 0448 Tomato	0.02	-
		SO 0691 Cotton seed	0.01*	-
		MO 0812 Cattle, Edible offal of	0.05	-
		MM 0812 Cattle meat	0.01*	-
		ML 0812 Cattle milk	0.005	-
		MO 0814 Goat, Edible offal of	0.1	-
		MM 0814 Goat meat	0.01*	-
		ML 0814 Goat milk	0.005	-
		Residue: Sum of avermectin B_{1a}, avermectin B_{1b} and Δ-8,9 isomer of avermectin B_{1a}		
ALDICARB (117)	0.003	Notes: ADI lowered from 0.005 mg/kg bw		
ALDRIN / DIELDRIN (001)	0.0001	FC 0001 Citrus fruits	0.05 E	Fruits 0.05 ET
		FP 0009 Pome fruits	0.05 E	Fruits 0.05 ET
		Fruits	W	0.05 ET
		VS 0621 Asparagus	W	0.1 ET
		VB 0400 Broccoli	W	0.1 ET
		VB 0402 Brussels sprouts	W	0.1 ET
		VA 0035 Bulb vegetables	0.05 E	Onion, Bulb 0.1 ET
		VB 0041 Cabbages, Head	W	0.1 ET
		VB 0404 Cauliflower	W	0.1 ET
		VO 0440 Egg plant	W	0.1 ET
		VC 0045 Fruiting vegetables, Cucurbits	0.1 E	Cucumber 0.1 ET
		VL 0053 Leafy vegetables	0.05 E	Lettuce, Head 0.1 E; Radish leaves 0.1 ET
		VP 0060 Legume vegetables	0.05 E	-
		VO 0051 Peppers	W	0.1 ET
		VO 0445 Peppers, Sweet	W	0.1 ET
		VD 0070 Pulses	0.05 E	-
		VR 0075 Root and tuber vegetables	0.1 E	Carrot 0.1 E; Horseradish, Parsnip, Potato,

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
		GC 0080 Cereal grains	0.02 E	Radish 0.1 ET
		PM 0112 Poultry meat	0.2 (fat) E	0.02 E, except Rice 0.02 ET
				-
		Residue: sum of HHDN and HEOD (fat-soluble)		
ANILAZINE (163)	0.1	MO 0812 Cattle, Edible offal of	0.02*	-
			0.02*	-
		MM 0812 Cattle meat	0.02*	-
		MO 0814 Goat, Edible offal of	0.02*	-
			0.01*	-
		MM 0814 Goat meat		
		ML 0106 Milks	0.02*	-
			0.02*	-
		PE 0112 Eggs	0.02*	-
		PO 0111 Poultry, Edible offal of		
			10	10 T
		PM 0110 Poultry meat	10	30 T
		AS 0640 Barley straw and fodder, dry		
		AS 0654 Wheat straw and fodder, dry		
		Residue: anilazine		
BIFENTHRIN (178)	0.02	FC 0203 Grapefruit	0.05* [1]	-
		FC 0204 Lemon	0.05* [2]	-
		FC 0208 Orange, Sweet	0.05* [2]	-
		FP 0230 Pear	0.5	-
		FB 0275 Strawberry	1 [3]	-
		VR 0589 Potato	0.05* [1]	-
		GC 0640 Barley	0.05* [1]	-
		GC 0645 Maize	0.05* [1]	-
		GC 0654 Wheat	0.05*	-
		MF 0812 Cattle fat	0.5 [4]	-
		MO 1280 Cattle, kidney	0.05*	-
		MO 1281 Cattle, liver	0.05*	-
		MM 0812 Cattle meat	0.5 (fat)	-
		ML 0812 Cattle milk	0.05* F	-

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		PO 0840	Chicken, edible offal of	0.05*	-
		PE 0840	Chicken eggs	0.01*	-
		PF 0840	Chicken fat	0.05*	-
		PM 0840	Chicken meat	0.05* (fat)	-
		AS 0640	Barley straw and fodder, dry	0.5	-
		AS 0645	Maize fodder	0.2[5]	-
		AF 0645	Maize forage	0.05* [6]	-
		AF 0654	Wheat forage (whole plant)	0.2	-
		AS 0654	Wheat straw and fodder, dry	0.5	-
		DH 1100	Hops	10	-
		Residue: bifenthrin (fat-soluble) Notes: [1] Residues are not expected to exceed 0.01 mg/kg [2] Residues may occur near this level [3] 3 mg/kg would be required if proposed uses become GAP [4] A higher MRL may be required if proposed uses on maize become GAP [5] 5 mg/kg would be required if proposed uses become GAP [6] 2 mg/kg would be required if proposed uses become GAP			
BROMIDE ION (047)	1	VP 0522	Broad bean (green pods and immature seeds)	500	-
		VB 0400	Broccoli	30	-
		VC 0424	Cucumber	100	50
		VP 0528	Garden pea (young pods)	500	-
		VO 0442	Okra	200	-
		VO 0445	Peppers, Sweet	20	-
		VR 0494	Radish	200	-
		VC 0431	Squash, Summer	200	-
		VR 0506	Turnip, Garden	200	-
		VL 0506	Turnip greens	1000	-
		Residue: bromide ion from all sources, but not including covalently bound bromine			
CHLOROTHALONIL (081)	0.03	Notes: ADI confirmed			
CHLORPYRIFOS-METHYL (090)	0.01	Notes: ADI increased from 0.001 mg/kg bw			
CLOFENTEZINE (156)	0.02	FB 0269	Grapes	1	0.2

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
		Residue: plant products: clofentezine animal products: sum of all compounds containing the 2-chlorobenzoyl moiety, expressed as clofentezine Notes: the residue in plant products was previously also defined as the sum of all compounds containing the 2-chlorobenzoyl moiety, expressed as clofentezine		
CYCLOXYDIM (179)	0.07			
CYFLUTHRIN (157)	0.02	FP 0226 Apple FS 0014 Plums (including Prunes) VO 0445 Peppers, Sweet VO 0448 Tomato GC 0645 Maize SO 0691 Cotton seed SO 0495 Rape seed ML 0812 Cattle milk AF 0645 Maize forage Residue: cyfluthrin (fat-soluble)	0.5 W 0.2 0.5 0.05 0.05 0.05 0.01 F V W	0.2 0.2 T 0.2 T 0.05 T 0.05 T 0.05 T 0.05 T 0.01 F V T 0.5 T
DELTAMETHRIN (135)	0.01	FT 0312 Tree tomato CF 1211 Wheat flour Residue: deltamethrin (fat-soluble)	0.02 0.2 Po P	- 0.1 Po P
DEMETON-S-METHYL (073)	0.0003	Residue: sum of oxydemeton-methyl, demeton-S-methyl and demeton-S-methylsulphon, expressed as oxydemeton-methyl (see oxydemeton-methyl) Notes: note changed definition of residue. Oxydemeton-methyl is also known as demeton-S- methyl sulphoxide		
DEMETON-S-METHYLSULPHON (164)	0.0003	Residue: sum of oxydemeton-methyl, demeton-S-methyl and demeton-S-methylsulphon, expressed as oxydemeton-methyl (see oxydemeton-methyl) Notes: note changed definition of residue. Oxydemeton-methyl is also known as demeton-S- methyl sulphoxide		

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
DICOFOL (026)	0.002	FS 0013	Cherries	5	5[1]
		FC 0001	Citrus fruits	5	5[1]
			Fruits (Except as otherwise listed)	W	5
				5	5[1]
		FB 0269	Grapes	5	5[1]
		FS 0247	Peach	1	5[1]
		FS 0014	Plums (including Prunes)	5	5[1]
				W	1
		FP 0009	Pome fruits		
		FB 0275	Strawberry	0.1	5[1]
				2	5[1]
		VD 0071	Beans (dry)		
		VP 0526	Common bean (pods and/or immature seed)	0.5	2
				2	5[1]
		VC 0424	Cucumber	W	2
		VP 0528	Garden pea (young pods)	0.2	5[1]
		VC 0425	Gherkin	1	5[1]
		VC 0046	Melons, except Watermelon	1	5[1]
		VO 0051	Peppers	1	1
		VC 0431	Squash, Summer	W	5
		VO 0448	Tomato		
			Vegetables (Except as otherwise listed)	0.01*	--
				0.01*	--
		TN 0678	Walnuts	0.1	--
		TN 0672	Pecan		
		SO 0691	Cotton seed	0.05*	--
				0.5 (fat)	--
		MO 0812	Cattle, edible offal of	0.05 F	--
		MM 0812	Cattle meat		
		ML 0106	Milks	0.05	--
				0.05*	--
		PE 0112	Eggs	0.5 (fat)	--
		PO 0111	Poultry, edible offal of		
		PM 0110	Poultry meat	50	5
				3	5[1]
		DH 1100	Hops, dry		
		DF 0014	Prunes	0.5	--
				0.5	--
		OC 0691	Cotton seed oil, crude	50	5
		OR 0691	Cotton seed oil, edible		
		DT 1114	Tea, Green, Black		
		Residue: dicofol (sum of *o,p_* and *p,p_* isomers) (fat-soluble)			
		Notes: ADI lowered from 0.025 mg/kg bw [1]Group MRL for fruits or vegetables (except as otherwise listed)			
DINOCAP (087)	0.001	FP 0226	Apple	W	0.1* T
		FS 0240	Apricot	W	0.1* T

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
		FB 0264 Blackberries	W	0.1* T
		FB 0266 Dewberries	W	0.1* T
		FB 0269 Grapes	W	0.1* T
		FS 0247 Peach	W	0.1* T
		FP 0230 Pear	W	0.1* T
		FB 0272 Raspberries, Red, Black	W	0.1* T
		FB 0275 Strawberry	W	0.1* T
		VC 0424 Cucumber	W	0.1* T
		VC 0046 Melons, except Watermelon	W	0.1* T
		VC 0429 Pumpkins	W	0.1* T
		VC 0431 Squash, Summer	W	0.1* T
		VC 0433 Winter Squash	W	0.1* T
		Residue: dinocap and related nitro-octylphenols, expressed as dinocap		
DITHIANON (180)	0.01	FB 0269 Grapes	3	-
		FS 0013 Cherries	1	-
		FC 0206 Mandarin	3	-
		FP 0009 Pome fruits	5	-
		FC 0005 Pomelos	3	-
		DH 1100 Hops, dry	100	-
		Residue: dithianon		
ENDRIN (033)	0.0002	FP 0226 Apple	W	0.02* ET
		VC 0045 Fruiting vegetables, Cucurbits	0.05 E	-
		VO 0447 Sweet corn (corn-on-the-cob)	W	0.02* ET
		GC 0640 Barley	W	0.02* ET
		GC 0651 Sorghum	W	0.02* ET
		GC 0654 Wheat	W	0.02* ET
		SO 0691 Cotton seed	W	0.1 ET
		MM 0095 Meat	W	0.1 (fat) E
		ML 0106 Milks	W	0.0008 F E
		PE 0112 Eggs	W	0.2 ET
		PM 0110 Poultry meat	0.1 (fat) E	1 (fat) ET
		CM 0649 Rice, husked	W	0.02* ET
		CM 1205 Rice, polished	W	0.02* ET
		OC 0691 Cotton seed oil, crude	W	0.1 ET
		OR 0691 Cotton seed oil, edible	W	0.1 ET

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
		Residue: Sum of endrin and delta-keto-endrin (fat-soluble)		
FENBUTATIN OXIDE (109)	0.03	Notes: ADI confirmed		
IPRODIONE (111)	0.2	Notes: ADI lowered from 0.3 mg/kg bw		
ISOFENPHOS (131)	0.001	MM 0095 Meat PM 0110 Poultry meat	0.02* (fat) 0.02* (fat)	0.02* 0.02*
		Residue: Sum of isofenphos and its oxygen analogue (fat-soluble)		
METALAXYL (138)	0.03	VL 0482 Lettuce, Head VA 0385 Onion, Bulb VL 0502 Spinach	2 2 2	2 T 0.2 T 2 T
		Residue: metalaxyl		
METHACRIFOS (125)	0.006	MO 0812 Cattle, Edible offal of MM 0812 Cattle meat	0.01* 0.01* (fat)	- -
		Residue: methacrifos (fat-soluble)		
METHIDATHION (051)	0.001	FP 0226 Apple FS 0240 Apricot FS 0013 Cherries FB 0269 Grapes FC 0002 Lemons and Limes FC 0003 Mandarin FS 0245 Nectarine FT 0305 Olives FC 0004 Oranges, Sweet, Sour FS 0247 Peach FP 0230 Pear FI 0353 Pineapple FS 0014 Plums, including Prunes FC 0005 Shaddocks or Pomelos VS 0620 Artichoke, Globe VD 0071 Beans (dry) VB 0041 Cabbages, Head VB 0404 Cauliflower VP 0526 Common bean (pods and/or immature seeds	0.5 W 0.2 1 2 5 W 1 2 0.2 1 0.05 0.2 W 0.05* 0.1 0.1 W W	0.5 0.2 0.2 0.2 2 5 0.2 - 2 0.2 0.5 - 0.2 2 - - 0.2 0.2 0.1

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
		VC 0424 Cucumber	0.05	-
		VL 0053 Leafy vegetables	W	0.2
		VA 0385 Onion, Bulb	0.1	-
		VD 0072 Peas (dry)	0.1	0.1
		VR 0589 Potato	0.02	0.02
		VR 0494 Radish	0.05*	-
		VR 0596 Sugar beet	0.05*	-
		VO 0448 Tomato	0.1	0.1
		GC 0645 Maize	0.1	0.1
		GC 0651 Sorghum	0.2	0.1
METHIDATHION (contd.)		TN 0660 Almonds	0.05*	-
		SO 0691 Cotton seed	1	0.2
		TN 0669 Macadamia nuts	0.01*	-
		TN 0672 Pecan	0.05*	-
		SO 0495 Rape seed	0.1	-
		SO 0699 Safflower seed	0.1	-
		SO 0702 Sunflower seed	0.5	-
		TN 0678 Walnuts	0.05*	-
		MF 0812 Cattle fat	0.02*	0.02*
		MO 0097 Edible offal of cattle, pigs and sheep	0.02*	0.02*
			0.02*	-
		MO 0814 Goat, Edible offal of	0.02*	0.02*
		MF 0814 Goat fat	0.02*	-
		MM 0814 Goat meat		
		MM 0097 Meat of cattle, pigs and sheep	0.02*	0.02*
		ML 0106 Milks	0.001	0.0008 F
		MF 0818 Pig fat	0.02*	0.02*
		MF 0822 Sheep fat	0.02*	0.02*
		PE 0112 Eggs	0.02*	0.02*
		PO 0111 Poultry, Edible offal of	0.02*	0.02*
		PF 0111 Poultry fats	0.02*	0.02*
		PM 0110 Poultry meat	0.02*	0.02*
		AL 1021 Alfalfa forage (green)	10	-
		DH 1100 Hops, dry	5	3
		OC 0691 Cotton seed oil, crude	2	1
		OC 0308 Olive oil, virgin	2	-
		DT 1114 Tea, Green, Black	0.5	0.1
		Residue: methidathion		
		Notes: ADI lowered from 0.005 mg/kg bw		
MYCLOBUTANIL	0.03	FS 0240 Apricot	0.2	-

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
(181)		FS 0013 Cherries	1	-
		FB 0269 Grapes	1	-
		FS 0247 Peach	0.5	-
		FS 0014 Plums (including Prunes)	0.2	-
		FP 0009 Pome fruits	0.5	-
		MO 0812 Cattle, Edible offal of	0.01*	-
		MM 0812 Cattle meat	0.01*	-
		ML 0812 Cattle milk	0.01*	-
		PE 0112 Eggs	0.01*	-
		PO 0111 Poultry, Edible offal of	0.01*	-
		PM 0110 Poultry meat	0.01*	-
		DF 0014 Prunes	0.5	-
		Residue: myclobutanil		
OXYDEMETON-METHYL (166)	0.0003	FP 0226 Apple	1 O,DS	1 T O,D,DS
		FB 0264 Blackberries	W	0.5 T
		FS 0013 Cherries	1 O,DS	1 T O,DS
		FC 0001 Citrus fruits	W	0.5 T
		FB 0021 Currants, Black, Red, White	W	2 T O,DS
			W	0.5 T
		FB 0268 Gooseberry	0.1 O	0.5 T[1]
		FC 0203 Grapefruit	0.5 O	2 T O,DS
		FB 0269 Grapes	1 O	0.5 T[1]
		FC 0204 Lemon	0.5 O	0.5 T[1]
		FC 0206 Mandarin	0.5 O	0.5 T[1]
		FC 0004 Oranges, Sweet, Sour	1 O	1 T O
		FS 0247 Peach	0.5 O,DS	0.5 T O,DS
		FP 0230 Pear	0.5 O,DS	1 T O,DS
		FS 0014 Plums (including Prunes)	W	0.5 T
		FB 0272 Raspberries, Red, Black	0.5 O	0.5 T O,DS
		FB 0275 Strawberry	0.01* O	-
		VD 0071 Beans (dry)	W	0.2 T O
		VB 0040 Brassica Vegetables	1 O	0.2 T
		VB 0400 Broccoli	1 O	0.2 T
		VB 0402 Brussels sprouts	W	0.1 T O
		VA 0035 Bulb vegetables	1 O	0.2 T O[2]
		VB 0441 Cabbages, Head	0.01* O	0.2 T O[2]
		VB 0403 Cabbage, Savoy	0.01* O	0.2 T O
		VB 0404 Cauliflower	0.2 O	0.2 T O
		VP 0526 Common bean (pods and/or immature seeds)	0.5 O	0.2 T O
		VC 0424 Cucumber	0.2 O	0.2 T
		VO 0440 Egg plant	0.1 O	0.2 T[3]
		VP 0528 Garden pea (young pods)	0.05 O	0.2 T
			0.01* O	0.2 T O[2]
		VL 0480 Kale	2 O	0.5 T O

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
		VB 0405 Kohlrabi	0.2 O	-
		VL 0483 Lettuce, Leaf	W	0.2 T
		VP 0534 Lima bean (young pods and/or immature beans)	0.05 O	0.1 T O[5]
		VC 0046 Melons, except Watermelon	W	0.2 T O
		VA 0385 Onion, Bulb	0.01* O	-
		VP 0063 Peas	1 O	1 T O
		VD 0072 Peas (dry)	0.2 O	0.2 T O,DS
		VO 0051 Peppers	0.1* O	0.2 T
		VR 0589 Potato	0.1* O	0.5 T
		VC 0429 Pumpkins	0.05* O	0.1 T O,DS
		VC 0431 Squash, Summer	0.05 O	-
		VR 0596 Sugar beet	0.05 O	-
		VO 0447 Sweet corn (Corn-on-the-cob)	0.5 O	0.2 T O
		VO 1275 Sweet corn (kernels)		
		VO 0448 Tomato		
		VR 0506 Turnip, Garden	0.1* O	0.1 T
		VC 0432 Watermelon	0.2 O	0.2 T
		VC 0433 Winter squash	0.1* O	0.2 T
		GC 0640 Barley	0.2 O	0.2 T[4]
		GC 0080 Cereal grains	W	0.2 T
		GC 0645 Maize	0.2 O	0.2 T[4]
		GC 0647 Oats	0.2 O	0.2 T[4]
		GC 0651 Sorghum	0.5 O	0.2 T[4]
		GC 0654 Wheat	0.2 O	0.2 T[4]
		SO 0691 Cotton seed	0.05 O	0.1 T
		SO 0699 Safflower seed	1 O	-
		TN 0085 Tree nuts	0.05* O	0.05* T
		HH 0738 Mints	20 O	-
		MF 0812 Cattle fat	0.05* O	0.05* T
		MM 0097 Meat of cattle, pigs and sheep	0.05* O	0.05* T
		Milk products	0.05* O	0.05* T
		ML 0106 Milks	0.01* O	0.05* T
		MF 0818 Pig fat	0.05* O	0.05* T
		MF 0822 Sheep fat	0.05* O	0.05* T
		PE 0112 Eggs	0.05* O	0.05* T
		PF 0111 Poultry fats	0.05* O	0.05* T
		PM 0110 Poultry meat	0.05* O	0.05* T
		AL 1020 Alfalfa fodder	5 O	5 T O
		AL 1031 Clover hay or fodder	5 O	5 T
		AS 0645 Maize fodder	5 O	5 T O
		AF 0651 Sorghum forage (green)	1 O	-
			3 O	5 T O
		AS 0651 Sorghum straw and fodder, dry	0.5 O	5 T O,D

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
		AV 0596 Sugar beet leaves or tops	5 (fresh wt) O	5 T
		AV 0506 Turnip leaves or tops		
		Residue: sum of oxydemeton-methyl, demeton-S-methyl and demeton-S-methylsulphon, expressed as oxydemeton-methyl Notes: source of data: O = oxydemeton-methyl; D = demeton-S-methyl; DS = demeton-S-methylsulphon [1]Group MRL for Citrus fruits; [2]Group MRL for Brassica vegetables [3]Group MRL for Peas; [4]Group MRL for Cereal grains; [5]Group MRL for Bulb vegetables Note changed definition of residue. Oxydemeton-methyl is also known as demeton-S-methyl sulphoxide		
PARATHION-METHYL (059)	0.02	FS 0013 Cherries	0.01*	Fruits 0.2
		Fruits	W	0.2
		FB 0268 Gooseberry	0.01*	Fruits 0.2
		FS 0014 Plums (including Prunes)	0.01*	Fruits 0.2
		FB 0272 Raspberries, Red, Black	0.01*	Fruits 0.2
		VB 0040 Brassica vegetables	W	0.2
		VC 0424 Cucumber	W	0.2
		VC 0046 Melons, except Watermelon	W	0.2
		VR 0596 Sugar beet	W	0.05*
		VO 0448 Tomato	W	0.2
		DH 1100 Hops, dry	W	0.05*
		OC 0691 Cotton seed oil, crude	W	0.05
		OR 0691 Cotton seed oil, edible	W	0.05
		DT 1114 Tea, Green, Black	W	0.2
		Residue: parathion-methyl		
PENCONAZOLE (182)	0.03	FP 0269 Grapes	0.2	-
		FS 0245 Nectarine	0.1	-
		FS 0247 Peach	0.1	-
		FP 0009 Pome fruits	0.2	-
		FB 0275 Strawberry	0.1	-
		VC 0424 Cucumber	0.1	-
		VC 0046 Melons, except Watermelon	0.1	-
		VO 0448 Tomato	0.2	-
		MO 0812 Cattle, Edible offal of	0.05*	-
		MM 0812 Cattle meat	0.05*	-
		ML 0812 Cattle milk	0.01*	-

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
		PE 0840 Chicken eggs	0.05*	-
		PM 0840 Chicken meat	0.05*	-
		DH 1100 Hops, dry	0.5	-
		Residue: penconazole		
PIPERONYL BUTOXIDE (062)	0.03	GC 0080 Cereal grains	W	20 Po
		GC 0654 Wheat	10 Po	20 for cereal grains
		SO 0089 Oilseed except peanut	W	8 Po
		SO 0697 Peanut	W	8 Po T
		TN 0085 Tree nuts	W	8 Po
		DF 0167 Dried fruits	W	8 Po
		DV 0168 Dried vegetables	W	8 Po
		MO 0180 Dried fish	W	20 Po
		Residue: piperonyl butoxide		
PIRIMIPHOS-METHYL (086)	0.03	Notes: ADI increased from 0.01 mg/kg bw		
PROFENOFOS (171)	0.01	FC 0004 Oranges, Sweet, Sour	W	1 T
		FS 0247 Peach	W	0.5 T
		VD 0071 Beans (dry)	W	0.05* T
		VB 0400 Broccoli	W	0.2 T
		VB 0402 Brussels sprouts	W	0.5 T
		VB 0041 Cabbages, Head	1	0.5 T
		VB 0404 Cauliflower	W	0.2 T
		VC 0424 Cucumber	W	0.1 T
		VA 0385 Onion, Bulb	0.2	0.2 T
		VO 0445 Peppers, Sweet	W	1 T
		VR 0589 Potato	0.05*	0.05* T
		VD 0541 Soya bean (dry)	0.05*	0.05* T
		VA 0388 Spring onion	W	2 T
		VR 0596 Sugar beet	0.05*	0.05* T
		VO 0448 Tomato	2	0.5 T
		GC 0645 Maize	W	0.05* T
		SO 0691 Cotton seed	3	1 T
		SO 0702 Sunflower seed	W	0.05* T
		MM 0095 Meat	0.02*	0.02* T
		ML 0106 Milks	0.01*	0.01* T

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity	Recommended MRL or ERL (mg/kg)	
		CCN Name	New	Previous
		PE 0112 Eggs	0.02*	0.02* T
		OR 0691 Cotton seed oil, edible	0.05*	0.05* T
		OR 0541 Soya bean oil, refined	0.05*	0.05* T
		DT 0171 Teas (tea and herb teas)	0.5 T	0.5 T
		Residue: profenofos		
PYRAZOPHOS (153)	0.004	Notes: as an ADI has now been estimated, previous GLs are converted to MRLs		
THIRAM (105)	0.01	Notes: a temporary ADI of 0.005 mg/kg was withdrawn in 1985		
TRIADIMEFON (133)	0.03	FB 0021 Currants, Black, Red, White	0.2	1
		FB 0269 Grapes	0.5	2
		FI 0345 Mango	0.05*	0.1*
		FI 0353 Pineapple	1 Po	3 Po
		FP 0009 Pome fruits	0.5	0.5
		FB 0272 Raspberries, Red, Black	1	2
		FB 0275 Strawberry	0.1	0.2
		VD 0524 Chick-pea (dry)	0.05*	0.1*
		VC 0045 Fruiting vegetables, Cucurbits	0.1	0.2
		VA 0387 Onion, Welsh	0.05*	0.1*
		VP 0063 Peas	0.05*	0.1*
		VO 0445 Peppers, Sweet	0.1	0.5
		VA 0389 Spring onion	0.05*	0.1*
		VR 0596 Sugar beet	0.1*[1]	0.1*
		VO 0448 Tomato	0.2	0.5
		GC 0640 Barley	0.5	1
		GC 0647 Oats	0.1	0.5
		GC 0650 Rye	0.1	0.5
		GC 0654 Wheat	0.1	0.5
		SB 0716 Coffee beans	0.05*	0.1*
		MM 0095 Meat	0.05*	0.1*
		ML 0106 Milks	0.05*	0.1*
		PE 0112 Eggs	0.05*	0.1*
		PM 0110 Poultry meat	0.05*	0.1*
		AS 0640 Barley straw and fodder, dry	2	5
		AM 1051 Fodder beet	0.05*	0.1*
		AV 1051 Fodder beet leaves or tops	0.05*	0.1*
		AS 0647 Oat straw and fodder, dry	2	5
		AS 0650 Rye straw and fodder, dry	2	5
		AV 0596 Sugar beet leaves or tops	2	2

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		AS 0654	Wheat straw and fodder, dry	2	5
		DH 1100	Hops, dry	10	15
		Residue: triadimefon			
		Notes: note changed definition of residue. Previous MRLs referred to the sum of triadimefon and triadimenol. See triadimenol for triadimenol MRLs covering uses of triadimefon and triadimenol [1]Residues may occur near this level			
TRIADIMENOL (168)	0.05	FP 0226	Apple	W	0.2
		FI 0327	Banana	0.2[2]	-
		FB 0021	Currants, Black, Red, White		-
		FB 0269	Grapes	0.5[1]	2
		FI 0345	Mango		-
		FI 0353	Pineapple	2[1,2]	-
		FI 0009	Pome fruits	0.05*[1]	-
		FB 0272	Raspberries, Red, Black	1 Po[1]	-
		FB 0275	Strawberry	0.5[1,2]	-
		VS 0620	Artichoke	0.5[1]	-
		VD 0524	Chick-pea (dry)	0.1[1]	-
		VC 0424	Cucumber		0.1
		VC 0045	Fruiting vegetables, Cucurbits	1[1,2]	-
		VA 0387	Onion, Welsh	0.05*[1]	-
		VP 0063	Peas	W	-
		VO 0445	Peppers, Sweet	2[1,2]	-
		VA 0389	Spring onion	0.05*[1,2]	-
		VR 0596	Sugar beet	0.1[1]	-
		VO 0448	Tomato	0.1[1]	-
				0.05*[1]	
		GC 0640	Barley	0.1*[1,2]	0.1
		GC 0647	Oats	0.5[1]	-
		GC 0650	Rye		0.1
		GC 0654	Wheat	0.5[1,2]	0.1
				0.2[1,2]	
		SB 0716	Coffee beans	0.2[1,2]	0.1*
				0.2[1,2]	
		MM 0812	Cattle meat		0.05* T
		ML 0812	Cattle milk	0.1*[1,2]	0.01* T
		MM 0095	Meat		-
		ML 0106	Milks	W	-
				W	
		PE 0112	Eggs	0.05*[1,2]	0.05* T
		PM 0110	Poultry meat	0.0*[1,2]	0.05* T
		AS 0640	Barley straw and fodder, dry	0.05*[1,2]	5
		AM 1051	Fodder beet	0.05*[1,2]	-

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)	
		CCN	Name	New	Previous
		AV 1051	Fodder beet leaves or tops		-
		AS 0647	Oat straw and fodder, dry	5[1,2]	-
		AS 0650	Rye straw and fodder, dry	0.05*[1]	5
		AV 0596	Sugar beet leaves or tops	0.2[1]	-
		AS 0654	Wheat straw and fodder, dry	5[1,2]	5
				5[1,2]	
		DH 1100	Hops, dry	1[1,2]	-
				5[1,2]	
				5[1]	
		Residue: triadimenol Notes: [1]resulting from triadimefon uses. [2]resulting from triadimenol uses. The limits accomodate triadimenol residues resulting from the use of triadimefon and/or triadimenol. As separate limits have now been proposed for triadimefon and triadimenol all limits for triadimenol, including those which have not been changed, are listed in the table 4			

ANNEX II

INDEX OF REPORTS AND EVALUATIONS

Numbers in parentheses are Codex Classification Numbers.

[1] T = Toxicology
R = Residue and analytical aspects

BIFENTHRIN (1778) 1992 (T,R)

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), 1992 (R)

BROMOMETHANE (052) 1965 (T,R), 1966 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R), 1985 (R), 1992 (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), 1992 (R), 1992 (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 rpt), 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 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), 1992 (corr. to 1991 rpt)
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 rpt and T evaluation), 1985 (T,R), 1987 (T), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation), 1992 (T)
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 (090)	1975 (T,R), 1976 (R, Annex I only), 1979 (R), 1990 (R), 1991 (T,R), 1992 (T)
CHLORTHION	1965 (T)
CLOFENTEZINE (156)	1986 (T,R), 1987 (R), 1989 (R), 1990 (R), 1992 (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)
CYCLOXYDIM (179)	1992 (T,R)
CYFLUTHRIN (157)	1986 (R), 1987 (T and corr. to 1986 rpt), 1989 (R), 1990 (R), 1992 (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), 1992 (R)
CYPERMETHRIN (118)	1979 (T,R), 1981 (T,R), 1982 (R), 1983 (R), 1984 (R), 1985(R), 1986 (R), 1987 (corr. to 1986 evaluation), 1988 (R), 1990 (R)
CYROMAZINE (169)	1990 (T,R), 1991 (corr. to 1990 R evaluation), 1992 (R)
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 rpt, 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), 1992 (R)
DEMETON (092)	1965 (T), 1967 (R), 1975 (R), 1982 (T)
DEMETON-S-METHYL (073)	1973 (T,R), 1979 (R), 1982 (T), 1984 (T,R), 1989 (T,R), 1992 (R)
DEMETON-S-METHYLSULPHON (164)	1973 (T,R), 1982 (T), 1984 (T,R), 1989 (T,R), 1992 (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), 1992 (T,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), 1992 (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), 1992 (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), 1992 (corr. to 1991 rpt, Annex I)
DITHIANON (180)	1992 (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), 1992 (T, thiram)
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), 1992 (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[1]), 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), 1992 (T)
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 rpt), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation)
FERBAM	see dithiocarbamates, 1965 (T), 1967 (T,R)
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)

GLUFOSINATE-AMMONIUM (175)	1991 (T,R), 1992 (corr. to 1991 rpt, Annex I)
GLYPHOSATE (158)	1986 (T,R), 1987 (R and corr. to 1986 rpt), 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), 1992 (corr. to 1991 rpt, Annex I)
HEXACHLOROBENZENE (044)	1969 (T,R), 1973 (T,R), 1974 (T,R), 1978(T), 1985 (R)

[1]R evaluation omitted. Published 1986.

HEXACONAZOLE (170)	1990 (T,R), 1991 (R and 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), 1992 (T)
ISOFENPHOS (131)	1981 (T,R), 1982 (T,R), 1984 (R), 1985 (R), 1986 (T,R), 1988 (R), 1992 (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), 1992 (R)
METHACRIFOS (125)	1980 (T,R), 1982 (T), 1986 (T), 1988 (T), 1990 (T,R), 1992 (R)
METHAMIDOPHOS (100)	1976 (T,R), 1979 (R), 1981 (R), 1982 (T,R[1]), 1984 (R), 1985 (T), 1989 (R), 1990 (T,R)
METHIDATHION (051)	1972 (T,R), 1975 (T,R), 1979 (R), 1992 (T,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 rpt), 1988 (R), 1989 (R)

[1]R evaluation omitted. Published 1989.

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)
MYCLOBUTANIL (181)	1992 (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 (166)	1965 (T, as demeton-S-methyl sulphoxide), 1967 (T), 1968 (R), 1973 (T,R), 1982 (T), 1984 (T,R), 1989 (T,R), 1992 (R)
OXYTHIOQUINOX	see chinomethionat

PACLOBUTRAZOL (161)	1988 (T,R), 1989 (R)
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), 1992 (R)
PENCONAZOLE (182)	1992 (T,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), 1992 (corr. to 1991 rpt)
2-PHENYLPHENOL (056)	1969 (T,R), 1975 (R), 1983 (T), 1985 (T,R), 1989 (T), 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), 1992 (R)

PHOSALONE (060)	1972 (T,R), 1975 (R), 1976 (R)
PHOSMET (103)	1976 (R), 1977 (corr. to 1976 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), 1992 (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), 1992 (T)
PROCHLORAZ (142)	1983 (T,R), 1985 (R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1991 (R and corr. to 1990 rpt, Annex I, and evaluation), 1992 (R)
PROCYMIDONE (136)	1981 (R), 1982 (T), 1989 (T,R), 1990 (R), 1991 (corr. to 1990 Annex I)
PROFENOFOS (171)	1990 (T,R), 1992 (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 (183)	1965 (T), 1992 (T,R)
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), 1992 (T,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), 1992 (T)
TOLYLFLUANID (162)	1988 (T,R), 1990 (R), 1991 (corr. to 1990 rpt)
TOXAPHENE	see camphechlor
TRIADIMEFON (133)	1979 (R), 1981 (T,R), 1983 (T,R), 1984 (R), 1985 (T,R), 1986 (R), 1987 (R and corr. to 1986 evaluation), 1988 (R), 1989 (R), 1992 (R)
TRIADIMENOL (168)	1989 (T,R), 1992 (R)
TRIAZOLYLALANINE	1989 (T,R)
TRIAZOPHOS (143)	1982 (T), 1983 (R), 1984 (corr. to 1983 rpt, Annex I), 1986 (T,R), 1990 (R), 1991 (T and corr. to 1990 evaluation), 1992 (R)
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), 1992 (R)
VINCLOZOLIN (159)	1986 (T,R), 1987 (R and corr. to 1986 rpt and R evaluation), 1988 (T,R), 1989 (R), 1990 (R), 1992 (R)

ZINEB (105)	see dithiocarbamates, 1965 (T), 1967 (T,R)
ZIRAM (105)	see dithiocarbamates, 1965 (T), 1967 (T,R)

ANNEX III

JMPR REPORTS - INDEX TO GENERAL ITEMS, 1965 - 1992

The index covers Section 2 and 3 of the reports for the years 1966-91, the introductory part of the 1965 Report (which was not divided into sections) and a few items of a general nature from other sections. Principal references, and where relevant those which supersede earlier ones, are shown **bold**.

References are shown as, e.g.:

65p3; 66-2.1, 2.3.1 = 1965 Report, page 3 and 1966 Report, Sections 2.1 and 2.3.1

Main headings are shown **bold.** Introductions (*as, and, for, in* etc.) in subheadings are *italicized*. Cross-references to other subheadings within the same main heading are underlined; the main heading is not repeated. Long subheading titles are abbreviated.

Entries are treated as single words and listed alphabetically, but plurals and introductions are ignored. Thus "**Pesticide(s)**" precedes "**Pesticide residue(s)**" and, under **ADI(s)**:, "Conditional" precedes "*and* Metabolites".

Note. Definitions of terms used by the JMPR are collected under the heading "Definitions [glossaries and explanatory notes]". With a few exceptions, they are not referenced in their alphabetical positions.

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ANNEX IV

INTAKE PREDICTIONS

At the request of the Meeting, the International Programme on Chemical Safety (IPCS) calculated the predicted intakes of residues of the pesticides on the agenda of the Joint Meeting, based on the methods described in Guidelines for Predicting Dietary Intake of Pesticide Residues[1].

Detailed EMDI (Estimated Maximum Daily Intake) calculations were not performed on those pesticides for which the TMDI (Theoretical Maximum Daily Intake), based upon global diets, exceeded the ADI, because there was insufficient opportunity at the Joint Meeting to review the detailed processing data that had been supplied on certain compounds. The results of EMDI calculations will be made available to the Twenty-fifth Session of the Codex Committee on Pesticide Residues (CCPR) in April 1993.

For the following compounds the TMDI did not exceed the ADI. The TMDI calculations were based on ADIs and MRLs current at the end of the present Meeting:

abamectin, aldicarb, anilazine, benalaxyl, bifenthrin, bromide ion, cadusafos, chlorothalonil, clofentezine, cycloxydim[2], cyfluthrin, cyromazine, deltamethrin, dinocap[3], dithianon, endrin, fenbutatin oxide, iprodione, metalaxyl, myclobutanil, parathion-methyl, penconazole, piperonyl butoxide, pirimiphos-methyl, prochloraz, profenofos, pyrazophos, thiram (dithiocarbamates), triadimefon, triadimenol, vamidothion, and vinclozolin.

The TMDI exceeded the ADI for the following compounds (information on processing factors must be reviewed before EMDIs can be calculated):

aldrin/dieldrin, chlorpyrifos-methyl, cyhexatin, demeton-S-methyl[4], dicofol[5], isofenphos, methacrifos, methidathion, oxydemeton-methyl[5], phorate[5], and triazophos.

ADIs have not been established for methyl bromide or propham; therefore, TMDIs were not calculated.

The TMDI is a gross over-estimate of the true pesticide intake. Therefore, it should not be concluded that the MRLs estimated by the Meeting are unacceptable when the TMDI exceeds the ADI. Instead, TMDI calculations should be used as a screening tool that eliminates the need for further consideration of the intake of a pesticide residue when its value is below the ADI. When the TMDI exceeds the ADI, EMDI and, if necessary, EDI (Estimated Daily Intake), calculations should be performed.

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[1] *Guidelines for Predicting Dietary Intake of Pesticide Residues*, World Health Organization, Geneva, 1989

[2] No MRLs have been recommended on this pesticide.

[3] The present Meeting recommended withdrawal of all temporary MRLs.

[4] According to information from a manufacturer, it is likely that all uses of this pesticide will be transferred to oxydemeton-methyl within a few years.

[5] Extensive processing information was made available to the Meeting, which will be valuable for the calculation of EMDIs.

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