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[1] T = Toxicology
R = Residue and analytical aspects
E = Evaluation of effects on the environment
*New compound
**Evaluation in CCPR periodic review programme

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1997 JOINT MEETING OF THE FAO PANEL OF EXPERTS ON PESTICIDE RESIDUES IN FOOD AND THE ENVIRONMENT AND THE WHO CORE ASSESSEMENT GROUP

Lyon (IARC), 22 September-1 October 1997

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ABBREVIATIONS WHICH MAY BE USED

(Well-known abbreviations in general use are not included)

Ache	acetylcholinesterase
acute RfD	acute reference dose
ADI	acceptable daily intake
AFI(D)	alkali flame-ionization (detector)
ai	active ingredient
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
bw (no stops)	body weight
CA	Chemical Abstracts
CAS	Chemical Abstracts Services
CCN	Codex Classification Number (this may refer to classification numbers for compounds or for commodities).
CCPR	Codex Committee on Pesticide Residues
ChE	cholinesterase
CNS	central nervous system
CoE	Council of Europe
cv	coefficient of variation
CXL	Codex Maximum Residue Limit (Codex MRL). See MRL.
DFG	Deutsche Forschungsgemeinschaft
DL	racemic (optical configuration, a mixture of dextro- and laevo-)
DP	dustable powder
DS	powder for dry seed treatment
EBDC	ethylenebis(dithiocarbamate)
EC	(1) emulsifiable concentrate (2) electron-capture [chromatographic detector]
EC_{50}	median effective concentration
ECD	electron-capture detector
EMDI	estimated maximum daily intake
EPA	Environmental Protection Agency
EPPO	European Plant Protection Organization
ERL	extraneous residue limit
ETU	ethylenethiourea
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 (not gm)	gram
ìg	microgram
GAP	good agricultural practice(s)
GC-MS	gas chromatography - mass spectrometry
GENEEC	Generic Expected Environmental Concentration Program
G.I.	gastrointestinal
GL	guideline level
GLC	gas-liquid chromatography
GLP	good laboratory practice
GPC	gel-permeation chromatograph or chromatography
GSH	glutathione
h (not hr)	hour(s)
ha	hectare
Hb	haemoglobin
hl	hectolitre
HPLC	high-performance liquid chromatography
HPLC-MS	high-performance liquid chromatography - mass spectrometry
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
JECFA	Joint Expert Committee on Food Additives
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 the WHO Core Assessment Group
K_{ads}	adsorption constant
K_{oc}	K_{ads} referred to organic carbon content
LC	liquid chromatography
LC_{50}	lethal concentration, 50%
LC-MS	liquid chromatography - mass spectrometry
LD_{50}	lethal dose, median
LOAEL	lowest observed adverse effect level
LOD	limit of determination (see also "*" at the end of the Table)
LSC	liquid scintillation counting or counter
M	molar
MATC	maximum acceptable toxicant concentration

MFO	mixed function oxidase
ìm	micrometre (micron)
min (no stop)	minute(s)
MLD	minimum lethal dose
mo (not mth.)	month(s)
MRL	Maximum Residue Limit. 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.
MS	mass spectrometry
MTD	maximum tolerated dose
n (not *n*)	normal (defining isomeric configuration)
NCI	National Cancer Institute (USA)
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NP(D)	nitrogen-phosphorus (detector)
NTE	neuropathy target esterase
OP	organophosphorus pesticide
OPP	Office of Pesticide Programs
PCV	packed cell volume
PEC	predicted environmental concentration
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/l are used).
PT	prothrombin time
PTDI	provisional tolerable daily intake. (See 1994 report, Section 2.3, for explanation)
PTT	partial thromboplastin time
PTU	propylenethiourea
RBC	red blood cell
r.d.	relative density. (Formerly called specific gravity)
RfD	reference dose, as in "acute reference dose"
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)
STMR	supervised trials median residue
t	tonne (metric ton)
T_3	tri-iodothyronine
T_4	thyroxine
TADI	Temporary Acceptable Daily Intake
TER	toxicity/exposure ratio
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
TRR	total radioactive residue
TSH	thyroid-stimulating hormone (thyrotropin)
UDMH	1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine)
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
UV	ultraviolet
WG	water-dispersible granule
WIIS	Wildlife Incident Investigation Scheme (UK)
WHO	World Health Organization
WP	wettable powder
WTO	World Trade Organization
<	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

USE OF JMPR REPORTS AND EVALUATIONS BY REGISTRATION AUTHORITIES

The summaries and evaluations contained in this book are, in most cases, based on unpublished proprietary data submitted for the purpose of the JMPR assessment. A registration authority should not grant a registration on the basis of an evaluation unless it has first received authorization for such use from the owner who submitted the data for JMPR review or has received the data on which the summaries are based, either from the owner of the data or from a second party that has obtained permission from the owner of the data for this purpose.

PESTICIDE RESIDUES IN FOOD

REPORT OF THE 1997 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 the WHO Core Assessment Group (JMPR) was held at the International Agency for Research on Cancer in Lyon, France, from 22 September to 1 October 1997. The FAO Panel of Experts had met in preparatory sessions from 17 to 21 September.

The Meeting was opened by Dr J. Rice, Chief, Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, on behalf of the Directors-General of FAO and WHO. Dr Rice emphasized the importance of the work of JMPR for the establishment of international standards and their key role in settling trade disputes brought before the World Trade Organization. He also highlighted the importance of making use of national evaluations to the greatest extent possible.

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 humans 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 residues limits (MRLs), and general principles for the evaluation of pesticides that have been evaluated. 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 residue and analytical aspects of the pesticides under consideration, including data on their metabolism, fate in the environment, and use patterns, 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 Toxicological Core Assessment Group was responsible for reviewing toxicological and related data and for estimating, where possible, ADIs for humans of the pesticides. The Meeting also considered risks to organisms in the environment of two pesticides that had been deferred from the 1996 Joint Meeting and had been evaluated at a Core Assessment Group meeting in Leicester, UK, in March 1997[i]. The recommendations of the Joint Meeting, including those for further research and the provision of additional information, are proposed for use by national governments, international organizations, and other interested parties.

The Joint Meeting was saddened to hear of the recent death of a former Temporary Adviser and Member of the WHO Core Assessment Group, Dr E.M. den Tonkelaar, National Institute of Public Health and Environmental Protection, Netherlands. Dr den Tonkelaar's many

contributions to the JMPR are gratefully acknowledged.

2.1. FAO MANUAL ON THE SUBMISSION AND EVALUATION OF PESTICIDE RESIDUES DATA FOR THE ESTIMATION OF MAXIMUM RESIDUE LEVELS IN FOOD AND FEED

The Meeting was pleased to note that the *FAO Manual on the Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed* had been published.

The Manual gives the historical background to the operation of the JMPR and describes the object of the work, the procedures involved in the selection of compounds, and the data requirements for estimating maximum residue levels and supervised field trials median residue (STMR) levels.

The Manual incorporates all relevant information on the principles which are currently used by the JMPR to estimate maximum residue levels and STMR levels and clarifies and consolidates the procedures followed by the FAO Panel in the evaluation of the experimental results and information provided. In this way it improves the transparency of the work of the JMPR and facilitates the acceptance of Codex MRLs by national governments and their use within the WTO Agreement on the Application of Sanitary and Phytosanitary Measures.

The principles in the Manual may also provide useful assistance to member countries in evaluating residue data for the registration of pesticides and in developing their national evaluation systems.

Chapter headings in the Manual comprise:

- Selection of compounds for evaluation
- Data and information required for JMPR evaluations
- Preparation of data submissions for the consideration of the FAO Panel of JMPR
- The JMPR practice in estimating maximum residues levels and proposing maximum residue limits
- Estimation of residue levels for calculation of dietary intake of pesticide residues
- Use of JMPR Recommendations by regulatory authorities.

Appendices provide information on abbreviations, definitions, sampling and the composition of animal feeds, as well as guidance on procedures and formats for the submissions of data.

The Meeting wishes to encourage manufacturers and member countries to follow, as far as possible, the guidance given in the Manual in preparing future submissions for the JMPR.

Because guidelines by their nature are subject to revision from time to time in order to accommodate new scientific developments and standards, users of the FAO Manual are urged to keep abreast of these changes by reading future JMPR reports where such updates are recorded.

2.2 SUBMISSION OF INFORMATION FOR CONSIDERATION BY THE FAO PANEL

In view of the publication of the FAO Manual (see section 2.1), the Meeting considers that the preparation of future submissions will be much more consistent and will further facilitate the evaluation of the experimental data and information provided. In order to assist the efficient and timely estimation of maximum residue levels, some of the deficiencies and problems experienced by the current Meeting in relation to recent submissions are described below.

The Meeting repeatedly found it very difficult or impossible to interpret the summary information on GAP supplied by manufacturers (FAO Manual, 3.1.4.1). The summary should not include any information on the use which is not specifically given on the label (e.g. do not define applications in terms of kg ai/hl if only the kg ai/ha rate is specified; do not specify calculated PHIs if application is authorized only at a specific growth stage; do not give a number of applications calculated from the specified application intervals and PHI). It is stressed (FAO Manual, 3.1.4, para 2) that valid copies of current labels must be provided, together with an English translation of the relevant sections (e.g. dosage, specifying whether the concentration of the spray or the kg/ha rate is primarily defined; application methods; growth stage of plants at the time of application of the pesticide; conditions of use; any restriction of the use). Crops included in groups (e.g. leafy vegetables, fruits) should be individually named. Labels reflecting current GAP should be clearly distinguished from "proposed" labels. Indexing of labels in such a manner as to allow easy cross-reference to GAP summaries and supervised field trials would facilitate the evaluation.

In future, the specific uses of a compound will not be evaluated if the relevant labels have not been provided.

If information on GAP is provided by responsible national regulatory authorities the above detailed information is required and the submission of labels is desirable. The submission of information on GAP by national authorities is especially important in the case of generic pesticides produced by several manufacturers. In such cases information on the chemical composition of technical products and their formulations used in the reporting country is also desirable.

The description of supervised trials (FAO Manual, 3.1.5) should include: the unambiguous description of the commodity, preferably with Codex Classification Numbers; detailed information on sampling and sample preparation with special emphasis on sample size; duration and temperature of storage during successive steps from sampling to analysis; the clear description of the portion of the commodity prepared for the analysis (e.g. measured relative weights of stone and pulp; measured relative weights of peel and pulp if they are analysed separately); blank values; whether the results were adjusted for blank and recovery values (FAO Manual, page 23).

Descriptions of analytical methods should include (FAO Manual, section 3.1.3), but not be limited to, the clear indication of the compound(s) determined, whether they were free or conjugated, the levels of fortification used in the validation of the methods, the limits of determination, and the recoveries okbtained.

Processing studies are among the critical supporting studies which are required for the evaluation of a new compound or a periodic review (FAO Manual, 3.1.6.2). The results of processing studies are used for dietary intake calculations and estimations of maximum residue

levels where appropriate. Because the studies submitted are often inadequate, guidance is provided in this section of the Manual, where it is stressed that studies which simulate commercial practices as closely as possible are required. Additional studies such as the effects of household jam preparation and small-scale laboratory studies may be submitted as useful supplementary information, but small-scale laboratory studies will not be accepted as a substitute for properly designed and implemented studies simulating large-scale industrial processes. The processing studies should always be on the raw agricultural commodity as it is marketed (e.g. a processing study on residues in fruits should always include the determination of the residues in or on the original unwashed fruits). The studies should be reported according to well-established guidelines such as the US EPA Hazard Evaluation Division's *Standard Evaluation Procedure Magnitude of the Residue: Processed Food/Feed Studies* EPA 540/9-86-145, or the Commission of the European Communities' *"Guidelines for the generation of data concening residues as provided as provided in Annex II, part A, section 6 and Annex III, section 8 of directive 91/414/EEC concerning the placing of plant protection products on the market."* 1607/VI/97. 7th January 1997.

2.3 MRLS FOR PESTICIDES FOR WHICH JMPR ESTIMATES OF DIETARY INTAKE EXCEED THE ADI

PROPOSAL

That MRLs for which the available information is insufficient for the JMPR to conclude that the ADI would not be likely to be exceeded be designated as MRLMs (maximum residue limits for monitoring)[ii].

BACKGROUND

The Codex Alimentarius Commission has agreed in principle to recommendations of the 1995 FAO/WHO Consultation[2] on strengthening the consideration of risk assessment in the elaboration and use of Codex MRLs, in particular making a clear distinction between risk assessment and risk management responsibilities. The subject was considered further at the 1997 FAO/WHO Consultation on Risk Management and Food Safety[3]. For pesticide residues in food, Codex has the primary responsibility at the international level for risk management and the JMPR for risk assessment. Both have attempted to implement steps to effect the recommendations of the two Consultations.

Until recently, estimates by the JMPR of the chronic dietary intake of pesticides have generally been gross over-estimates. Recently introduced procedures using supervised trials median residues (STMRs) and supervised trials median residues for processed products (STMR-Ps) have substantially improved the ability of the JMPR to make better estimates of dietary intake at the international level and thus improve the value of those estimates for risk assessment

[2] FAO/WHO. 1995. Application of risk analysis to food standards issues. Report of a Joint FAO/WHO Expert Consultation, 13-17 March 1995. Geneva. WHO/FNU/FOS/95.3 (E.S.T). World Health Organization, Geneva.

[3] FAO/WHO. 1997. Risk management and Food Safety. Report of a Joint FA/WHO Expert Consultation, 27-31, January 1997. Rome. FAO, Rome, Italy.

and risk management decisions.

When the JMPR cannot conclude that the dietary intake will not exceed the ADI (e.g. owing to the lack of sufficient data for the more refined estimation of dietary intake) uncertainty remains as to the toxicological significance of residues in food resulting from the application of pesticides according to GAP. This has resulted in the reluctance of countries to accept some MRLs recommended by the JMPR at the national level, has created risk management problems in Codex, and has the potential to create problems in the use of Codex MRLs in the WTO for the resolution of trade disputes.

Once recommendations by the JMPR for MRLs are taken up in the Codex procedure, the draft MRLs for chemicals whose ADIs might be exceeded are not readily distinguishable from those whose ADIs would not be exceeded according to the dietary intakes estimated by the JMPR. An "implicit" JMPR endorsement is therefore attached to MRLs of both types, although one is clearly a better estimate for risk management decisions than the other. There is clearly a need to ensure that risk managers in Codex and at the national level are able to recognize which dietary estimates have more, and which less, uncertainty. In view of the importance of Codex standards in WTO mechanisms for the resolution of disputes concerning pesticides, the JMPR considers it especially important that its estimates of dietary intake and their relation to the ADI be clearly conveyed to Codex in such a way that potential health concerns are not overlooked.

One approach would be for the JMPR to continue to estimate maximum residue levels when there is insufficient information to determine that the ADI would not be exceeded, but not to recommend them to Codex for use as MRLs. That would provide the strongest incentive for the submission of better data for the estimation of dietary intake. However in some cases this might not be equitable for those countries who are capable of making more refined national estimates of dietary intake than are possible at the international level, or those for which there would be no dietary intake problem simply because their food consumption does not include significant quantities of those commodities which contribute most to the total dietary intake of the pesticide.

Another option (and the one preferred by the JMPR) is to coin another term in order to distinguish those compounds whose intakes can be concluded to be below their ADIs from those for which there is insufficient information to come to that conclusion. The JMPR believes that this approach would better convey the significance of JMPR estimates of dietary intake and would contribute to better risk management decisions within Codex and at the national level. The JMPR therefore proposes a new term: **MRLM** (maximum residue limit for monitoring), to be defined as an MRL for a pesticide for which an ADI has been allocated, but for which insufficient information has been provided for the JMPR to estimate whether its dietary intake would be below the ADI. The JMPR recommends that MRLMs be applied to new or periodic review chemicals reviewed by future FAO Panels of the JMPR, and that they be clearly indicated as such, and further recommends that the information needed for the JMPR to refine its estimates of dietary intakes continue to be clearly stated in JMPR reports and evaluations.

2.4 THE ESTIMATION OF MAXIMUM RESIDUE AND STMR LEVELS FOR PRODUCTS OF ANIMAL ORIGIN WHEN RESIDUES ARE TRANSFERRED FROM FEED ITEMS

1. The 1996 Meeting agreed that guidance was required on the estimation of maximum residue levels and STMRs for products of animal origin to aid in the preparation of future JMPR evaluations and to improve the transparency of the procedures. The Meeting agreed that this guidance should supersede the recommendation made in the report of the FAO Panel Workshop[iii], which met in the Hague in April 1996.

2. The present Meeting recognized that it is appropriate to use a different residue value for the estimation of acute intake from that used for the estimation of chronic intake. For chronic dietary exposure the York Consultation[4] had developed the concept of using the median residues from supervised field trials (STMRs) to represent the most likely residue level if the pesticide is used according to maximum GAP conditions. However, the scope for the estimation of a median residue for products of animal origin directly from the feeding trials is limited, since usually only one or very few feeding studies are available at an appropriate level.

3. The Meeting agreed that the problems of estimating STMRs and maximum residue levels for products of animal origin are different from those of estimating these values for crop commodities from supervised residue trials. For example, the main residue in feed items may be a metabolite and this may need to be taken into account. The Meeting concluded therefore that this recommendation of the Workshop, although providing useful guidance, would not be appropriate in all situations.

4. The Meeting noted that the continuous consumption of feed items containing residues at the MRL is unlikely and therefore recognized that the magnitude of the residues in animal products following the consumption of treated feed items would depend on the rate at which the compound reached a steady state in tissues, milk and eggs. The residues of some compounds transfer into milk or eggs fairly rapidly, whereas those of other compounds do not reach a plateau unless dosing is sustained for 1-2 weeks or more.

5. The Meeting agreed that in deciding which dosing level to use from feeding studies on farm animals, account must be taken of whether the dosing levels in the feeding studies are expressed on a wet or a dry weight basis. The Meeting recommended that reports of future feeding studies should record the feeding levels primarily on a dry weight basis. It agreed that interpolation between dosing levels from the feeding studies was appropriate in cases where reasonable linearity of the relation between residue level and dosing level could be assumed (where three or more dosing levels show reasonable linearity), whereas extrapolation substantially beyond the range of dose levels was not appropriate.

6. The Meeting agreed that maximum residue levels and STMRs for products of animal origin should normally be derived as shown below and summarized in Table 1.

a) For compounds which reach a plateau rapidly in milk or eggs.

Maximum residue levels should be calculated from the MRL for each feed item, the maximum feed incorporation rates and the highest residues determined in the milk, eggs and tissues in

[4] Anon 1996. Report of an Joint FAO/WHO Consultation on the Revision of the guidelines for the estimation of dietary intake of pesticide residues. York, UK, May 1995.

the feeding studies.

STMRs should be calculated from the STMR for each feed item, the maximum feed incorporation rates and the mean residues determined in the milk, eggs and tissues in the feeding studies.

b) For compounds which reach a plateau slowly in milk or eggs.

Maximum residue levels should be calculated from the STMR for each feed item, the maximum feed incorporation rates and the highest residues determined in the milk, eggs and tissues in the feeding studies.

STMRs should be calculated from the STMR for each feed item, the maximum feed incorporation rates and the mean residues determined in the milk, eggs and tissues in the feeding studies.

In deciding between options a) and b), the persistence of the residue in the feed items should be taken into account.

Table 1. Summary of procedures for the estimation of maximum residue levels and STMRs for products of animal origin when residues are transferred from feed items.

	Residue reaches plateau rapidly		Residue reaches plateau slowly	
	Max. residue level	STMR	Max. residue level	STMR
Feed item residue level	MRL	STMR	STMR	STMR
Feed incorporation rates	maximum	maximum	maximum	maximum
Feeding study residue level	highest	mean	highest	mean

7. The Meeting recommended that worked examples should be developed in time for the 1998 JMPR.

2.5 EXTRAPOLATION OF RESIDUE DATA TO MINOR CROPS

The 29th Session of the CCPR (1997, ALINORM 97/24A paragraph 99.3) requested the JMPR to give particular consideration to the concerns of developing countries when elaborating criteria for extrapolating residue data to minor crops in the proposed revision of the *FAO Manual on the Submission and Evaluation of Residue Data* with particular attention to the commodities identified in CX/PR 97/16 Appendix 1 and CX/PR 97/17 Appendix 1, question 4.

The issue was previously considered by the 1989 JMPR (report, Section 2.11) and briefly by the 1996 JMPR (report, Section 2.5) as part of the estimation of group maximum residue levels. The report of the 1996 JMPR formed the basis for Section 5.4.2 of the FAO Manual. The 1996 JMPR also drew attention to the development of minimum data requirements which are under consideration by governments, industry and the Organisation for Economic Cooperation and Development (OECD). Minimum data requirements and situations where extrapolation is valid are closely related.

The 1989 JMPR confirmed that decisions to extrapolate are on a case-by-case basis when adequate relevant information is available. Adequate information would include information on GAP for the relevant crops, a reference to the residue data used to support the original MRL, and an explanation of the logic for the extrapolation.

The FAO Manual provides advice on extrapolations and the nature of the information needed to support an extrapolation.

Section 5.1.4.2 of the Manual states that selective surveys may provide supplementary information which will assist in extrapolations. The approved use pattern of the pesticide on the minor crop should be the same as or similar to that on a major crop for which an MRL is already adequately supported by data. The selective survey should be fully documented and should focus on samples of the minor crop produced under typical commercial conditions where the pesticide is known to have been used.

Section 5.4.2 discusses the estimation of group maximum residue levels and gives examples and limitations. Adequate data for the major crops of a group may be sufficient to estimate maximum residue levels for the whole group.

The Meeting examined the list of pesticides frequently encountered in commodities from developing countries in Appendix 1 of document CX/PR 97/16. Many of the commodities listed, e.g. apples, grapes, oranges, potatoes, are major commodities and extrapolation to major crops is generally not acceptable. Where residues are a problem or potential problem for trade, national governments are invited to submit data for review by the JMPR. A number of the pesticides listed in document CX/PR 97/16 are scheduled for periodic review in the near future and the ideal time to submit data on a pesticide is at the time of its periodic review.

The data submitted to support extrapolation to a minor crop must include the following information.

1. Background information on the reasons for describing the crop as minor, the importance of the use of the pesticide in terms of pests controlled, the extent of its use on the minor crop, and the nature of the problems or potential problems for international trade

2. A description of the cultural practices for the production of the major crop and the approved or registered uses of the pesticide on the major crop from which extrapolation is proposed.

3. A description of the cultural practices for the production of the minor crop, the approved or registered uses of the pesticide on the minor crop, and the reasons for expecting similar residue levels on the minor crop to those on the major crop.

4. Supervised residue trials on the major crop supporting the MRL or reference to the JMPR Evaluations if trials data have already been reviewed by the JMPR.

The data submission should also include the following supporting information where available.

1. Data on supervised trials with approved or registered uses on the minor crop.

2. A copy of the label describing the registered or approved uses and an English translation of the instructions for use.

3. Monitoring data from selective surveys on the minor crop produced under typical commercial conditions where the pesticide is known to have been used.

The Meeting recommended that the CCPR request national governments to provide information on situations where extrapolation of residue data to minor crops is considered feasible at the national level.

The Meeting welcomed the initiative by the CCPR *ad hoc* Working Group on Problems Relative to Pesticide Residues in Food in Developing Countries and recommended that national governments prepare data submissions for commodities of concern when the specific pesticides are scheduled for review by the JMPR.

2.6 CALCULATION OF DIETARY INTAKE OF PESTICIDE RESIDUES

Theoretical Maximum Daily Intakes (TMDIs) were calculated for the JMPR by WHO (GEMS/Food) using the methods described in *Guidelines for predicting dietary intake of pesticide residues* (WHO, 1997). When information was available, International Estimated Dietary Intakes (IEDIs) were also calculated. Dietary intake assessments were not performed for amitrole or fipronil because no MRLs exist and none have been proposed. The ADI for guazatine has been withdrawn. Excepting fenamiphos and lindane, the intake assessments for all the pesticides evaluated at the present Meeting were below their ADIs. The results are summarized in Annex III. Details of the calculations will be made available at the 30th Session of the CCPR in April 1998.

The TMDI exceeded the ADI of fenamiphos in one of the five GEMS/Food regional diets. However, residue aspects of fenamiphos are scheduled for re-evaluation by the 1999 JMPR, at which time the dietary intake concerns are likely to be resolved. The Meeting recommended that a full re-evaluation of the toxicological and residue aspects of lindane be undertaken at a future Meeting, after which an assessment of intake can take into account the latest information.

Acute hazard intake assessments were not performed on fenthion or methidathion, *inter alia*, even though acute RfDs were established for them at the present Meeting, because a large portion size database has not yet been established by WHO. An FAO/WHO Consultation on Food Consumption and Exposure Assessment to Chemicals held in February 1997 provided further guidance in calculating acute hazard dietary intake, particularly to address the existence of single commodity units with residues well above the MRL. The Meeting looked forward to the publication of the report of this Consultation.

In response to concern expressed at the 29th Session of the CCPR about the MRL of 3 mg/kg for fenthion in virgin olive oil, the Meeting noted that a 60 kg person would have to consume 200 ml of virgin oil before the acute RfD would be exceeded. In the absence of data on the consumption of virgin olive oil relevant to acute hazard intake assessment at the international

level, the Meeting invited governments to make available appropriate information on the consumption of food commodities by high-percentile consumers.

3. SPECIFIC PROBLEMS

3.1 HARMONISATION OF RECOMMENDATIONS FROM THE JMPR AND JECFA FOR MRLS FOR PESTICIDES WITH BOTH AGRICULTURAL AND VETERINARY USES

Pesticide residues may arise in animal commodities (meat, milk and eggs) either from residues in animal feed or from the application of a compound directly to the animal. The levels of residues in animal commodities are unlikely to be the same from these two sources.

Registration or approval of uses of a pesticide is granted by national registration authorities when the pesticide is used for effective pest control in a manner which leaves no higher residues in food than are unavoidable and the amount of the resulting residue consumed in the food is not harmful to health.

An MRL should be high enough to include residues arising from registered or approved uses supported by valid data. For animal commodities MRLs should be high enough to include residues resulting from registered or approved veterinary uses of the compound as well as those which might occur from residues in feed items.

The Meeting recommended that Codex MRLs should accommodate the maximum residue levels estimated both by the JMPR and JECFA. Where the two estimates do not agree the Codex MRL should be based on the higher one.

The *FAO Manual on the Submission and Evaluation of Pesticide Residues Data* describes in Section 5.3 the principles and practices of the FAO Panel of the JMPR in establishing residue definitions. The definition of residues for enforcement (compliance with MRLs) is the definition relevant to Codex MRLs.

The Meeting recommended that the JMPR and JECFA take note of each other's definitions of residues for enforcement purposes and that these should be harmonized to provide definitions suitable for compliance with Codex MRLs. Usually the wider residue definition would cover both proposals if they were not in agreement.

3.2 NATURE OF FAT SAMPLES IN STUDIES ON FAT-SOLUBLE COMPOUNDS

Section 3.1.5.1 of the *FAO Manual on the Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed* describes the information and data required from livestock transfer (feeding) and external animal treatment studies.

In particular the Manual draws attention to additional requirements for studies on fat-soluble pesticides:

"For fat-soluble pesticides in both feeding and direct animal treatment trials, the fat samples analysed should be fully described because residue levels may vary in fat from several fat depots within the body of the same animal. The fat description should include:

- the nature of the fat (e.g., peri-renal, subcutaneous);
- location in the animal body (if more than one possibility); and
- lipid content (rendered or extracted fat may be assumed as 100% lipid).

Residue levels of fat-soluble pesticides may also depend on the condition of the animal, which should also be recorded."

The Meeting considered further the requirements for animal studies on fat-soluble compounds with a view to ensuring that MRLs are recommended to cover the types of fat which may be sampled in monitoring and compliance programmes. Ideally the types of fat taken in the initial studies should match the types taken by regulatory authorities. In low-fat animals and poultry, where it may not be possible to trim off sufficient fat for residue analysis, the analyst may have to extract fat from the sample tissues.

Reports of metabolism and transfer studies and trials involving external treatment with fat-soluble compounds on cattle, goats and pigs in JMPR Evaluations for 1993-1995 were examined for the recorded descriptions of fat. The results are summarized in Table 1. It is clear that a variety of types of fat were analysed in the studies and trials. In an individual study one or more types of fat may be taken and analysed separately or as a composite. In the past it has been assumed that the levels of residues are approximately the same in the different fat depots within an animal (except at the site of a direct treatment), but this is not necessarily the case.

Table 1. Summary of descriptions of different types of fat classified according to animal and route of intake for studies on fat-soluble pesticides recorded in JMPR Evaluations, 1993-1995.

Animal	Intake	Fa[1]	SC[2]	Abdomen[3]	Renal	Back	Tr[4]	Non-tr[5]	TOTAL
Cow	direct		4	8	9	6	1	1	29
Cow	oral	3	2	3		1			9
Goat	direct								0
Goat	oral	1	1	4	3				9
Pig	direct			1			1	1	3
Pig	oral	1							1
TOTAL		**5**	**7**	**16**	**12**	**7**	**2**	**2**	**51**

[1] Unspecified or composite fat
[2] Subcutaneous fat
[3] Includes omental, peritoneal and mesenteric fat
[4] Fat from treatment site
[5] Fat from non-treatment site

Information was also obtained on the nature of the fat samples taken in monitoring and compliance programmes. At the abattoir there is the option to sample all the different fat depots in a carcase but at later points in the distribution chain the possibilities are limited or the depot sampled may not be known. In practice, any type of fat may be sampled.

The information obtained from feeding and direct treatment studies must allow an MRL to be recommended which is suitable for the various types of fat which may be subsequently sampled by regulatory authorities.

Livestock transfer (feeding) and external animal treatment studies with fat-soluble compounds should provide information on the highest residue levels likely to occur in any fat depot when the directions for registered uses of the pesticide are followed. The highest levels would be the basis for a recommendation for an MRL. In such studies fat samples from the various fat depots need to be analysed separately.

The residue levels of fat-soluble compounds in the fat of lean animals are likely to be higher than in fat animals for the same feeding regime. Ideally in feeding studies the animals should be lean rather than fat.

The Meeting noted that the description of "fat" in some studies is not always clear. It could be taken to mean "trimmable fat" containing moisture and possibly some other tissue or it could mean the lipid portion.

The Meeting recognized that JECFA faced similar problems when evaluating the veterinary uses of fat-soluble compounds, and considered that information should be obtained on the approach used by JECFA for dealing with the issues described above.

The Meeting recommended as follows.

1. In livestock transfer (feeding) studies with fat-soluble pesticides samples of sub-cutaneous, abdominal (omental, peritoneal, mesenteric) and renal fat should be taken from an animal and analysed separately.

2. In external animal treatment studies a sample of the fat at the treatment site, in addition to the three fat types required in the feeding studies specified in recommendation 1, should be taken and analysed separately.

3. In animal studies residue levels should be expressed on the lipid content of the fat (rendered or extracted fat may be assumed to be 100% lipid). The lipid content of the fat in trimmable fat or fatty tissue should also be reported.

4. The CCPR *ad hoc* Working Group on Methods of Analysis and Sampling should include a more precise description of carcase fat in the tables of "Portion of Commodities to which Codex Maximum Residue Limits Apply and which is Analysed." Carcase fat could be taken to mean "trimmable fat" containing moisture and possibly some other tissue or it could mean the lipid portion.

5. In recommending an MRL the JMPR should estimate the maximum residue level which

might occur in any fat depot in the animal, recognizing the possibility that a regulatory authority may take a sample of any type of fat.

6. The recommendations for changed JMPR practices would initially apply only to evaluations of data on new and periodic review compounds.

7. The content and recommendations of this section of the report should be referred to JECFA for information and comment, with the intention of harmonising requirements and procedures relating to the nature of fat samples in studies with fat-soluble compounds.

3.3 ASSESSMENT OF CHRONIC DIETARY RISK OF DITHIOCARBAMATE PESTICIDES

In response to a question raised at the 29th Session of the CCPR, the present Meeting discussed the principles used in assessing the chronic dietary risk of dithiocarbamate pesticides. The dithiocarbamates considered by the JMPR and Codex consist of eight agricultural pesticides which are listed as a group on the basis of a common analytical method for their determination. Residues of ferbam, mancozeb, maneb, metiram, propineb, thiram, ziram, and zineb are all determined by a method that depends upon the generation of carbon disulfide. The Codex MRLs for these pesticides are grouped under the heading Dithiocarbamates (105)'.

After reviewing previous JMPR reports the Meeting concluded that the dithiocarbamate pesticides should be divided into two groups on the basis of toxicity. The ADIs for mancozeb, maneb, metiram, propineb, and zineb are based on thyroid toxicity; the 1993 JMPR allocated a group ADI of 0 - 0.03 mg/kg bw for mancozeb, maneb, metiram, and zineb. The thyroid toxicity of these compounds is mediated by their common metabolite, ethylenethiourea (ETU), and an ADI of 0 - 0.004 mg/kg bw has been allocated to this compound. The 1993 JMPR also allocated ADIs of 0 - 0.007 mg/kg bw to propineb and 0 - 0.0002 mg/kg bw to its metabolite propylenethiourea (PTU).

After reviewing previous JMPR reports on thiram, ferbam, and ziram, the Meeting concluded that their toxicity was similar enough for them to be considered together, but that this group was distinct from the other group of dithiocarbamates since the toxic end-point upon which their ADIs are based is not associated with thyroid toxicity. Ferbam and ziram were evaluated by the 1996 JMPR, when a group ADI of 0 - 0.003 mg/kg bw was allocated. The current ADI of 0 - 0.01 mg/kg bw for thiram was allocated by the 1992 JMPR.

On the basis of these considerations the Meeting recommended that the chronic dietary risk for the two groups of dithiocarbamate pesticides be assessed using STMR levels and other factors, as described in *Guidelines for predicting dietary intake of pesticide residues* (WHO, 1997. For those commodities potentially containing more than one pesticide for which residue data have been accepted by the JMPR, the risk assessment should be based on the pesticide that contributes most to the estimated intake in relation to its ADI.

The Meeting drew attention to the use of data on processing in assessing the 'thyroid-active' dithiocarbamates. Processing food commodities containing residues of these pesticides generally decreases the amount of the parent pesticide and increases that of ETU or PTU. This has clear

implications for risk assessment, in view of the greater toxicity of ETU and particularly PTU. ETU is generally short-lived when applied to plant leaves in plant metabolism studies and it is rapidly degraded by UV radiation[iv]. In supervised trials with ethylenebisdithiocarbamates (EBDCs), the ETU residues in raw agricultural commodities were generally ≤ 0.1 mg/kg or ≤ the LOD of 0.01-0.02 mg/kg. In some cases ETU residues were reported to be an artifact of the analysis, because a small percentage of EBDC residues can be converted to ETU during their determination, especially if the method includes a heating step. The ETU levels in processed commodities depend on the levels of the parent EBDC present at crucial stages during heating. For an overall risk assessment of 'thyroid-active' dithiocarbamates, the Meeting agreed that it is necessary to combine not only the intake of different parent pesticides but also the intake of ETU or PTU. It recommended that an ADI adjustment approach be used, and that an example of this approach should be developed in 1998.

The Meeting recognized that it is difficult to incorporate data on processing into risk assessments carried out at the international level, because data on food consumption are not always available. Processing factors for commodities for which consumption data are not provided by GEMS/Food may be incorporated into risk assessments at the national level as appropriate.

4. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE FOR HUMANS, MAXIMUM RESIDUE LEVELS, AND STMR LEVELS

4.1 ABAMECTIN (177)

TOXICOLOGY

Abamectin (a mixivture containing ≥80% avermectin B1a and ≤20% avermectin B1b) was evaluated toxicologically by the Joint Meeting in 1992 and 1994. An ADI of 0-0.0002 mg/kg bw was allocated in 1994 on the basis of an NOAEL of 0.12 mg/kg bw per day in a multigeneration study of reproductive toxicity in rats, using a safety factor of 500. The increased safety factor was used because of concern about the teratogenicity of the 8,9-*Z* isomer (earlier identified as the Ä-8,9 isomer), which is a photolytic degradation product that forms a variable proportion of the residue on crops. In 1995, the Joint Meeting established a separate ADI of 0-0.001 mg/kg bw for abamectin itself, as the basis for risk assessment when abamectin is used as a veterinary drug and the residue does not contain the 8,9-*Z* isomer. The present Meeting reviewed information that was requested by the 1994 JMPR and reconsidered the decision of the 1995 JMPR.

Data submitted to the 1994 JMPR indicated that the high sensitivity of CF-1 mice to the neurotoxicity of avermectins is associated with P-glycoprotein deficiency in the small intestine and in the capillary endothelial cells of the blood/brain barrier. It was speculated that the heterogeneity of the response in CF-1 mice may explain the absence of a dose-response relationship for maternal toxicity in the studies of teratogenicity. Data submitted to the present Meeting resolved the issue of the variability seen in earlier studies in CF-1 mice.

In a study to establish the LD_{50} in CF-1 mice genotyped for P-glycoprotein expression, similar signs of toxicity were seen in +/+ (homozygous) and +/- (heterozygous) mice. The oral LD_{50} for +/+ mice was 28 mg/kg bw, and that for +/- mice was 14 mg/kg bw. Separate studies indicated an LD_{50} for -/- mice of 0.3-0.4 mg/kg bw. Thus, in CF-1 mice, the oral LD_{50} appears to be related to the genotype for P-glycoprotein.

A four- to five-day study with CF-1 and CD-1 mice given 0.8 mg/kg bw per day resulted in severe toxicity in 17% of the CF-1 mice after the first dose. P-Glycoprotein was not detectable in the brain or jejunum of these mice, except in one mouse which had minimal expression in the brain. Insensitive CF-1 mice showed slight to intense P-glycoprotein staining, and CD-1 mice showed intense P-glycoprotein staining. Oral administration of challenge doses (10 mg/kg bw) to groups of insensitive CF-1 mice after five days of treatment at 0.8 mg/kg bw per day caused slight toxicity, with complete recovery within one to two days. The results indicate severe toxicity in mice of the -/- genotype and variable toxicity in those of the +/- and +/+ genotypes. No toxicity was seen in CD-1 mice, which are probably of the +/+ genotype. These results indicate that the genotype of CF-1 mice with respect to P-glycoprotein expression governs the toxicity of abamectin. There is no evidence that mutations of this genotype occur in CD-1 mice.

8,9-*Z* isomer

Studies of tissue distribution in genotyped CF-1 mice after administration of radiolabelled 8,9-*Z* isomer indicated marked differences according to genotype. In the brain, the levels in -/- mice of each sex were about 60 times those in +/+ mice. By 24 h, the difference was even greater, since clearance occurred in +/+ mice but not in -/- mice. A similar pattern was seen in the testes, with the highest levels in -/- mice. At 24 h, the testicular levels in +/- and +/+ genotype mice were in equilibrium with those in plasma. In plasma, the level of radioalabel was highest in -/- mice, but the differences between the +/+ and -/- genotypes were much less than in the organ systems.

A single oral dose to CD-1 and CF-1 mice resulted in oral LD_{50} values of 220 mg/kg bw for female CD-1 mice and about 20 mg/kg bw for male CF-1 mice. Data on other avermectins indicates no sex difference for acute toxicity. Since the signs fit the pattern for neurotoxicity, it is probable that the low LD_{50} value (i.e. increased susceptibility) in CF-1 mice is related to the accessibility of the target organ to the test material and hence to the presence or absence of P-glycoprotein expression.

A number of studies of developmental toxicity were performed in CF-1 mice. In the first study, the NOAEL for both maternal and developmental toxicity was 0.06 mg/kg bw per day, the highest dose tested. Cleft palate and exencephaly were observed, but the incidence was within historical control limits. A second study showed an NOAEL for maternal toxicity of 0.1 mg/kg bw per day and an LOAEL, based on signs of toxicity, of 0.5 mg/kg bw per day. The NOAEL for teratogenicity was 0.03 mg/kg bw per day, the incidences of cleft palate at doses of 0.1 mg/kg bw per day and above being greater than those in historical controls; however, at 0.1 mg/kg bw per day, cleft palates were seen in only one litter; at 0.5 mg/kg bw per day, the incidence of cleft palate showed clumping within litters. A third study with the 8,9-*Z* isomer was performed in female CF-1 mice which had been screened for sensitivity to abamectin before the start of the study. Sensitive and insensitive female mice were paired with males of unknown sensitivity, and the doses given to sensitive female mice were varied during exposure. Marked effects on sensitive mice occurred at doses above 0.5 mg/kg bw, only 4/18 animals surviving to term. Of these, only one mouse had a live litter. No effects were seen on insensitive mice at doses up to 1.5 mg/kg bw per day; however, cleft palates were observed at all doses between 0.05 and 1.5 mg/kg bw per day. This study demonstrates that the incidence of malformations is not related to maternal toxicity.

Yet another study of developmental toxicity was performed using parental mice of known genotype for the *mdr-1* gene, which encodes for P-glycoprotein expression. This study indicated a relationship between the parental genotype and the incidence of cleft palate: at 1.5 mg/kg bw per day, cleft palate was observed in none of the offspring of +/+ x +/+ crosses, in 12% of those of +/+ male x +/- female crosses, and 58% of those of -/- male x +/- female crosses; one cleft palate occurred in the control +/- x +/- cross and none in the -/- x -/- cross. Genotypic analysis of the fetuses from treated females showed no cleft palates in +/+ mice, 41% in +/- mice, and 97% in -/- mice. Analyses of the placentae for P-glycoprotein showed a correlation with the genotype of the fetus, the levels being highest in +/+ fetuses and absent in -/- fetuses; the +/- control matings yielded a Mendelian distribution of 15 +/+, 32 +/-, and 18 -/- pups. The close relationship between fetal genotype and the presence of P-glycoprotein in the placenta would be expected, since much of the placenta is formed from fetal tissue. The relationship between the incidence of cleft palate and genotype appears to be a reflection of prevention by P-glycoprotein

expression of penetration of the test material through placental membranes.

The presence of placental P-glycoprotein was investigated in+/+ male and +/+ female CF-1 mice. Western blotting of the placentae indicated the presence of P-glycoprotein on day 9 of gestation, the levels increasing with the duration of gestation. Levels present at the time of palatal closure (~ day 15) would be sufficient to hinder placental transfer of the 8,9-*Z* isomer of abamectin. Passage of the radiolabelled isomer across the placenta was investigated after administration to +/- female mice on day 17 of gestation. The maternal plasma levels of radiolabel were variable but maximal 8 h after treatment. The levels of radiolabel in the fetus depended on the fetal genotype, being lowest in +/+ fetuses and highest in -/- fetuses, indicating that blockage of placental transfer depends on genetically controlled expression of placental P-glycoprotein.

A study of developmental toxicity in CD-1 mice treated by gavage with doses of 0, 0.75, 1.5, or 3 mg/kg bw per day of the 8,9-*Z* isomer showed no adverse effects on the maternal mice. The incidences of cleft palate were 0, 2, 1, and 4 (or 0, 0.73, 0.31, and 1.4%) at 0, 0.75, 1.5, and 3 mg/kg bw per day, respectively. These incidences were not dose-related and fell within control incidences seen after oral or intravenous administration of vehicles in the same laboratory. The NOAEL for maternal, embryo-, and fetal toxicity was 3 mg/kg bw per day.

Ivermectin

A multigeneration study in rats given doses of 0.4 mg ivermectin/kg bw per day and above resulted in early mortality of pups *post-partum* and reduced pup body-weight gain. The study was terminated early. A further study at doses of 0.05-0.4 mg/kg bw per day showed no effects, except increased pup mortality in the F_{3a} litters at 0.4 mg/kg bw per day between days 1 and 7 *post-partum*. Postnatal toxicity was assessed in a series of cross-fosterings of newborn pups; toxicity was shown to be due to postnatal, not in-utero, exposure. The postnatal toxicity was further investigated with radiolabelled ivermectin either before or throughout mating and gestation. In the rats dosed *post-partum*, the levels of radiolabel in the plasma were initially low but were comparable to those observed after long-term exposure by day 9 *post-partum*. The levels of radiolabel in the milk were consistently three to four times the plasma levels in both groups, which may reflect mobilization of ivermectin from fatty tissues. In the offspring of parents treated *post-partum*, radioalabel was not detected in plasma on day 1 *post-partum*, but was half that in the long-term group of offspring on days 4 and 6, and equivalent on day 9. The tissue levels in the pups on day 9 were two to three times those in the parents. The plasma:brain ratios of radiolabel in the offspring of both groups were 1 on days 1 and 4 *post-partum* and 2-3 on days 6-9. These data can be interpreted to indicate that the development of the blood/brain barrier in rat offspring is delayed, occurring some time after parturition. The postnatal toxicity observed in rats may be a function of the accessibility of the target organ to the toxin, owing to the late formation of the blood/brain barrier and to possible mobilization of ivermectin from adult fatty tissues.

P-Glycoprotein distribution in adult and young animals

In the immature rat (about six weeks old), P-glycoprotein is present in the brain and in the brush border epithelial cells of the jejunum. In fetal animals (day 20 of gestation), however, minimal P-glycoprotein was detected in the brain, the levels being less than 10% of that in adult animals up to day 14 and then increasing rapidly. No P-glycoprotein was detected in the jejunum of fetal rats or in rats on days 2 or 5 *post-partum;* P-glycoprotein was detectable by day 8 *post-partum*, and the levels increased with time thereafter. These data indicate late expression of P-glycoprotein, occurring some 10-15 days *post-partum*. In non-pregnant adult rats, P-glycoprotein was not observed in the uterus; it was present, however, on the luminal surface of the uterine epithelium in pregnant rats.

P-Glycoprotein was present on the endothelial surface of capillaries in the cerebrum, cerebellum, cerebellar peduncle, and pons of rhesus monkey fetuses. The staining intensity was comparable in all areas of the brain. P-Glycoprotein was also present in the placenta, but none was detected in fetal jejunum. The brain levels of P-glycoprotein in monkey fetuses were comparable to those in the brains of one- to two-year-old rhesus monkeys examined in another study.

In humans, P-glycoprotein was detected in the brain capillaries of fetuses aborted at 28 weeks, but not at earlier gestational ages. The levels found were comparable to that in the adult brain. In human placenta, P-glycoprotein was found in the syncytiotrophoblast microvillus border and in some placental macrophages in the first trimester, but mainly in the placental macrophages at term.

Species sensitivity to avermectins

Increased sensitivity has been seen in CF-1 mice and in Collie dogs. In no other species or strain of animal has increased sensitivity to avermectins been observed. In humans, 50 000 000 doses of 0.2 mg/kg bw ivermectin have been administered for treatment of parasitic diseases, with no report of toxicity directly attributable to the drug. Higher doses (1.6 mg/kg bw) have also not resulted in toxicity. Treatment of humans is not usually required more often than yearly.

The data reviewed on the effects of the 8,9-*Z* isomer on developmental toxicity in the CF-1 mouse clearly indicate a strong relationship between the increased incidence of cleft palate and reduced expression of P-glycoprotein in this strain of mouse. Since the phenomenon is seen only in these animals, the Meeting considered that the use of the results of studies with this strain is not appropriate in establishing the ADI. The NOAEL for teratogenic activity in the CD-1 mouse was 3 mg/kg bw per day.

Data on the avermectins have been used in the overall review of abamectin. In the multigeneration studies of reproductive toxicity of ivermectin and abamectin in rats, the critical adverse effects were those on pups during early lactation. The data on ivermectin indicate that the pup mortality and reduced body-weight gains seen early in lactation may be associated with delayed development of P-glycoprotein expression. Reduced glycoprotein expression in early lactation correlates with the mortality of pups. Young pups are not only more susceptible to abamectin because they lack P-glycoprotein expression, but they are also exposed to levels of abamectin in milk that are two to three times those in maternal plasma. P-Glycoprotein

expression in humans is fully developed by week 28 of gestation. The appropriateness of the multigeneration study of reproductive toxicity of abamectin as the basis for the ADI is, therefore, questionable.

Because of the hypersusceptibility of rats postnatally, the Meeting determined that a reduced interspecies safety factor would be appropriate for establishing an ADI. A safety factor of 50 was therefore applied to the NOAEL from the multigeneration study in rats (0.12 mg/kg bw per day) to give an ADI of 0-0.002 mg/kg bw, which is supported by the NOAEL of 0.24 mg/kg bw per day in the one-year study in dogs, applying a safety factor of 100. A single ADI for both abamectin and its 8,9-Z isomer was deemed to be appropriate, since the potential teratogenicity of the isomer has been satisfactorily explained.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxicological effect

Abamectin

Mouse: 4 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 1.5 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
0.12 mg/kg bw per day (two-generation study of reproductive toxicity)

Dog: 0.25 mg/kg bw per day (one-year study of toxicity)

8,9-*Z* isomer

Mouse: 3 mg/kg bw per day (study of developmental toxicity in CD-1 mice)

Estimate of acceptable daily intake for humans (sum of abamectin and 8,9-*Z* isomer)

0-0.002 mg/kg bw

Studies that would provide information useful for the continued evaluation of the compound

Further observations in humans, possibly involving repeated exposure

RESIDUE AND ANALYTICAL ASPECTS

Abamectin was first evaluated at the 1992 JMPR and subsequently in 1994. MRLs have been recommended for a number of crops and animal commodities.

The Meeting received information on current registered uses, methods of analysis and data on residues in supervised trials on the additional crops apples, potatoes and hops as well as new trials on pears, cucurbits, lettuce and tomatoes. Processing data were available for apples, pears,

potatoes and hops.

The predominant residues from the use of abamectin on crops are avermectin B_{1a}, avermectin B_{1b} and the photoisomers 8,9-*Z*-avermectin B_1 (B_{1a} and B_{1b}) produced during exposure to sunlight. Analytical methods that measure the components of the residue rely on HPLC separation and fluorescence detection of derivatives formed by converting the cyclohexene ring to an aromatic ring. The abamectin residue appears as two peaks on the chromatogram (B_{1a} and its photoisomer in one peak and B_{1b} and its photoisomer in the other). The LOD for each peak is in the range 0.002-0.005 mg/kg.

Abamectin residues were shown to be stable in samples of fresh and dried hops during freezer storage for the periods tested (150-190 days).

The Meeting noted that the definition proposed by JECFA (1997) for residues in the liver, kidney and fat of animals subject to veterinary treatment with abamectin does not include the 8,9-*Z*- isomer *(Ä*-8,9- isomer), because it is not present in animal tissues when abamectin is used directly on the animal. However, residues in animal tissues arising from residues in animal feed would include the 8,9-*Z*- isomer. The Meeting agreed that the wider definition (including the 8,9-*Z*- isomer) was appropriate for a laboratory carrying out enforcement or monitoring analyses because the analyst would not know whether the residue in the animal originated only from veterinary treatment or also from the feed. The wider definition accommodates both situations.

Inclusion or exclusion of avermectin B_{1b} from the definition of the residue is a matter of judgement. In many crop situations B_{1b} is present at approximately 10% of the total residue and the analytical methods measure B_{1a} and B_{1b} by the same procedure so B_{1b} results are always available and may as well be used.

Avermectin B_{1b} forms a photoisomer 8,9-*Z*-avermectin B_{1b} in sunlight in the same way as avermectin B_{1a} does. The studies of photolysis were with avermectin B_{1a}, so when the JMPR reviewed the studies in 1992 the possibility of 8,9-*Z* avermectin B_{1b} being produced was not taken into account. In practice the contribution of 8,9-*Z* avermectin B_{1b} to the residue will be small but it should be recognized that the HPLC measurement of avermectin B_{1b} residues includes any 8,9-*Z* avermectin B_{1b}. The Meeting agreed to revise the definition of the residue accordingly, and recommended the following definition for compliance with MRLs and for the estimation of dietary intake.

Sum of avermectin B_{1a}, avermectin B_{1b}, 8,9-Z avermectin B_{1a} and 8,9-Z avermectin B_{1b}.

The Meeting received data from supervised residue trials on apples, pears, cucumbers, melons, summer squash, tomatoes, lettuce, potatoes and hops.

The B_{1b} component, when its residues were measurable, was consistently about 10% or less of the total residue. For the purposes of evaluation, when B_{1a} was positively detected and B_{1b} was not detectable the total residue was calculated by taking the undetectable residue to be zero.

When both components in a trial were not detectable (ND) the total residue was taken as below the limit of detection. A residue reported as NQ (not quantifiable, detected but below the

limit of determination LOD) is treated as equal to the LOD when it is to be added to a measurable residue.

The method of calculating the total residue for various situations is illustrated by the examples below.

B_{1a}	B_{1b}	Total residue
0.013	NQ (>0.001 but <0.002)	0.015
0.006	ND (<0.001)	0.006
NQ	ND	<0.002
ND	ND	<0.001

Abamectin is registered for single applications on apples in Australia at 0.014 kg ai/ha with harvest after an interval of 14 days. In three trials corresponding to this use pattern the abamectin residues were <0.002, 0.003 and 0.005 mg/kg.

Abamectin is permitted for use on pome fruit in New Zealand with one application at 0.027 kg ai/ha and a PHI of 14 days. Abamectin residues on apples were 0.004 and 0.007 mg/kg in two New Zealand trials where GAP was followed except that two applications were made instead of one.

Abamectin is registered in the USA for two applications on apples at a rate of 0.026 kg ai/ha with harvest 28 days after the final application. In 14 US trials according to these conditions abamectin residues in rank order (median underlined) were <0.001 (2), <0.002 (3), 0.002, 0.003 (4), 0.004, 0.006, 0.007 and 0.012 mg/kg.

The residue data from Australia, New Zealand and the USA appear to be from one population and can therefore be combined. The residues of abamectin in apples in rank order in the 19 trials (median underlined) were <0.001 (2), <0.002 (4), 0.002, 0.003 (5), 0.004 (2), 0.005, 0.006, 0.007 (2) and 0.012 mg/kg.

The Meeting estimated a maximum residue level of 0.02 mg/kg and an STMR level of 0.003 mg/kg for abamectin in apples.

In the USA abamectin is registered for use on pears at 0.013-0.026 kg ai/ha with two applications permitted at the higher rate and a 28-day PHI. Data from four US trials were provided. The results of supervised trials on pears had previously been reported to the 1992 JMPR. A number of residue decline trials on pears in the USA had shown that the typical half-life was approximately 18 days. At such a rate residues at harvest 21 and 37 days after the final treatment would be ±30% of those at 28 days. The range of pre-harvest intervals for acceptance of the residues was therefore taken as 21-37 days. Abamectin residues in pears from the four trials according to US GAP were 0.004, 0.006, 0.009 and 0.011 mg/kg.

The 1992 monograph recorded one pear trial according to Argentinian GAP, (abamectin <0.005 mg/kg), one according to French GAP (<0.002 mg/kg) and four according to Italian GAP (<0.002 and <0.005 (3) mg/kg).

The residues in the trials in different countries appear to be of the same order, giving residues

in rank order (median underlined) of <0.002 (2), 0.004, <0.005 (4), 0.006, 0.009 and 0.011 mg/kg.

The Meeting estimated a maximum residue level for abamectin in pears of 0.02 mg/kg, to replace the previous estimate of 0.01* mg/kg, and an STMR level of 0.005 mg/kg.

In the USA melons may be treated with abamectin at 0.011-0.021 kg ai/ha on three occasions at the higher rate and harvested 7 days after the final treatment. Abamectin residues were not detectable (<0.002 mg/kg) in 9 trials in the USA on cantaloupes according to US GAP, except that there were 4 or 5 applications instead of 3, or in two trials on watermelons under the same conditions. Because the use patterns are the same, watermelons and melons can be evaluated together.

Melons may be treated with abamectin three times at rates up to 0.022 kg ai/ha and harvested three days after the final application according to the registered use in Spain. Abamectin residues were not detected (<0.002 mg/kg) in cantaloupes treated according to Spanish GAP, except that there were four applications, in two glasshouse trials in Spain. Three trials on cantaloupe in France with the same treatment yielded residues of <0.002, <0.005 and <0.005 mg/kg.

Trials on cantaloupes in Brazil and Mexico and on honey-dew melons in Mexico could not be evaluated because there was no information on corresponding GAP. In the Brazilian trials the edible pulp was analysed for abamectin and no residues were detected in any samples in any trial, suggesting that abamectin residues are probably absent from the edible parts of melons.

In summary abamectin residues in melons from trials according to GAP were <0.002, <0.005 and <0.005 mg/kg in France, <0.002 mg/kg (2)) in Spain, <0.002 (9) mg/kg in the USA and <0.002 mg/kg (2) in watermelons in the USA. The residues in melons and watermelons in rank order were <0.002 (14) and <0.005 (2) mg/kg.

The Meeting estimated maximum residue levels of 0.01* mg/kg as being a practical limit of determination, and an STMR level of 0.002 mg/kg, for abamectin in melons and watermelons.

Abamectin is registered for use in the USA on cucumbers and squash at 0.011-0.021 kg ai/ha with three applications at the higher or six at the lower rate, and harvest 7 days after the final treatment. In four US trials on cucumbers at 0.021 or 0.022 kg ai/ha, but with four applications instead of three, residues were undetectable in three trials (<0.002 mg/kg) and below the LOD in the other (<0.005 mg/kg). In four US trials on zucchini (summer squash) under the same conditions no abamectin residues were detectable (<0.002 mg/kg).

Mexican trials on cucumbers and pickling cucumbers could not be evaluated because no information on relevant GAP was available.

The registered use of abamectin on glasshouse cucumbers in Germany permits 5 applications of 0.023 kg ai/ha with harvest three days after the final application. Treatment is not permitted between November and February. Two French trials according to this use pattern were recorded in the 1992 monograph. The resultant abamectin residues were <0.002 and <0.005 mg/kg. A third trial with applications during October and November produced a residue of 0.034 mg/kg, but the conditions were no longer according to GAP.

GAP for abamectin on cucumbers in Spain permits three applications at 0.022 kg ai/ha with harvest three days after the last. Two glasshouse trials in Spain and three trials in Italy (one glasshouse) according to this use pattern but with 4 or 5 applications were recorded in the 1992 monograph. The residues were <0.002, <0.005 (2), 0.006 and 0.008 mg/kg.

GAP for glasshouse cucumbers in The Netherlands allows 5 applications of 0.023 kg ai/ha and harvest three days after the final application. In two trials on cucumbers under these conditions the residues were 0.007 and 0.008 mg/kg, as recorded in the 1992 monograph.

In summary, the residues in cucumbers from trials according to GAP were <0.002 (3) and <0.005 mg/kg in the USA, <0.002 and <0.005 mg/kg in France, <0.002, <0.005 (2), 0.006 and 0.008 mg/kg in Spain and Italy, and 0.007 and 0.008 mg/kg in The Netherlands. The residues in rank order (median underlined) were <0.002 (5), <u>0.005</u> (4), 0.006, 0.007 and 0.008 (2) mg/kg.

The Meeting estimated a maximum residue level for abamectin in cucumbers of 0.01 mg/kg, to replace the previous estimate of 0.05 mg/kg, and an STMR of 0.005 mg/kg.

The four trials on summer squash in the USA were evaluated with the support of the four on cucumbers. Abamectin residues from the 8 trials were <0.002 (7) and <0.005 mg/kg.

The Meeting estimated a maximum residue level for abamectin on summer squash of 0.01* mg/kg as being a practical limit of determination, and an STMR of 0.002 mg/kg.

Abamectin is registered for four applications to glasshouse <u>tomatoes</u> in The Netherlands at 0.023 kg ai/ha with a PHI of three days. Abamectin residues in tomatoes from trials which complied with GAP were 0.007 (2), 0.009, 0.012 (2) and 0.017 mg/kg. Two of the tomato trials in The Netherlands reported in the 1992 monograph (refs 211 and 212) were not according to current GAP because applications were made during the months of November and December. Current GAP restricts the treatment of glasshouse tomatoes to the months of March to October when photodegradation of abamectin residues is sufficient. Two other trials (refs 217 and 218) were according to current GAP because abamectin was applied in May and June. The residues from these two trials were 0.008 and 0.005 mg/kg.

GAP in Argentina permits 9 applications of abamectin at 0.022 kg ai/ha to tomatoes with a 3-day PHI. In the three trials with conditions close to GAP (0.020-0.028 kg ai/ha and 5-9 applications) recorded in the 1992 monograph the residues were <0.002 (2) and <0.005 mg/kg.

In Brazil abamectin may be applied to tomatoes at 0.022 kg ai/ha with harvest three days after the final application. Three Brazilian trials recorded in the 1992 monograph were close to these conditions, with residues of <0.005 (2) and 0.017 mg/kg.

Three French trials recorded in 1992 were evaluated according to German GAP (5 applications of 0.023 kg ai/ha applied to glasshouse tomatoes with harvest three days after the final application). Tomatoes were treated 10 times in one trial, but it was evaluated because residues apparently disappeared quickly and the number of applications would not influence the final residue. The residues were <0.002 (2), and <0.005 mg/kg.

Two Italian trials recorded in 1992 complied with the Italian application rate (0.022 kg ai/ha) and PHI (7 days), but there were ten applications instead of two. The results were again considered acceptable because the residues were disappearing quickly. The residues in both trials were <0.002 mg/kg.

In Spain abamectin may be used on tomatoes at 0.022 kg ai/ha with a PHI of three days. The residues in tomatoes from four trials recorded in the 1992 monograph with application rates in the range 0.015-0.027 kg ai/ha were <0.005 (3) and 0.009 mg/kg.

GAP in the USA specifies three applications of 0.021 kg ai/ha and harvest 7 days after the final application. Eighteen US trials are recorded in the 1992 monograph at this application rate and a PHI of 7 days or less, but with 8-12 applications. The residues had usually disappeared within a few days so it is unlikely that early applications had any influence on the final residues. The residues were <0.002 (13), <0.005 (4) and 0.005 mg/kg.

In summary, the residues in tomatoes from trials according to GAP were 0.005, 0.007 (2), 0.008, 0.009, 0.012 (2) and 0.017 mg/kg in The Netherlands, <0.002 (2) and <0.005 mg/kg in Argentina, <0.005 (2) and 0.017 mg/kg in Brazil, <0.002 (2) and <0.005 mg/kg in France, <0.002 (2) mg/kg in Italy, <0.005 (3) and 0.009 mg/kg in Spain and <0.002 (13), <0.005 (4) and 0.005 mg/kg in the USA. The residues in rank order (median underlined and Netherlands results in bold) were <0.002 (19), <0.005 (11), 0.005, **0.005**, **0.007 (2)**, **0.008,** 0.009**, 0.009, 0.012 (2), 0.017** and 0.017 mg/kg.

The residues in The Netherlands appear to belong to a different population from the others, with a median of 0.0085 mg/kg.

The Meeting estimated a maximum residue level for abamectin in tomatoes of 0.02 mg/kg, the same as the previous estimate, and an STMR of 0.0085 mg/kg.

GAP in The Netherlands permits four applications of abamectin to lettuce at 0.014 kg ai/ha with harvest 14 days after the final application, but only from 1 March to 1 November. In four glasshouse trials in The Netherlands according to GAP the residues in head lettuce were 0.016, 0.025, 0.029 and 0.029 mg/kg.

Abamectin may be used four times on lettuce in France at 0.009 kg ai/ha with harvest 7 days after the final application. In three French trials where the application rate was approximately 25% higher than this, but within the acceptable range for evaluation, the residues were <0.001, 0.004 and 0.023 mg/kg.

In Spain abamectin may be applied three times to lettuce at 0.022 kg ai/ha with harvest 14 days after the final application. In two Spanish and three French trials at this rate and PHI, but with four applications instead of three, the abamectin residues were <0.002, 0.005, 0.013, 0.028 and 0.040 mg/kg.

Trials on lettuce in the USA recorded in the 1992 monograph could not be evaluated because the number of applications, 6-10, was excessive for a sometimes persistent residue compared with the three applications permitted.

In summary, the residues in head lettuce from trials according to GAP were 0.016, 0.025, 0.029 and 0.029 mg/kg in The Netherlands, <0.001, 0.004 and 0.023 mg/kg in France and <0.002, 0.005, 0.013, 0.028 and 0.040 mg/kg in Spain. The residues in rank order (median underlined) were <0.001, <0.002, 0.004, 0.005, 0.013, 0.016, 0.023, 0.025, 0.028, 0.029, 0.029 and 0.040 mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg, and an STMR of 0.020 mg/kg for abamectin in head lettuce.

Only two trials according to GAP were available on leaf lettuce (in Spain). The residues were <0.002 and 0.002 mg/kg. The Meeting agreed that two trials were insufficient and that results could not be extrapolated from head lettuce to leaf lettuce.

Abamectin is registered in Brazil for foliar application to potatoes at 0.018 kg ai/ha with a PHI of 14 days. Abamectin was not detected (<0.005 mg/kg) in three trials at the GAP rate and three at twice that rate in potatoes harvested 0, 3 and 7 days after the last of four applications.

In the USA three foliar applications to potatoes are permitted at 0.021 kg ai/ha with harvest 14 days after the last. No abamectin residues were detected (<0.002 mg/kg) in 11 trials with treatment at 0.021 kg ai/ha or in 9 trials at the exaggerated rate of 0.11 kg ai/ha.

The Meeting estimated a maximum residue level for abamectin in potatoes of 0.01* mg/kg as being a practical limit of determination. Because no residues were detected in a number of trials, some of which were at exaggerated rates, the Meeting estimated an STMR level of 0 mg/kg.

In the USA abamectin is registered for foliar use on almonds with two applications at 0.014-0.028 kg ai/ha and harvest 21 days after the second. Residues were not detected (<0.002 mg/kg) in almonds from 6 US trials according to maximum US GAP and recorded in 1992, or from four additional trials at a double rate.

The residues on the almond hulls from the six US trials reported in 1992 in rank order (median underlined) were 0.016, 0.016, 0.033, 0.047, 0.059 and 0.077 mg/kg.

The Meeting estimated a maximum residue level for abamectin in almonds of 0.01* mg/kg as being a practical limit of determination and, because no residues were detected in the trials at normal and double rates, an STMR of 0 mg/kg. The Meeting also estimated maximum residue and STMR levels for abamectin on almond hulls of 0.1 mg/kg and 0.040 mg/kg respectively.

GAP in the USA for walnuts is the same as for almonds. Abamectin residues were not detected (<0.002 mg/kg) in walnuts from six US trials recorded in 1992 according to the maximum US application rate but harvested after 14 days, or in those from four other trials at a double rate.

The Meeting estimated a maximum residue level for abamectin in walnuts of 0.01* mg/kg as being a practical limit of determination, and an STMR of 0 mg/kg.

Abamectin is registered for use on hops in Germany and the USA with two applications of 0.023 and 0.022 kg ai/ha respectively and a PHI of 28 days. The residues in dry hops from 12

German and 4 US trials according to GAP in rank order (median underlined) were <0.003 (4), <0.005, 0.011, 0.012, 0.015, 0.017, 0.022 (2), 0.023, 0.025, 0.030, 0.062 and 0.086 mg/kg.

The Meeting estimated maximum residue and STMR levels of 0.1 mg/kg and 0.016 mg/kg respectively.

A feeding study on dairy cows recorded in the 1992 monograph showed that residues in the milk, liver, muscle, fat and kidney did not exceed 0.004, 0.020, 0.002, 0.014 and 0.005 mg/kg respectively at a feeding level of 0.1 ppm. The residues in animal commodities arising from the consumption of abamectin-treated almond hulls should not exceed current draft MRLs.

Information on the fate of abamectin residues during the processing of apples, pears, potatoes and hops was provided.

Abamectin residues were not detectable in the juice or sauce produced from treated apples, but were concentrated in pomace, a result expected from the nature of abamectin as a surface residue. The calculated processing factors were <0.062 for juice, <0.12 for apple sauce and 17.3 for dry pomace. The "<" signs indicate derivation from the LOD for abamectin in the processed commodities.

The supervised trials median residues for the processed commodities (STMR-Ps) calculated from the processing factors and the STMR level for apples (0.003 mg/kg) are apple juice 0.00019 mg/kg, apple sauce 0.00036 mg/kg and dry apple pomace 0.052 mg/kg.

Abamectin residues were not detectable in pear halves or pear purée produced from treated pears. The calculated processing factors were canned pear halves <0.046 and pear purée <0.048.

The STMR-Ps for the processed commodities calculated from the processing factors and the STMR for pears (0.005 mg/kg) were canned pear halves 0.00023 mg/kg and pear purée 0.00024 mg/kg.

The processing study on potatoes could not be completed because no abamectin residues were detectable in the treated potatoes.

Abamectin-treated hops were processed by exhaustive hexane extraction of dry hops to produce a solvent extract and spent hops. The extract contains flavour components and is used in the brewing industry while the spent hops become a minor feed commodity. Most of the abamectin residues remained in the spent hops. The mean processing factor from dry hops to spent hops was 0.71.

The mean processing factor for abamectin residues during the conversion of fresh hops to dry hops was 4.09, suggesting that approximately 80% of the abamectin survived the drying process.

The 1992 JMPR recommended MRLs for cattle meat and offal of 0.01* and 0.05 mg/kg respectively on the basis of possible abamectin residues in animal feed commodities.

On the basis of veterinary uses the 1996 JECFA recommended MRLs for residues defined as avermectin B_{1a} of 100 ìg/kg for cattle fat and liver, and 50 ìg/kg for kidney.

The Meeting agreed that MRLs should accommodate both agricultural and veterinary uses where the necessary information is available, and agreed to replace the recommendation for edible offal with recommendations for MRLs in fat, liver and kidney in line with the levels recommended by JECFA.

It is not clear whether the current recommendation for cattle meat (0.01 mg/kg) would accommodate veterinary uses. The Meeting recommended that JECFA be requested to suggest an appropriate maximum residue level in cattle meat, and to consider accepting the broader definition of the residue to accommodate the residues which occur as a result of agricultural as well as veterinary uses.

4.2 AMITROLE

TOXICOLOGY

Amitrole was first considered by the Joint Meeting in 1974. A conditional ADI of 0-0.00003 mg/kg bw was established at that time, which was extended by the 1977 Meeting after consideration of additional data on the basis of an NOAEL of 0.025 mg/kg bw per day in a three-month study in rats and a 1000-fold safety factor. In 1993, amitrole was re-evaluated within the CCPR periodic review programme, and the Meeting established a temporary ADI of 0-0.0005 mg/kg bw on the basis of an NOAEL of 0.5 mg/kg bw per day in a two-year study in rats and a 1000-fold safety factor because of the inadequacy of the database. The 1993 Meeting requested submission of the results of a two-generation study of reproductive toxicity in rats, a one-year study in dogs, a study of developmental toxicity after oral administration in rabbits, and a study of metabolism in rats. The results of these studies and of a study of effects on the thyroid gland of pregnant rabbits were reviewed at the present Meeting.

In rats, amitrole was rapidly absorbed, approximately 90% of the administered dose being eliminated within 48 h. The primary route of elimination was the urine, which accounted for over 87% of the administered dose; faecal elimination accounted for less than 6% of the dose and volatile metabolites represented only 0.1%. Forty-eight hours after dosing, the tissue residues amounted to less than 3% of the dose, with the majority found in the liver. Most of the radiolabel (62-90%) was excreted as the parent compound. Several metabolites were present at very low concentrations, a mercapturic acid derivative being predominant (2.1-7.3% of the administered ^{14}C).

In a one-year study of toxicity, dogs were fed diets containing 0, 10, 500, or 1500 ppm amitrole. At 500 ppm (equal to 13 mg/kg bw per day) and above, the levels of tri-iodothyronine and thyroxine were reduced and there were increases in the incidence of rough coats, in thyroid weights, and in the frequency of lesions of the thyroid (follicular-cell hyperplasia, capsular fibrosis, vasculitis, and dilatation of the vasculature). In addition, ectopic thyroids with follicular hyperplasia and capsular fibrosis were noted, and changes in the pituitary (hyperplasia and hypertrophy) were evident in both males and females. At 1500 ppm (equal to 32 mg/kg bw per day), both males and females were anaemic and had increased platelet counts, decreased food intake, decreased brain weights (with histopathological lesions), and neurological effects. At this dose, males also had decreased weight gain, increased lactate dehydrogenase and cholesterol

levels, decreased heart weights, and decreased P- and R-wave amplitudes. The NOAEL was 10 ppm, equal to 0.29 mg/kg bw per day.

In a two-generation study of reproductive toxicity, rats were fed diets containing 0, 0.5, 2, 15, or 110 ppm amitrole. At 15 ppm (equal to 0.9 mg/kg bw per day), the only effect observed was a slight increase in the severity of some histopathological changes in the thyroid, including small follicles, decreased colloid content, and follicular epithelial hypertrophy. Parental toxicity at 110 ppm was severe and was characterized by mortality, clinical signs, considerably decreased weight gain, thyroid effects (increased relative thyroid weights, follicular epithelial hyperplasia, and vascular ectasia), changes in relative organ weights (increased weights of pituitary, testes, epididymides, seminal vesicles, prostate, uterus, spleen, and kidneys and decreased weights of ovaries, adrenal glands, and liver), and histopathological lesions in the liver, adrenal glands, kidneys, and numerous reproductive tissues. In pups, the only observations were increased thyroid weights with accompanying histopathological lesions. The effects on reproduction included decreased mating and fertility indices, increased gestation length, and decreased prenatal survival, litter size, pup body weight, and viability. The NOAEL for systemic toxicity was 2 ppm, equal to 0.12 mg/kg bw per day. This value is supported by the findings of the range-finding study, in which enlarged, reddened thyroids and decreased colloid content were noted at 10 ppm (equal to 0.62 mg/kg bw per day). The NOAEL for reproductive toxicity was 15 ppm, equal to 0.9 mg/kg bw per day.

In a study of developmental toxicity, rabbits were treated with 0, 5, 20, or 80 mg/kg bw per day amitrole on days 6-18 of gestation. At 80 mg/kg bw per day, maternal food consumption and body-weight gain were reduced during the treatment period. Male fetal body weights and mean litter weights were reduced at 80 mg/kg bw per day. Clinical chemistry was not evaluated in this study. The NOAEL for maternal and fetal toxicity was 20 mg/kg bw per day.

In a special study to further characterize toxicity in pregnant rabbits, the animals were treated with 0, 5, 20, or 80 mg amitrole/kg bw per day on days 6-18 of gestation and were killed on day 19 of gestation. At 20 and 80 mg/kg bw per day, albumin and protein levels were decreased and absolute and relative liver weights were decreased. At 80 mg/kg bw per day, there were reductions in food consumption, increased creatine kinase levels, decreased tri-iodothyronine and thyroxine levels, and thyroid follicular-cell hypertrophy. The NOAEL for maternal toxicity was 5 mg/kg bw per day.

The results of these supplemental studies correlate well with the results of the studies reviewed by the1993 JMPR, showing that the thyroid is the primary target organ of amitrole. Contrary to the conclusions of the 1993 JMPR, the results demonstrate that amitrole is also goitrogenic in the dog. In the one-year study in dogs reviewed previously, no effects on the thyroid were noted at a dose of 12.5 mg/kg bw per day. In the current one-year study, however, there were extensive effects at 13 mg/kg bw per day.

The rat was the most sensitive species, the NOAELs being 2 ppm in both the two-generation study of reproductive toxicity (equal to 0.12 mg/kg bw per day) and the 90-day dietary study (equivalent to 0.1 mg/kg bw per day), on the basis of histopathological changes in the thyroid. The Meeting noted that the rat is more sensitive to the development of thyroid hyperplasia and subsequent neoplasia after exposure to goitrogenic compounds than are humans. Therefore, a smaller safety factor (50) to take into account the lower uncertainty of interspecies extrapolation

was used, giving an ADI of 0-0.002 mg/kg bw. This ADI provides a 150-fold margin of safety over the NOAEL of 0.29 mg/kg bw per day in the one-year study in dogs.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION
(based on studies from this and earlier JMPR evaluations)

Levels that cause no toxic effect

Mouse: 10 ppm, equivalent to 1.5 mg/kg bw per day (18-month study of toxicity and carcinogenicity)

Rat: 10 ppm, equivalent to 0.5 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
100 mg/kg bw per day (maternal and fetal toxicity in a study of developmental toxicity)
2 ppm, equal to 0.12 mg/kg bw per day (parental toxicity in a two-generation study of reproductive toxicity)

Rabbit: 5 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
20 mg/kg bw per day (fetal toxicity in a study of developmental toxicity)

Hamster: 10 ppm, equivalent to 1 mg/kg bw per day (18-month study of toxicity)

Dog: 10 ppm, equal to 0.29 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.002 mg/kg bw

Studies that would provide information useful for the continued evaluation of the compound

1. Clarification of the genotoxic potential of amitrole (e.g. DNA adducts *in vivo*)

2. Further observations in humans.

Toxicological criteria for estimating guidance values for dietary and non-dietary exposure to amitrole

Human exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	**Error!** Oral, acute toxicity, rat	LD_{50} > 2500 mg/kg bw
	Dermal, acute toxicity, rat	LD_{50} > 2500 mg/kg bw
	Inhalation, acute toxicity, 4 h, rat	LC_{50} > 439 mg/l
	Dermal, irritation, rabbit	Minimally irritating

Human exposure	Relevant route, study type, species	Results, remarks
	Ocular, irritation, rabbit	Mildly irritating
	Dermal, sensitization, guinea- pig	Moderately sensitizing (Magnusson-Kligman test) Non-sensitizing (Klecak open epicutaneous test)
Medium-term (1-26 weeks)	Repeated oral, 2-4 weeks, rat	NOAEL = 3 mg/kg bw per day: effects on the thyroid, food consumption and body weight
	Repeated oral, drinking-water, 4 weeks, rat	NOAEL = 10 mg/l water: decreased weight gain, enlarged thyroids
	Repeated oral, 6-13 weeks, rat	NOAEL = 0.1 mg/kg bw per day: effects on the thyroid
	Repeated dermal, 3 weeks, rabbit	NOAEL = 100 mg/kg bw per day (highest dose tested)
	Repeated inhalation, 4 weeks, rat	NOAEL = 0.1 mg/l: effects on the thyroid
	Repeated oral, special maternal toxicity, rabbit	NOAEL = 5 mg/kg bw per day: decreased liver weights and protein/albumin levels
	Repeated oral, developmental toxicity, rabbit	NOAEL = 20 mg/kg bw per day: developmental toxicity
	Repeated dermal, developmental toxicity, rabbit	NOAEL = 1500 mg/kg bw per day: maternal and developmental toxicity
	Repeated oral, reproductive toxicity, rat	NOAEL = 0.12 mg/kg bw per day (systemic): effects on the thyroid
		NOAEL = 0.9 mg/kg bw per day: reproductive toxicity
Long-term (≥1 year)	Repeated oral, 1 year, dog	NOAEL = 0.29 mg/kg bw per day: effects on the thyroid
	Repeated inhalation, intermittent dosing, 2 years, carcinogenicity, rat	LOAEL = 50 µg/l (lowest dose tested): effects on the thyroid

4.3 BIFENTHRIN (178)

RESIDUE AND ANALYTICAL ASPECTS

Information was provided to the 1995 and 1996 Meetings on the use of bifenthrin as a stored grain protectant. The 1996 Meeting recommended MRLs for wheat and milled commodities related to this use. It was suggested at the CCPR that the CXLs for animal products might be affected by revised GAP for cereals.

The 1996 JMPR listed the following information as desirable in connection with the use of bifenthrin as a grain protectant.

Validation of the analytical method for recoveries of bifenthrin residues from bread at the levels occurring in practice and at the LOD.

Information on the degree of extraction of bifenthrin residues from bread by the current procedure.

Information on national registrations and MRLs for bifenthrin covering its use on stored grain.

Information on the fate of bifenthrin during the commercial malting of barley treated with it post-harvest. The studies should simulate the commercial process. (From 1995 JMPR).

No additional information was available on the analytical method for bifenthrin residues in bread.

Croatia and Romania have issued temporary registrations for the treatment of stored grain with bifenthrin.

The results of a barley malting trial were made available. It suggested that bifenthrin residues decreased substantially during the malting process but the study was defective because no barley samples were taken for analysis at the time the malting commenced.

The Meeting received additional data from trials with bifenthrin on stored grain. Bifenthrin residues are generally persistent during storage.

The recommendations of the 1992 JMPR for MRLs for bifenthrin in cattle fat, kidney, liver, meat and milk were based on the assumption that levels of bifenthrin in the diet of cows were unlikely to exceed 2 ppm, on the basis of a feeding study in which bifenthrin was fed at 5 ppm for 28 days. The 1995 Meeting recommended MRLs of 0.5 mg/kg in wheat and 2 mg/kg in wheat bran because of the post-harvest use on wheat. Because these levels do not exceed the level of 2 ppm in the feed on which the 1992 recommendations were based no change to the draft MRLs for cattle commodities is needed.

In a study of metabolism in laying hens (1992 JMPR) bifenthrin constituted 51.5% of the total residue in abdominal fat of 1.0 mg/kg produced by a feeding level of 40 ppm. In a feeding study on laying hens also reported in 1992 birds were fed for 28 days at 0.25 ppm. Total residues at the limit of detection of 0.01 mg/kg were detected only in fat, suggesting that the residue of bifenthrin in fat was 0.005 mg/kg. Bifenthrin residues in the eggs were 0.002-0.004 mg/kg.

The current CXLs for bifenthrin in chicken fat and the fat of chicken meat are 0.05* mg/kg, which should be adequate for a feed level of 2.5 ppm bifenthrin if the proportionality between levels in the feed and fat is the same as in the trial. The current CXL for bifenthrin in eggs is 0.01* mg/kg, which should be adequate for a feed level of 0.6-1.2 ppm bifenthrin.

The draft MRL for bifenthrin in wheat (to cover post-harvest use) is 0.5 mg/kg, and the STMR is 0.255 mg/kg. The current CXLs for chicken eggs, fat, meat and edible offal should be adequate for chickens consuming bifenthrin-treated wheat, which can be a major part of a poultry diet.

The 1996 Meeting estimated maximum residue and STMR levels for bifenthrin in bran produced from post-harvest-treated wheat of 2 and 0.89 mg/kg respectively. Bran may constitute 50% of the poultry diet; at this level the CXLs for chicken fat, meat and offal should be adequate. The CXL for eggs is probably adequate. It is at the LOD and its adequacy depends on assumptions about the proportion of bran in the poultry diet.

The Meeting made no recommendations to change the existing CXLs or draft MRLs for bifenthrin.

The Meeting noted that the data submitted had not provided the information which the 1995 and 1996 Joint Meetings needed to recommend MRLs for stored grains, except wheat, and their products.

Future submissions of data should meet the requirements of the *FAO Manual on the Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed.* The studies should be valid and supply the information listed in the 1995 and 1996 Evaluations.

FURTHER WORK OR INFORMATION

Desirable

1. Validation of the analytical method for recoveries of bifenthrin residues from bread at the levels occurring in practice and at the LOD.

2. Information on the degree of extraction of bifenthrin residues from bread by the current procedure.

3. Information on national registrations and MRLs for bifenthrin covering its use on stored grain.

4. Valid studies on the fate of bifenthrin during the malting of barley treated with it post-harvest. The studies should simulate the commercial process.

4.4 CAPTAN (007)

RESIDUE AND ANALYTICAL ASPECTS

Captan was extensively reviewed in 1994 and recommendations were made for new and revised MRLs for a number of fruits, and for tomatoes. Information was made available to the present Meeting on GAP and supervised trials in the USA on apples, cherries, grapes, nectarines, pears, plums and strawberries. The residue data were evaluated together with the relevant data evaluated in 1994 to produce revised recommendations.

MRLs for captan are for residues defined as captan. Captan breaks down under some conditions to form THPI (1,2,3,6-tetrahydrophthalimide) and when a raw agricultural commodity is found to contain captan and THPI it is likely that some captan was converted to THPI during storage of the sample. In most cases the THPI residue is a negligible or minor part of the residue and its inclusion or exclusion makes little difference. The Meeting agreed that the definition of the residue for the estimation of STMR levels should also be captan alone.

Captan is registered for use on apples in the USA at 2.2-4.5 kg ai/ha with up to 36 kg ai/ha

applied in a crop cycle, equivalent to 8 applications at the maximum rate. Harvest is permitted on the day of the final application. The decline of captan residues was measured in 7 trials on apples with sampling on at least 5 occasions after the final application. The median half-life of captan from the 7 trials was 11.9 days, which suggested that an increased number of applications would not influence the final residue levels because the contribution from applications more than 40-50 days before harvest would be negligible in comparison with that from the final application. A trial with only one application at the GAP rate was also included (captan residue 14 mg/kg on the day of application).

The residues from the US trials at GAP application rates (3.4-5.0 kg ai/ha) and PHI (0-1 days) but with 1-14 applications were 3.7, 4.0, 5.7, 6.1, 6.6, 14 and 16 mg/kg.

US GAP also permits a post-harvest spray or dip for apples at 0.15 kg ai/hl, which may be used in combination with the pre-harvest treatment. In 13 US trials reported in the 1994 evaluation where captan had been used before, after, or both before and after harvest, the captan residues were 0.86, 1.4, 1.5, 2.3, 3.3, 3.9, 4.0, 4.7, 4.9, 5.2, 5.5, 5.9 and 7.7 mg/kg.

Captan trials on apples in Argentina, Brazil, Canada, Japan and the UK were evaluated against the relevant GAP for these countries in 1994. The residues from 22 trials according to GAP were 0.005, 0.44, 0.68, 0.98, 1.0, 1.4, 2.5, 2.8, 2.9, 2.9, 3.5, 3.8, 4.1, 4.2, 4.2, 4.3, 4.4, 4.5, 4.5, 4.8, 7.2 and 13 mg/kg.

The residues in rank order (median underlined) from the total of 42 trials were 0.005, 0.44, 0.68, 0.86, 0.98, 1.0, 1.4, 1.4, 1.5, 2.3, 2.5, 2.8, 2.9, 2.9, 3.3, 3.5, 3.7, 3.8, 3.9, 4.0, <u>4.0</u>, <u>4.1</u>, 4.2, 4.2, 4.3, 4.4, 4.5, 4.5, 4.7, 4.8, 4.9, 5.2, 5.5, 5.7, 5.9, 6.1, 6.6, 7.2, 7.7, 13, 14 and 16 mg/kg.

The Meeting estimated a maximum residue level of 20 mg/kg for captan on apples to replace the 1994 recommendation of 10 mg/kg, and an STMR level of 4.05 mg/kg.

Information from US supervised trials on pears was made available but could not be evaluated because there was no corresponding GAP.

Captan may be applied in the USA at 2.2 kg ai/ha up to 7 times to cherries, which may be harvested on the day of the final application. It may also be used as a post-harvest spray or dip at a concentration of 0.15 kg ai/hl, and the two treatments may be used in combination. Details of 7 trials according to GAP were available to the Meeting. The captan residues were 2.4, 4.3, 5.5 14, 20, 20 and 21 mg/kg. Two trials where the application rate was 1.1 kg ai/ha (half the label rate) should also be included because residues were 16 and 17 mg/kg. In most of the trials there was no explicit description of the sample for analysis (e.g. whole fruit + stems).

Ten US trials on cherries reported in 1994 included pre-harvest, post-harvest and combined applications according to GAP. The captan residues were 7.3, 10, 11, 14, 14, 15, 19, 23, 25 and 35 mg/kg.

In summary, the captan residues in rank order (median underlined) from the 19 trials on cherries were 2.4, 4.3, 5.5, 7.3, 10, 11, 14, 14, 14, <u>15</u>, 16, 17, 19, 20, 20, 21, 23, 25 and 35 mg/kg.

The Meeting estimated a maximum residue level of 40 mg/kg for captan on cherries to

replace the 1994 estimate of 20 mg/kg, and an STMR of 15 mg/kg.

Data from 11 US supervised trials on nectarines could not be evaluated because the trial conditions were not sufficiently close to GAP.

US GAP permits the use of captan on plums at 3.4 kg ai/ha with harvest on the day of the final application. The total application permitted per season is 30 kg ai/ha, which corresponds to 9 applications. Data from 2 US trials on plums were reported to the Meeting and the use pattern in one of them exactly complied with GAP while in the other the application rate was correct but there were 13 applications and the PHI was 2 days. The use pattern in the 3 trials reported in the 1994 monograph complied with US GAP. The captan residues in the 5 valid trials (median underlined) were 0.45, 0.60, 0.71, 5.6 and 7.9 mg/kg.

The Meeting concluded that the results suggest that a higher limit than the present draft MRL of 5 mg/kg is required, but the database is limited. The Meeting agreed not to estimate a revised maximum residue level, but to await the periodic review of captan in 1998 when complete information on GAP and residues resulting from supervised trials should be available.

In the USA captan may be applied to grapes at 1.1-2.2 kg ai/ha with no more than 13 kg ai/ha used in a growing season, equivalent to 6 applications at the higher rate. Harvest is permitted on the day of the last application. The conditions in 9 US trials closely matched the maximum conditions of US GAP. Seven of the trials were reported to the present Meeting and 2 had been reported in 1994. The residues in the 9 trials were 1.3, 3.5, 3.7, 6.4, 7.2, 7.4, 8.4, 11 and 22 mg/kg.

Trials on grapes in Argentina, France, Germany and Japan were evaluated in 1994. The residue was 0.74 mg/kg in an Argentinian trial according to Argentinian GAP (1.3 kg ai/ha, 3 applications, 25 days PHI). A French trial and 12 German trials were evaluated against French GAP (10 applications of 3.5 kg ai/ha with a PHI of 33 days). Pre-harvest intervals of 28-38 days in these trials were accepted. The residues in the 13 trials were 1.4, 1.7, 1.7, 1.9, 2.8, 3.0, 3.6, 4.4, 6.5, 7.0, 8.3, 9.8 and 15 mg/kg. In Japan captan may be sprayed 5 times on grapes at a concentration of 0.10 kg ai/hl, with harvest 14 days after the final application. The residues on grapes from 6 Japanese trials complying with GAP were 3.2, 5.8, 6.1, 6.1, 12 and 14 mg/kg.

In summary, the residues in rank order (median underlined) from the 29 trials were 0.74, 1.3, 1.4, 1.7, 1.7, 1.9, 2.8, 3.0, 3.2, 3.5, 3.6, 3.7, 4.4, 5.8, 6.1, 6.1, 6.4, 6.5, 7.0, 7.2, 7.4, 8.3, 8.4, 9.8, 11, 12, 14, 15 and 22 mg/kg.

The Meeting estimated a maximum residue level of 25 mg/kg for captan on grapes to replace the current draft MRL of 20 mg/kg, and an STMR of 6.1 mg/kg.

US GAP permits application rates for captan on strawberries of 1.7-3.4 kg ai/ha and a PHI of 0 days, with a total application for the growing season of 27 kg ai/ha, equivalent to 8 applications at the highest rate. Six US and one Canadian trial according to the US application rate and PHI were reported to the Meeting. The number of applications varied from one to 11 but apparently the number had little effect on the residue levels. The residues in the 7 trials were 3.4, 3.9, 5.8, 6.4, 7.3, 13 and 27 mg/kg.

Trials in the USA, Canada, Chile and Hungary were recorded in the 1994 evaluations. In nine US trials complying with US GAP the residues were 1.0, 2.6, 3.9, 4.4, 5.2, 7.7, 12, 13 and 15 mg/kg. The residue was 3.0 mg/kg in a Canadian trial according to Canadian GAP (3.4 kg ai/ha, PHI 2 days). Chilean GAP allows 2 applications of 3.2 kg ai/ha and a PHI of 2 days. In trials at this rate but with 1 application and a 3-day PHI the residues were 3.8, 4.2 and 4.8 mg/kg. The residue in a Hungarian trial according to GAP (1.3 kg ai/ha, 3 applications, 10-day PHI) was 0.93 mg/kg.

In summary, captan residues in strawberries from the 21 trials (median underlined) were 0.93, 1.0, 2.6, 3.0, 3.4, 3.8, 3.9, 3.9, 4.2, 4.4, 4.8, 5.2, 5.8, 6.4, 7.3, 7.7, 12, 13, 13, 15 and 27 mg/kg.

The Meeting estimated a maximum residue level of 30 mg/kg for captan on strawberries to replace the 1994 estimate of 15 mg/kg, and an STMR of 4.8 mg/kg.

Information was provided to the Meeting on the fate of captan during the processing of apples and grapes.

Details of the processes for producing juice and pomace from apples were very limited. Heating and cooking are very influential on the fate of captan but no information on these operations was provided. Calculated processing factors for the production of juice, wet pomace and dry pomace from apples were 0.30, 0.48 and 0.064 respectively.

More detailed studies were provided to the 1994 JMPR, and that Meeting concluded that captan is not present in processed commodities such as apple sauce, canned apple slices, apple jelly or canned juice because it is destroyed by cooking and heating.

The supervised trials median residues for the processed commodities (STMR-Ps) calculated from the processing factors and the STMR for apples (4.05 mg/kg) were apple juice (unheated) 1.2 mg/kg, apple juice (heated) 0 mg/kg, apple sauce 0 mg/kg and dry apple pomace 0.26 mg/kg.

The Meeting also used the processing factor to estimate a maximum residue level for dry apple pomace of 2 mg/kg after rounding (maximum residue level in apples 20 × processing factor 0.064).

The processing factors for captan in the production of grape products were highly variable from one experiment to another, probably reflecting the sensitivity of captan to degradation under some heating conditions. The processing factors (mean and range) from grape processing studies supplied to the current Meeting and to the 1994 JMPR were grapes to juice 1.2 (range 0.23-4.9), grapes to wet pomace 0.94 (range 0.19-1.4), grapes to dry pomace 0.67 (range 0.12-1.7) and grapes to raisins 1.66 (range 0.11-4.8).

The STMR-Ps calculated from the processing factors and the STMR for grapes (6.1 mg/kg) were grape juice 7.3 mg/kg, dry grape pomace 4.1 mg/kg and raisins 10.4 mg/kg.

The Meeting also used the processing factor for raisins to estimate a maximum residue level for dried grapes of 50 mg/kg after rounding (maximum residue level in grapes 25 mg/kg × processing factor 1.66).

4.5 CARBOFURAN (096)

RESIDUE AND ANALYTICAL ASPECTS

Carbofuran, 2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate, is a widely used insecticide, nematicide, and acaracide. Its uses include seed treatment, at-plant soil application, and directed or foliar applications. A periodic review of the toxicology of carbofuran was carried out by the 1996 JMPR and the present evaluation is a periodic review of its residue and analytical aspects.

Carbosulfan produces carbofuran as a major metabolite. The periodic review of carbosulfan at the present Meeting includes an evaluation of its use on citrus fruit. In evaluating carbofuran, account was taken of its residues arising from the use of carbosulfan on citrus.

Animal metabolism

Studies were provided by the sponsors on rats, houseflies, laying hens, and lactating goats. The metabolism is similar in all species and consists of oxidation at the C-3 position and hydrolysis of the carbamate ester. The major metabolites observed in the urine from rats treated orally with single doses of carbonyl- or phenyl-labelled [^{14}C]carbofuran were 3-hydroxycarbofuran (14%), 3-ketocarbofuran (48%), the 7-phenol (20%), and the 3-hydroxy-7-phenol (1.4%). The major compounds found from the topical treatment of houseflies with radiolabelled carbofuran were carbofuran (12% internal), 3-hydroxycarbofuran (6%), and conjugated 3-hydroxycarbofuran (11%).

Hens were given 3 mg of phenyl-labelled [^{14}C]carbofuran for 7 consecutive days, about 2 mg/kg bw/day, equivalent to about 25 ppm in the feed. Eggs and tissues were collected and subjected to a series of extractions and hydrolyses. The residues in muscle and fat were negligible, and radiolabelled residues in the kidneys, liver, and eggs ranged from 0.03 to 0.15 mg/kg expressed as carbofuran. The major metabolite found in eggs was the 3-hydroxy-7-phenol (39% of the TRR). About 5% of the TRR in the liver and kidneys was identified as the 7-phenol, and significant proportions were characterized as releasable by treatment with protease or strong acid.

[^{14}C]Carbofuran, uniformly labelled in the phenyl ring, was administered orally to goats for 7 consecutive days at a rate equivalent to 25 ppm carbofuran in the diet. Milk and excreta were collected daily, and tissues were taken within 24 hours of the final dosing. The total radioactive residue in the milk remained fairly constant (0.10 mg/kg), and residues in the fat and tissues were negligible (<0.01 mg/kg). The milk and tissues were extracted with a series of solvents and subjected to enzymatic and acid/base hydrolyses. The major metabolites released and subsequently identified in the milk were 3-hydroxycarbofuran (10% of the TRR), the 7-phenol (15% of the TRR), and the 3-keto-7-phenol (32% of the TRR). Protease released 13% and 16% of the TRR from the kidneys and liver respectively. Major metabolites in the kidneys were 3-hydroxycarbofuran (11% of the TRR) and the 3-hydroxy-7-phenol (16% of the TRR, enzyme-released).

Plant metabolism

Studies were reported on potatoes, soya beans, and maize. The major metabolites identified in potato tubers were the 7-phenol (45% of the TRR) and the 3-hydroxy-7-phenol (13%). Immature foliage contained 3-hydroxycarbofuran (23% of the TRR) and a metabolite unique to the potato, 5-hydroxycarbofuran (34%). In soya bean forage (45-day PHI), the major compounds were identified as carbofuran (11% of the TRR) and 3-hydroxycarbofuran (28%). At a longer pre-harvest interval (139 days), the beans showed a substantial residue (40% of the TRR) releasable only by enzymes and acid and base hydrolyses. Only 12-13% the residue in the beans and hay was identified. The major metabolites in the beans were 3-ketocarbofuran (5% of the TRR) and the 3-keto-7-phenol (9%). The main compounds identified in maize forage were carbofuran and 3-hydroxycarbofuran (14% and 13% of the TRR).

The metabolites identified or characterized in the plants are consistent with hydroxylation at C-3 and hydrolysis of the carbamate, as in animals. Substantial conjugation of the metabolites and incorporation of the radiolabel into plant constituents occur.

The Meeting concluded that the animal and plant metabolism studies were fully adequate and showed a common metabolic pathway.

Environmental fate

Studies were reported on aerobic soil degradation, aerobic and anaerobic aquatic degradation, soil photolysis, terrestrial field dissipation, aqueous photolysis, and aquatic field dissipation.

The major pathway of degradation of [^{14}C]carbofuran in aerobic soil was by hydroxylation and oxidation at the C-3 position, yielding 3-hydroxycarbofuran and 3-ketocarbofuran. The half-life of carbofuran was calculated to be 320 days under acidic conditions and 150 days under alkaline conditions.

In an anaerobic water/sediment study more than 50% of the [^{14}C]carbofuran was converted to the 7-phenol, which was also a major product of anaerobic aquatic degradation where the carbofuran half-life was 120 days.

The aerobic aquatic half-life in a water/sediment system at pH 5.4 was 40 days.

The photolysis half-life of carbofuran in soil was about 78 days. Carbofuran is photolytically stable in aqueous solution, with a half-life of 450-1200 days.

From the soil dissipation studies it was determined that the half-life of carbofuran at a 0-6 inch depth was 13-43 days. The aquatic field dissipation study showed a carbofuran half-life of <10 days for carbofuran in rice paddy water. Thus, transfer of carbofuran via irrigation water is not anticipated to be a serious concern.

It was shown that carbofuran can be leached from four different types of soil under vigorous conditions.

The Meeting concluded that carbofuran is readily degraded in aquatic systems and that it is somewhat persistent is soil. Degradation in soil and water involves hydroxylation at the C-3

carbon and hydrolysis of the carbamate.

Methods of residue analysis

The methods of analysis are adequate for monitoring and for use in supervised trials, and at least one multi-residue method exists which is suitable for monitoring and enforcement.

The commonly used HPLC method involves solvent extraction of the homogenized sample, purification on a solid-phase extraction column, and determination on a reverse-phase column. A post-column reactor converts the eluted methylcarbamates to an indole, which is measured fluorimetrically. The method has a demonstrated limit of determination of about 0.05 mg/kg for carbofuran, 3-hydroxycarbofuran, and 3-ketocarbofuran. The limit of determination in milk is 0.025 mg/kg. A variation of the method involves initial hydrolysis of the homogenized sample with 0.25 N HCl to release any conjugates.

Several GLC methods exist for the determination of the carbamate metabolites. A macerated sample is refluxed with 0.25 N HCl, partitioned into methylene chloride, and purified on a Florisil column. A methyl silicone capillary column and a nitrogen-phosphorus or mass spectrometric detector are used. The method may be modified by ethylating the 3-hydroxycarbofuran. Limits of determination of 0.05 to 0.10 mg/kg were demonstrated.

In an older variation of the GLC method the initial extraction of the sample is with methanol/chloroform. The residual aqueous fraction is then hydrolysed with acid. A limit of determination of 0.1 mg/kg is claimed, but recoveries of the conjugate of 3-hydroxycarbofuran were generally unacceptable below 1 mg/kg. A variation of this method did not include acid hydrolysis, and the limit of determination for carbofuran and 3-hydroxycarbofuran was 0.1 mg/kg.

Stability of residues in stored analytical samples

Information was submitted on the stability of carbofuran, 3-hydroxycarbofuran, and 3-ketocarbofuran in or on several diverse raw agricultural commodities. The Meeting concluded that carbofuran and its carbamate metabolites are stable for at least 2 years in or on frozen plant commodities and milk, and for 1 year in meat.

Definition of the residue

The residue is defined for compliance with MRLs as the sum of carbofuran and 3-hydroxycarbofuran, expressed as carbofuran. For the estimation of dietary intake the residue should be defined as the sum of carbofuran, free 3-hydroxycarbofuran and conjugated 3-hydroxycarbofuran, expressed as carbofuran. The metabolism studies on soya beans and maize showed that the concentration of conjugated 3-hydroxycarbofuran was equal to or greater than that of 3-hydroxycarbofuran. For example, in soya bean forage (63 mg/kg of ^{14}C expressed as carbofuran) the free 3-hydroxycarbofuran was 11% of the TRR and the conjugated (acid-released) 3-hydroxycarbofuran was 17%. In the beans the concentrations were approximately equal. Where the analytical method used for a field trial did not include an acid hydrolysis step (refluxing with 0.1 N HCl) to release conjugates of 3-hydroxycarbofuran, the results were not used in the determination of the STMR levels.

Supervised trials

Residue trials were reported on numerous crops: alfalfa, bananas, Brussels sprouts, cantaloupes, cauliflower, celeriac, celery, coffee, cucumbers, grapes, head cabbages, kohlrabi, leeks, maize, oilseed plants (cotton, sunflower, rape, peanuts), onions, peppers, potatoes, rice, sorghum, soya beans, strawberries, sugar beet, sugar cane, summer squash, sweet corn, tomatoes, turnips, and wheat.

Fruits

Citrus fruits. Residues of carbofuran, 3-hydroxycarbofuran, and 3-ketocarbofuran may occur on citrus from the use of carbosulfan. On the basis of the concurrent review of carbosulfan the Meeting estimated a maximum residue level for carbofuran plus 3-hydroxycarbofuran in oranges of 0.5 mg/kg, and an STMR of 0.1 mg/kg.

Grapes. Field trials in the USA, Germany, and Mexico were reported. The four trials in Germany were not considered because the residue determined and the maturity of the crop samples were not clearly explained; the report consisted only of a simple summary. US GAP was used to evaluate the trials in Mexico and the USA (11.2 kg ai/ha of 4 F formulation, applied after harvest with a PHI of 200 days and soil-incorporated; pre-harvest drip irrigation with 4F at 3.4 kg ai/ha, 60-day PHI). One US and three Mexican trials complied with GAP for the vine treatment after harvest, and one US trial with GAP for the pre-harvest treatment. The residues were <0.05 mg/kg in all five trials, but five trials were considered to be insufficient for the estimation of a maximum residue level.

Strawberries. Supervised field trials were reported from France (0.89-1 kg ai/ha, PHI 13-48 days), the UK (2 kg ai/ha, 300-day PHI), and the USA (2.2 kg ai/ha, 250-day PHI). The results constituted two distinct sets, one for the after-harvest application to vines (UK and USA) where residues were below the limit of determination, 0.05-0.1 mg/kg, and the other with residues from <0.1 to 0.94 mg/kg (France). No information on GAP was provided for France or the UK or a neighbouring nation. The US trials conformed to US GAP, 2.2 kg ai/ha applied post-harvest after 1 October. The residues in the three trials were all 0.02 mg/kg. The results were insufficient to estimate a maximum residue level and the Meeting recommended the withdrawal of the existing CXL (0.1* mg/kg).

Bananas. Field trials in Spain, Central America and South America with the application of carbofuran to banana trees were reported. No residues of carbofuran plus 3-hydroxycarbofuran (<0.02-<0.10 mg/kg, n = 8) were found in any trial. GAP was available only for Spain, where the trial was according to GAP and undetectable residues were <0.02 mg/kg. Because none of the trials, some of which were at higher rates than GAP, yielded detectable residues the Meeting estimated a maximum residue level of 0.1* mg/kg, the same as the existing CXL, and an STMR of 0.1 mg/kg.

Vegetables

Leeks. Curaterr 200 SC was applied to the soil before planting leeks at two locations in The Netherlands. Carbamate residues were above the limit of determination in one trial, with a

maximum of 0.15 mg/kg. The number of trials was inadequate to estimate a maximum residue level.

Onions. Curaterr 5G or 200 SC was applied to onions at three locations after or before sowing. The carbamate residues were below the limit of determination. There were too few trials to estimate a maximum residue level. The Meeting recommended withdrawal of the existing CXL for bulb onion (0.1* mg/kg).

Head cabbages. Two supervised field trials were reported for the application of Curaterr 200 SC to head cabbage in The Netherlands. No residues were detected (<0.1 mg/kg). Two trials are too few for the estimation of a maximum residue level and the Meeting recommended the withdrawal of the existing CXL (0.5 mg/kg).

Brussels sprouts. Again only two trials in The Netherlands were reported. The Meeting recommended the withdrawal of the existing CXL (2 mg/kg).

Cauliflower. Five trials were carried out in The Netherlands with Curaterr 200 SC applied to cauliflower plants at 0.038 g ai/plant. The mode and timing of the application were not reported. No GAP was available for The Netherlands or other EU country and the data could not be evaluated. The Meeting recommended the withdrawal of the existing CXL (0.2 mg/kg).

Kohlrabi. Two field trials were carried out in Germany with single applications of a granular formulation at 0.64 g/m 38 and 52 days after planting but no GAP was reported. The Meeting recommended the withdrawal of the existing CXL (0.1* mg/kg).

Cucumbers. Field trials were carried out in the USA. US GAP specifies the at-plant application of 2.2 kg ai/ha of a G formulation or 1.7 kg ai/ha of an F formulation. The trials were conducted at 1.1 and 3.4 kg ai/ha with both the 15 G and 4 F formulations. The lower rate is below maximum GAP and the higher exceeds it. The results from the two rates were comparable and could therefore be used to represent the GAP rate. The residues from the 1.1 kg ai/ha rate were 0.02 (6), 0.04, 0.05, 0.08, 0.09, 0.15 (2), 0.16 and 0.21 mg/kg (n = 14), and those from the 3.4 kg ai/ha rate were 0.02 (4), 0.04 (2), 0.05 (2), 0.13, 0.16, 0.18, 0.21, 0.26 and 0.29 mg/kg, n = 14. The STMR for the 3.4 kg ai/ha rate is 0.05 mg/kg, and that for the 1.1 kg ai/ha rate 0.045 mg/kg. The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.05 mg/kg from the combined results.

Cantaloupes. Supervised field trials in the USA were reported, with the application of Furadan 15G or 4F to cantaloupes at planting, with PHIs of 60-92 days. The application rates were 1.1 or 3.4 kg ai/ha. Four trials were conducted in each of seven states. GAP specifies at-plant application of the G formulation at 2.2 kg ai/ha or the F formulation at 1.7 kg ai/ha. Some trials were below and others above maximum GAP. The results from the high and low application rates were similar, and could be used to represent residues resulting from GAP applications. The residues from the 1.1 kg ai/ha rate were 0.02 (8), 0.05 (2), 0.11 (3) and 0.13 mg/kg (n = 14), and those from the higher rate 0.02 (7), 0.05 (5), 0.11 and 0.12 mg/kg (n = 14). The STMR for the 1.1 kg ai/ha rate would be 0.02 mg/kg, and for the 3.4 kg ai/ha rate 0.035 kg ai/ha. Combining the distributions, the STMR is 0.02 mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg.

Summer squash. GAP in the USA is the same as for cucumbers and cantaloupes. Supervised field trials were carried out in seven states of the USA with the at-plant application of carbofuran 15G and 4F formulations at 1.1 and 3.4 kg ai/ha, some therefore below and some above maximum GAP. The results from the high and low application rates were similar, and the trials may be taken to represent applications according to GAP. The residues in rank order from 1.1 kg ai/ha were 0.02 (7), 0.05 (2), 0.07, 0.10, 0.11, 0.13 and 0.26 mg/kg (n = 14), and from 3.4 kg ai/ha 0.02 (5), 0.04, 0.06 (3), 0.07, 0.08, 0.09, 0.12 and 0.15 mg/kg (n = 14). The STMR for the 1.1 kg ai/ha rate is 0.035 mg/kg, and for both 3.4 kg ai/ha and for all the trials combined 0.05 mg/kg. The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.05 mg/kg.

Peppers (hot). Carbofuran was applied to the soil before planting hot peppers in two trials in the USA, with a second post-emergence side-dress application. The trials were according to, but not at the maximum, US GAP. No maximum residue level could be estimated.

Peppers (sweet). Furadan 4F was applied to sweet peppers in Canada and the USA. GAP was not available for Canada. US GAP specifies two applications of a 4 F formulation, one at-plant and the second as a side-dress, with a 21-day PHI. Each application is 3.4 kg ai/ha. The Canadian applications were in excess of US GAP at 5 x 0.56 kg ai/ha, 1-3-day PHI, and the results were not evaluated. In the US trials the application rate was ≤50% of the maximum GAP rate. The Meeting concluded that the data were insufficient to estimate a maximum residue level.

Tomatoes. Field trials were carried out in Brazil, Canada, France, Mexico, and the USA. The government of Thailand provided information on field trial conditions but did not include any analytical results. Most of the treatments were with a granular formulation applied to the soil round the plants. No GAP was reported for France, Mexico, or Canada, and the results from these countries could not be evaluated. There is no GAP in the USA. Two trials in Brazil which complied with GAP gave results of 0.05 mg/kg, but two samples are not enough to estimate a maximum residue level. The Meeting recommended withdrawal of the existing CXL (5 mg/kg).

Sweet corn (corn-on-the-cob). The findings of sixteen field trials on sweet corn were submitted from the USA. A combination of at-planting, at whorl, and foliar applications were made with granular and flowable formulations in accordance with the current label, at the maximum rate and with a minimum PHI. The commodity analysed was corn and cob, less husk. GAP was followed (1.12 kg ai/ha at-plant, followed by 4 foliar applications, each 0.56 kg ai/ha, 7-day PHI), and the total carbamate residues (carbofuran + 3-hydroxycarbofuran) in rank order were <0.03 (6), 0.03 (4), 0.04 (4), 0.05 and 0.08 mg/kg (n = 16). The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.03 mg/kg.

Soya beans. Trials were reported from Brazil, France, and the USA. Brazilian GAP specifies at-plant application of a 10% G at 1.5 kg ai/ha. US GAP allows 2.0 kg ai/ha at-plant or 2 applications at 0.56 kg ai/ha/application. No information on GAP was available for France or a neighbouring country. Only two trials according to GAP were reported, one from Brazil and the other from the USA. The residue in Brazil was below the limit of detection (0.05 mg/kg) and that in the USA was at the limit of determination (0.10 mg/kg). Two results are inadequate to estimate a maximum residue level, and the Meeting recommended withdrawal of the existing CXL for soya bean (dry) of 0.2 mg/kg.

Yard-long beans. The government of Thailand submitted a description of the in-field aspects of trials on yard-long beans but included no residue data. The Meeting took no action.

Carrots. The government of The Netherlands reported six field trials with at-plant application of an SC formulation to carrots. No GAP is available for The Netherlands or an EU country. The Meeting recommended withdrawal of the existing CXL (0.5 mg/kg).

Celeriac. The government of The Netherlands reported the results of one field trial with the application of an SC carbofuran formulation to celeriac. No GAP was reported and one trial is inadequate even for a very minor crop.

Potatoes. Field trials were carried out in Colombia, France, the UK and the USA. Applications according to GAP range from at-planting in Europe to banded treatment at hill-up and multiple foliar sprays in the USA. No GAP was available for Colombia, and the trials there were not evaluated. France and the UK each reported one trial in accordance with GAP. Six trials in the USA complied with the appropriate GAP, 3.4 kg ai/ha at-plant and 8 foliar applications at 1.1 kg ai/ha each, PHI 17 days. The residues in the whole tubers in the eight trials were <0.01 (3), <0.03 (2), 0.03, 0.04 and <0.05 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.03 mg/kg.

Sugar beet. Field trials were carried out in France, Italy, Germany, the UK and the USA. European GAP specifies 2 kg ai/ha at planting, and US GAP early post-emergence foliar treatment (2.2 kg ai/ha, 90-day PHI). Five trials were at the maximum GAP rate and minimum PHI. The residues on the foliage were <0.01 (3), 0.05 and 0.15 mg/kg and in the roots <0.01 (4) mg/kg. The data were insufficient to estimate a maximum residue level. The Meeting recommended withdrawal of the existing CXLs for sugar beet and sugar beet leaves or tops.

Turnips. Five field trials on the application of carbofuran to turnips in France, the UK and Norway were reported. No information on GAP was available, and the Meeting could take no action.

Celery. In two field trials in The Netherlands carbofuran was applied to the soil immediately before planting. The Meeting could not estimate a maximum residue level.

Cereal grains

Maize. Reports of trials in Brazil, France, Germany and the USA were submitted. The trials represented a combination of at-planting (France, USA, Germany) and foliar (USA, Brazil) treatments. The reports from Brazil, France, and Germany were abbreviated summaries and did not provide the detail required to evaluate the trials. The results were not used in attempting to estimate a maximum residue level and an STMR.

Eleven trials were conducted in the USA, but only two residues in silage were from trials according to current GAP. In the trials with at-plant applications the rate was 34% higher than the GAP rate and a granular formulation was used in place of the specified soluble concentrate. All the samples of forage, fodder and grain were harvested well outside the GAP PHI (>30% deviation). The two silage residues (1.1 and 1.2 mg/kg) were insufficient to estimate a maximum residue level or an STMR, nor could the Meeting estimate maximum residue levels for maize,

maize fodder or maize forage It therefore recommended withdrawal of the CXLs for maize and maize fodder.

Oats. Field trials on 3 varieties at one location were reported from Germany. The treatment was at-planting, and no residues (<0.10 mg/kg) were found in the oats. The number of trials was inadequate and the report consisted of a short summary that lacked the detail required for evaluation. The Meeting recommended withdrawal of the existing CXL (0.1* mg/kg).

Rice. Field trials in Australia, Brazil, Japan, the Philippines, and the USA were reported. The Brazilian summary report lacked the detail needed to evaluate the trials. The trials in the USA, Japan, and Philippines were not according to GAP. Only one trial in Australia accorded with GAP. The Meeting recommended withdrawal of the existing CXL (0.2 mg/kg).

Sorghum. See Sorghum forage etc., below.

Wheat. Field trials in South Africa and the USA were reported. Information on GAP was not available for the at-plant trials in South Africa. The six US trials were at the maximum GAP rate, with two foliar treatments and a 21-day PHI. The total carbamate residues in the grain in rank order were 0.02, 0.02 and 0.04 (4) mg/kg. The Meeting concluded that six trials were insufficient to estimate a maximum residue level and recommended withdrawal of the existing CXL (0.1* mg/kg).

Other crops

Sugar cane. Supervised field trials with the application of carbofuran to sugar cane were carried out in Brazil and the USA. In Brazil, the carbofuran (G or SC) was applied as a soil treatment about 5 months after planting. The PHI was 90 days. No residues were found (<0.1 mg/kg) in the four trials, two of which complied with GAP and two were at twice the GAP rate. In five trials in three states of the USA with the 4F formulation an in-furrow application at planting (1.1 kg ai/ha) was followed by two aerial foliar applications (2 x 0.84 kg ai/ha), with a 30-day PHI. This was according to GAP, and the maximum carbofuran residue was 0.06 mg/kg. The Meeting estimated a maximum residue level of 0.1* mg/kg, the existing CXL and the practical limit of quantification, and an STMR of 0.1 mg/kg.

Oilseed (cotton, sunflower, peanut, rape). Field trials in the USA and Brazil on cotton were reported, and the sponsor stated that trials were now in progress in southern Europe. The trials in Brazil were with seed treatment or a single post-emergence foliar treatment (2.1 kg ai/ha, 45-day PHI). The US trials involved two foliar applications of a flowable formulation (2 x 0.28 kg ai/ha). Neither set of trials complied with the relevant GAP, which is for at-plant use in both countries.

Trials on peanuts in Brazil and the USA were reported. The government of Thailand submitted information on field trials but no data on residues. Carbofuran was applied to peanut plants in two trials in Brazil as a foliar spray (1.75 or 3 kg ai/ha) with a 14-day PHI. In 14 US trials, peanut fields were treated at pegging. In some cases an initial treatment was also made at planting. The maximum carbamate residue was 0.53 mg/kg. Most of the US trials (80%) showed no quantifiable residues. GAP in Brazil is for at-plant treatment, and the USA has no GAP for the use of carbofuran on peanuts. Neither the Brazilian nor the US results could be used to

estimate a maximum residue level.

Field trials on rape (canola) were carried out in Canada (seed treatment, at-plant, post-emergence) and France (at-plant). No GAP was reported for Canada or France, and the Canadian trials did not comply with US GAP. The trials could not be evaluated.

Field trials on sunflowers were carried out in Canada, France and the USA. The trials in France were discounted, because the method of analysis was described as semi-quantitative and was not explained. The US trials were not according to GAP; the PHI was >150% of the GAP PHI of 28 days, and the at-plant application was below the maximum rate. Six trials in Canada complied with maximum US GAP and all the residues were 0.04 mg/kg. The Meeting estimated a maximum residue level for sunflower seed of 0.1* mg/kg and an STMR of 0.1 mg/kg, but concluded that the trials were inadequate to support an MRL for oilseed and recommended withdrawal of the existing CXL (0.1* mg/kg).

Coffee. Two field trials in Brazil and four in the USA, all according to national GAP, on the application of carbofuran to coffee bushes were reported. The use patterns are quite similar in both countries. GAP in Brazil specifies 0.35 g ai/tree of SC formulation or 0.5-3 g ai/tree of G formulation, and US GAP specifies two applications of 1.7 g ai/tree, 10 G formulation. The residues in rank order were 0.02 (3), 0.08, 0.12 and 0.79 mg/kg (n = 6). The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.10 mg/kg. The two Brazilian residues of 0.02 mg/kg were not used for the estimation of the STMR because the analysis did not include a hydrolysis step to release conjugated 3-hydroxycarbofuran.

Alfalfa. Three field trials in each of seven states in the USA were according to the current maximum use rate and minimum PHI. Green forage and fodder were analysed. The carbamate residues in the fodder ranged from the limit of detection (<0.1 mg/kg) to 7.6 mg/kg. The trials involved foliar application of a flowable formulation at 1.12 kg ai/ha with a 28-day PHI. The maximum residues of carbofuran plus 3-hydroxycarbofuran in each trial in rank order were <0.1 (2), 0.28, 0.32, 0.64, 0.74, 0.87, 0.90, 0.92, 1.2, 1.4, 1.5, 1.6, 2.6, 2.8, 3.0, 3.4, 3.8, 4.2, 4.5, 4.6, 4.7, 5.2 and 7.6 mg/kg (n = 24). The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 1.6 mg/kg. The residues in the green forage in rank order were <0.1 (5), 0.13, 0.29, 0.30, 0.34, 0.38, 0.52, 0.92, 0.9 4, 1.2 (3), 1.3, 1.4, 1.6 (2), 1.7, 1.8, 2.2 and 4.3 mg/kg (n = 24). The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 0.93 mg/kg.

Sorghum forage (green), sorghum straw and fodder, dry . Six trials in India and six in the USA were reported. The trials in India were with seed treatment or at-plant treatment, whereas the US trials were at-plant plus two foliar applications, with a total rate of 2.3 kg ai/ha. GAP was not available for India or a neighbouring country. In the US trials the residues in rank order were 0.055 (6), 0.06, 0.07, 0.11 (2), 0.13, 0.19, 0.26 and 1.2 mg/kg (n = 14) in sorghum forage (green), 0.05 (2), 0.06 and 0.20 mg/kg (n = 4) in sorghum fodder, and <0.01 (5) mg/kg in sorghum grain. The Meeting estimated maximum residue levels of 2 mg/kg for forage, 0.5 mg/kg for fodder, and 0.1* mg/kg for grain, with respective STMRs of 0.065 mg/kg, 0.055 mg/kg and 0.01 mg/kg. Although no residues were found in the grain at an estimated limit of detection of 0.01 mg/kg, the practical limit of quantification for carbofuran and 3-hydroxycarbofuran individually in plant commodities is 0.1 mg/kg.

Barley, egg plant, hops (dry), mustard seeds, peaches, pears. No trials were reported. The

Meeting recommended withdrawal of the existing CXLs.

Feeding studies on poultry and cows were reported. The poultry study was defective because although residues were reported as <0.05 mg/kg from feeding 5 ppm in the diet, the uncertainties surrounding the method of analysis cast doubts on the reliability of the results. A study conducted over 7 days at 25 ppm however showed negligible concentrations of radiolabelled residue (<0.01 mg/kg as carbofuran) in muscle and fat and a residue of 0.15 mg/kg in eggs, of which the carbamate content was below 20%. Potential poultry feed items include small grain (maize, barley, oats, wheat, sorghum, 80% of the diet) and alfalfa meal (10% of the diet). Thus, the diet might contain 80% x the 0.04 mg/kg STMR of maize + 10% x the 1.2 mg/kg STMR of alfalfa hay = 0.15 mg/kg. Note that this includes a commodity (maize) for which the withdrawal of a CXL has been recommended. Residues of carbofuran and its carbamate metabolites in poultry commodities are unlikely from such feeding levels. The Meeting concluded that MRLs are not needed for poultry commodities.

The ruminant feeding study was conducted with carbosulfan, not carbofuran. Carbosulfan is metabolized rapidly to carbofuran in ruminants, and the carbofuran is converted to 3-hydroxycarbofuran and phenol metabolites. Goats were fed carbosulfan at a level of 50 ppm in the diet for 28 days. The milk contained no detectable residues of carbosulfan on days 1-4, but it was present at very low concentrations, 0.005-0.011 mg/kg, from days 7 to 27. Carbofuran was detected on day 4 at a maximum concentration of 0.006 mg/kg and on day 7 at a maximum of 0.008 mg/kg. The carbofuran metabolite 3-hydroxycarbofuran appeared on day 1 (0.022 mg/kg) and continued through day 27 (0.013 mg/kg). The tissues contained no detectable residues of carbosulfan or carbofuran, but 0.060 mg/kg of 3-hydroxycarbofuran was found in the liver and 0.13 mg/kg in kidney. The Meeting concluded that feeding with carbosulfan may be substituted for feeding with carbofuran.

The study of metabolism in goats, conducted for 7 consecutive days with 25 ppm carbofuran in the feed, revealed no radiolabelled residues (<0.01 mg/kg as carbofuran) in the muscles or fat. Significant residues occurred in the milk (0.14 mg/kg) and in the liver and kidneys (0.11, 0.18 mg/kg). About 50% of the TRR in the milk was shown not to include carbamate compounds, and about 11% was carbofuran plus 3-hydroxycarbofuran (0.02 mg/kg). The kidneys and liver each contained <15% carbamates (0.02 mg/kg).

On the basis of the MRLs recommended by the present Meeting, the ruminant diet would contain no more than 2 mg/kg of carbofuran plus 3-hydroxycarbofuran. This is based on a diet containing 80% of alfalfa fodder (0.8 x the STMR of 1.6 mg/kg = 1.3 mg/kg). Owing to the substantial number of MRLs recommended for withdrawal there are few animal feed items. The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.05 mg/kg for residues (as defined above) in various animal products and milks.

Processing

Studies were conducted with sorghum, sugar beet, potatoes, maize, rice, sunflowers, cotton seed, sugar cane, coffee, pimento peppers, and grapes. Most of them were of limited value because the raw agricultural commodities contained carbamate residues below the limit of detection or between the limit of detection and the limit of determination. In most cases the same applied to the processed commodities. On the basis of the recommendations of the Meeting, processing

studies would be appropriate for coffee, potatoes, sunflowers, and sugar cane. The sugar cane and potato processing studies, with applications at 1.8 times and twice the GAP rate respectively, were inadequate because there were no residues in the raw agricultural commodities. The sunflower processing study was acceptable: the residue was unchanged in the edible oil and increased in the hulls and extracted meal by factors of 1.2 and 1.8 respectively. The coffee processing study showed a reduction factor of approximately 0.05-fold for instant and roast coffee. The value is approximate because the residues in the processed commodities were at the limit of detection.

FURTHER WORK OR INFORMATION

Desirable

1. A feeding study with cows fed carbofuran.

2. Processing studies on potatoes and sugar cane. Exaggerated treatment rates (five- to tenfold) should be used to obtain weathered residues in or on the raw agricultural commodities.

4.6 CARBOSULFAN (145)

RESIDUE AND ANALYTICAL ASPECTS

Carbosulfan, 2,3-dihydro-2,2-dimethylbenzofuran-7-yl (dibutylaminothio)methylcarbamate is a broad-spectrum carbamate pesticide used on a variety of crops, but mainly on citrus fruits, and this use is the focus of the present evaluation. Carbosulfan was first evaluated by the 1984 JMPR, which recommended a temporary ADI and a temporary MRL of 2 mg/kg for citrus fruits. The temporary ADI was converted to an ADI of 0-0.01 mg/kg bw by the 1986 JMPR.

Because information required by the 1984 and 1991 Meetings had not been provided, the 1993 JMPR recommended withdrawal of the proposed TMRLs for carbofuran and carbosulfan in citrus fruits. The 1993 Meeting was informed that additional studies were under way. Carbosulfan was subsequently scheduled for periodic review by the FAO Panel in 1997. New studies on citrus fruit have been reviewed by the Meeting, together with supporting data.

Carbofuran is a major metabolite of carbosulfan as well as being itself a pesticide. The present periodic review of carbosulfan includes estimates of maximum residue levels, an STMR and STMR-Ps for carbosulfan *per se* resulting from its use on citrus fruit. The concurrent review of carbofuran includes estimates to accommodate residues of carbofuran and 3-hydroxycarbofuran resulting from the use of carbosulfan on citrus fruit.

Metabolism studies on rats and goats were available. The distribution, excretion and fate of carbosulfan was investigated in rats by oral gavage administration of dibutylamine- or phenyl-labelled [^{14}C]carbosulfan at low (4 mg/kg) or high (30 mg/kg) dosing levels. About 66-88% was eliminated in the urine, 5-22% in the faeces and 10 to 17% as CO_2 from the dibutylamine (DBA) label but none from the phenyl label. Up to about 2% remained in the carcase. Eighty to 90% was excreted within 24 to 48 hours of dosing at the lower dose and within 72 hours or so at the

higher dose. The main excreted compounds identified from the phenyl label in decreasing order were the 7-phenol, 3-keto-7-phenol, 3-hydroxycarbofuran, 3-hydroxy-7-phenol and carbosulfan, with minor residues of 5-hydroxycarbofuran, 3-ketocarbofuran, carbofuran, 3-ketocarbosulfan sulfone, 3-hydroxycarbosulfan and 3-ketocarbosulfan. From the DBA label DBA, hydroxy-DBA, CO_2 and carbosulfan were found in decreasing order. No major sex differences were observed. Higher residues of ^{14}C were found in tissues from the DBA label than from the phenyl. This was attributed to incorporation of the DBA moiety into natural stored fat by oxidation, *N*-dealkylation or deamination and further oxidation to fatty acids.

The metabolites are consistent with metabolic routes which include a series of hydrolyses, oxidations and conjugations. A main indicated route includes hydrolysis to the 7-phenol, oxidation to 3-hydroxy-7-phenol and further to 3-keto-7-phenol, and conjugation as sulfates or glucuronides. Another route involves oxidation to 3-hydroxycarbosulfan which may be hydrolysed to 3-hydroxycarbofuran or oxidized further to 3-ketocarbosulfan, which in turn may be oxidized again to 3-ketocarbosulfan sulfone or hydrolysed to 3-ketocarbofuran. The 3-hydroxycarbofuran or 3-ketocarbofuran may be hydrolysed to their phenols before conjugation. Hydrolysis also results in the release of DBA which may be oxidized at different carbons to hydroxydibutylamines. The authors also postulate the *N*-dealkylation/deamination and oxidation to fatty acids which may be incorporated in natural fats as described above, or result in the release of CO_2 by the citric acid cycle as indicated by the detection of radiolabelled CO_2.

Lactating goats were dosed with either phenyl- or DBA-labelled carbosulfan for 7 days at levels corresponding to approximately 25 ppm in the diet. Samples of urine, faeces, milk and tissues were analysed. As in rats, most of the ^{14}C was eliminated in the urine, approximately 82% of the phenyl label and 68% of the DBA label. About another 7% and 3% respectively were eliminated in the faeces. Approximately 0.2% of the dose (0.04-0.09 mg/kg carbosulfan equivalent) was found in the milk, 0.02% (0.06 mg/kg) in liver and 0.01% (0.2 mg/kg) in kidney from the phenyl label, but less than 0.01% (≤0.01 mg/kg) in muscle or fat. Because of these low levels, the identification of ^{14}C residues in muscle and fat from the phenyl label was not attempted.

The residues were higher from the DBA label: 2.3% (0.3-0.94 mg/kg) in the milk, 0.34% (1.13 mg/kg) in the liver, 0.04% (0.75 mg/kg) in the kidneys, 0.08% (0.18 mg/kg) in the muscle, and 0.15% (1.2 mg/kg) in the omental fat. The higher levels were attributed to incorporation into natural body constituents such as carbohydrates and proteins. The detection of radioactivity in fatty acids, amino acids, triglycerides and amines was consistent with that hypothesis.

A series of extractions, partitions, pH adjustments and acid or enzymatic hydrolyses were used to separate metabolites for comparison with authentic standards by HPLC, TLC, GC-MS, HPLC-MS and size-exclusion chromatography. From the phenyl label 98.6% of the TRR was extractable from milk, 37.3% from liver and 62% from kidney.

The major metabolites identified in milk, liver and kidney from the phenyl label were 3-hydroxycarbofuran and the 3-keto-7-phenol, 3-hydroxy-7-phenol and 7-phenol, accounting for approximately 94.4% of the TRR in milk (reaching a plateau after about 2 days), 32.7% in liver (37.1% for all identified residues) and 52% in kidney (59.6% for all identified residues). 3-hydroxycarbofuran (34.2% of the TRR) and the 3-keto-7-phenol (29.9% of the TRR) predominated in the milk, 3-hydroxycarbofuran in kidney (21.5% of the TRR) and the 3-

hydroxy-7-phenol in liver (15.6% of the TRR). Minor identified residues included 5-hydroxycarbofuran, 3-ketocarbofuran, *N*-hydroxymethyl-carbofuran, carbofuran, carbosulfan, 3-ketocarbosulfan sulfone, 3-hydroxycarbosulfan and carbosulfan sulfone. None of these exceeded 4% of the TRR in milk, liver or kidney. Carbosulfan and carbofuran were detected only at very low levels in the milk and tissues (0.001 mg/kg).

Although only 37.1% of the phenyl label radioactivity was extractable from the liver with the initial solvent extraction, enzymatic and HCl hydrolysis allowed further characterization. Unidentified radioactivity was characterized as very polar (10.4% of the TRR), protein-associated (22.6% of the TRR) or unextractable (12.7% of the TRR).

In the kidney very polar unidentified metabolites accounted for 18.4% of the TRR, with another 17.4% characterized, but not identified.

Residue levels were much higher from the DBA label and this was attributed largely to incorporation into natural products as in rats. Residues in the fat and muscle from the phenyl label were too low for identification or characterization, but were high enough with the DBA-labelled samples (1.3 and 0.2 mg/kg carbosulfan equivalent in fat and muscle respectively). Approximately 80.1% of the DBA TRR (0.6 mg/kg carbosulfan equivalent) in milk and 90% in fat was organo-extractable, but only 45% in liver, slightly more than with the phenyl label. Approximately 70% of the TRR was extractable from kidney and 52% from lumbar muscle.

Residues in milk and tissues from the DBA label consisted mainly of aminobutanols, dibutylamine-related compounds, material incorporated into natural constituents (fatty acids, amino acids, carbohydrates, triglycerides etc.), amines (conjugated , non-conjugated and bound) and polar water-soluble metabolites. In milk aminobutanols accounted for approximately 30% of the TRR and another 30% was found in natural constituents. 87% of the TRR in fat, 32% in muscle and 30% in liver was found in natural constituents. In liver another 21% was in the form of aminobutanols or dibutylamine and related compounds. In kidney 24% of the TRR was characterized as non-conjugated amines, approximately 19% as polar water-soluble metabolites, and 14% as natural constituents.

The main metabolic routes in goats are similar to those in rats, starting with hydrolysis either directly to the 7-phenol or to carbofuran and dibutylamine. The 7-phenol is oxidized progressively to the 3-hydroxy-7-phenol and 3-keto-7-phenol and carbofuran to 3-hydroxy- or 5-hydroxycarbofuran. The 3-hydroxycarbofuran may be oxidized to 3-ketocarbofuran and each of these hydrolysed to the corresponding phenol. Dibutylamine may be oxidized to 4-(butylamino)butanol and further to the corresponding butanoic acid, or undergo a series of reactions to form butylamines and butanols. The degradation of DBA may also lead to incorporation into fatty acids, amino acids and carbohydrates and presumably through the citric acid cycle to CO_2, but CO_2 was not trapped.

The minor residues derived from the phenyl-labelled compound also indicate a subsidiary metabolic route in which the carbamate structure is retained with either direct oxidation to the sulfone or via 3-hydroxycarbosulfan and 3-ketocarbosulfan to 3-ketocarbosulfan sulfone.

Plant metabolism. Metabolism studies with both phenyl- and DBA-labelled carbosulfan were conducted in the field on navel oranges with spray application at a nominal rate of 0.5 g ai/l.

Orange samples were taken at 0, 7, 15 and 30 days and leaves at 0 and 30 days. Oranges were rinsed and samples of peel rinse, peel, pulp and juice were analysed by HPLC, TLC, MS and LSC. The TRR in whole oranges amounted to 0.81 and 0.7 mg/kg carbosulfan equivalent from the phenyl and DBA labels on day 0 to 0.78 and 0.59 mg/kg on day 30.

Nearly all of the residue in the whole fruit was in or on the peel (99.9% of the phenyl ^{14}C, 99.6 of the DBA) on day 0 and these proportions remained essentially unchanged even after 30 days. Almost all of the residue was on the peel surface on day 0 (95.8% of the phenyl TRR, 93.9% of the DBA), but by 30 days more of the residue had penetrated into the peel (45.9% of the ^{14}C from the phenyl label and 41.5% from the DBA). No more than 0.3% of the TRR (<0.01 mg/kg carbosulfan equivalent) from both labels was in the pulp or juice over the 30-day period. More than 90% of the TRR in rinsed peel from both labels was extractable throughout the 30 days with the proportion of polar and conjugated material increasing with time, especially that from the DBA label where it reached 57% by day 30.

The peel rinses and extracts were examined to identify the residues. Residues from the phenyl label after 30 days as a proportion of the TRR were carbosulfan 40.1%, carbofuran 33.9%, carbosulfan sulfone 3.1%, 3-hydroxycarbofuran and 3-keto carbofuran 2% each and *N*-hydroxymethyl-carbofuran, dicarbofuran sulfide and the 7-phenol less than 2% each, making a total of 83.7% of the TRR. From the DBA label carbosulfan and DBA accounted for 31.2 and 58.2% of the TRR respectively. This is consistent with the primary metabolic cleavage of the two N-S bonds to form carbofuran and DBA. Some oxidation to carbosulfan sulfone occurs before cleavage of these bonds and a minor route resulted in the formation of dicarbofuran sulfide. The rest of the metabolism is effectively that of carbofuran. This includes direct oxidation to the 7-phenol or retention of the intact carbamate with oxidation at the *N*-methyl to form *N*-hydroxymethylcarbofuran or on the ring to form 3-hydroxycarbofuran which may be further oxidized to 3-ketocarbofuran.

The only metabolite found in oranges which was not also identified in goats was dicarbofuran sulfide at very low levels. The other notable difference between plants and animals is that only very low levels of intact carbamates were detected in animals (apart from 3-hydroxycarbofuran at exaggerated feeding levels), whereas they were the main residues in plants after 30 days.

Environmental fate. Although limited information was available on photolysis in soil and water, other environmental studies noted as being necessary in the 1995 JMPR report (Section 2.5.2) were not provided. The degradation of carbosulfan in dry soil and soil at 70% water capacity exposed to a sun lamp was investigated with phenyl- and DBA-labelled [^{14}C]carbosulfan. The spectral characteristics of the sun lamp were not reported, nor was the temperature.

The half-life of carbosulfan with both labels was less than 10 minutes in the dry soil. After 8 days the main residue from the phenyl label was carbofuran (54.5% of the TRR), with 3.5% of 3-hydroxycarbofuran, 2.6% of carbosulfan sulfone, and lesser amounts of phenols or oxidized carbamate metabolites of carbosulfan or carbofuran. The predominant residues from the DBA label after 10 minutes were dibutylamine (38.6% of the TRR), carbosulfan (11.4%), *N*-formyldibutylamine (6.4%) and *N*-acetyldibutylamine (1.1%). After 8 days the same compounds were detected, but at very low levels (the rest was unidentified). Degradation was substantially slower with the wet soil treated with DBA-labelled carbosulfan. After 48 hours carbosulfan was still 76.2% of the TRR.

The authors concluded that as the results from irradiated and control soils with both labels were so similar exposure to light had very little effect, suggesting that degradation resulted from soil contact rather than the effect of light. The Meeting could not draw such a firm conclusion from the data, although it is likely that the soil was the main contributor to the degradation.

Photolytic and hydrolytic degradation were also investigated in water buffered at pH 7 and distilled water with both DBA- and phenyl-labelled [^{14}C]carbosulfan (5 mg/l) and irradiation for up to 8 days with a sun lamp. Apart from specifying that the radiation was above 300 nm, the spectral characteristics of the sun lamp were not reported nor was the kept. The half-life was about 1.4 days in buffered water and 4-8 days in distilled water. Degradation was much more rapid in irradiated samples than in controls, although the identified products were the same. Degradation was mainly to carbofuran and dibutylamine. Other lesser products from the phenyl label were carbosulfan sulfone, the 7-phenol and the 3-keto-7-phenol. From the DBA label the main product was dibutylamine, with lesser amounts of *N*-formyldibutylamine and *N*-acetyldibutylamine.

No other studies on environmental fate were submitted to the Meeting.

Methods of analysis. A number of analytical procedures are available for the determination of carbosulfan, its carbamate and phenolic metabolites and dibutylamine in citrus and animal products. Recent methods used in some of the field trials with citrus fruit and animals are based on the extraction of carbosulfan with dichloromethane (from citrus) or acetone (from animals products) and clean-up on solid-phase extraction (SPE) cartridges before analysis. Carbamate and phenolic metabolites are hydrolysed with HCl before SPE column extraction and dibutylamine is extracted with methanol/water. Some procedures include liquid-liquid partitions.

The HPLC configuration for the determination of carbosulfan includes two post-column reactors, one with H_2SO_4 to hydrolyse carbosulfan to carbofuran and the other with *o*-phthalaldehyde + *N*,*N*-dimethyl-2-mercaptoethylamine to form a chromophore for fluorescence detection. The configuration is the same for carbamate metabolites, except that only the second reactor is used. Phenolic fractions are derivatized with pentafluorobenzyl bromide (PFBBr), and 3-hydroxy-7-phenols also by ethylation, before analysis. Dibutylyamine fractions are derivatized with dansyl chloride for analysis. Both the phenolic and DBA derivatives are analysed by GC-MS with single ion monitoring.

In citrus a limit of determination of 0.05 mg/kg for all analytes would appear to be supported for this group of methods by adequate recoveries and sample chromatograms, but citrus controls consistently had apparent DBA levels up to 0.02 mg/kg. For this reason 0.1 mg/kg may be a more realistic limit of determination for DBA. For animal products limits of determination of 0.025 mg/kg in milk and 0.05 mg/kg in tissues also appear to be supported for all compounds on the basis of adequate recoveries and sample chromatograms, but DBA was again reported near the limit of determination in some milk samples (0.005-0.037 mg/kg). The methods were independently validated.

The methods used in some other citrus trials involved hexane/propanol extraction of carbosulfan and carbofuran, and HCl reflux extraction of 3-hydroxycarbofuran after ethoxylation, followed by liquid/liquid partition, Florisil column clean-up and GLC with NP

detection. The reported limit of determination was 0.01 mg/kg and the methods were validated at that level. However sample chromatograms and corroborating information from multi-residue methods indicated that 0.05 mg/kg would appear to be a more practical limit of determination; it was also recommended as the reporting level.

Older methods used in citrus processing studies were similar to that just described, including GLC with NP detection, but with different clean-up columns. A limit of determination of 0.05 mg/kg is again reasonable, except perhaps for citrus oil where 0.1 mg/kg might be more realistic. Published multi-residue methods were not adequate for carbosulfan, mainly owing to low detector sensitivity.

Stability of residues in stored analytical samples. In a 1980 storage stability study no significant losses of carbosulfan were observed when orange and alfalfa samples fortified with carbosulfan were stored for one year at -18°C. Carbofuran was the predominant metabolite. However, in a pH 4.8 silt loam soil in this same study carbosulfan was almost completely degraded after only three hours at -18°C. This was attributed to the acidity, although carbosulfan was stable in the orange samples, also likely to be acidic. It was more stable in a pH 6 silty clay loam and a pH 6.8 sandy loam at -18°C, with half-lives of about 220 and 144 days respectively.

An interim report described studies of the stability of carbosulfan, its carbamate and phenolic metabolites and DBA in laboratory-fortified oranges and processed orange products stored for up to a year at -18°C. Samples of whole oranges, dried pulp, juice, molasses and oil were fortified at 0.25 mg/kg and most samples were taken for analysis on day 0 and after approximately 3, 6, and 12 months. On day 0 no residues were detected in the juice, and residues in molasses and oil were only 0.08 and 0.12 mg/kg respectively. In these cases carbofuran was the main product of carbosulfan degradation as demonstrated by mass balance investigations. Later samples of juice, molasses and oil were therefore analysed for carbosulfan. Orange oil was analysed for carbosulfan metabolites only on day 0 and after 12 months. There were no appreciable losses of the other carbamate or phenolic residues in any of the samples. It was reported that results of analyses for DBA after 18 and 24 months will be available at an unspecified future time.

The stability and mass balance of residues in cow milk and tissues fortified at 0.25 mg/kg with carbosulfan and DBA were investigated after storage at -18°C for intervals up to 8 months. Carbosulfan was shown to be degraded rapidly in milk, muscle and liver with losses of 16 and 4% from milk and liver respectively in the first month and of 84% from milk, 100% from muscle and 80% from liver after 8 months. Losses of DBA from milk and liver were 8 and 4% respectively after 6 months, but DBA residues in muscle showed an apparent increase of 52% after 6 months. Overall the analyses for DBA were erratic over the test period. Mass balance studies showed that carbosulfan + carbofuran accounted for 68% of the fortification level in milk after 3 months and 88 and 44% in muscle and liver respectively after 6 months. After 8 months carbofuran and the 7-phenol together accounted for over half of the fortification level in milk and liver and 148% in muscle.

These results confirm the instability of carbosulfan *per se* in animal products even under frozen storage conditions, and add confidence to the prediction that there is little likelihood of finding it in animal products as a result of using carbosulfan on citrus. The results also confirm that degradation is likely to be mainly to carbofuran and its metabolites. The trials did not include analyses for 3-ketocarbofuran, 3-hydroxycarbofuran, or other minor carbamate

metabolites. On the basis of the results of the cow feeding study it is likely that 3-hydroxycarbofuran especially may constitute a significant proportion of the residue unaccounted for in these studies.

Citrus residue trials. 30 supervised trials were conducted in 1993-4 in Brazil, Mexico and Spain using the analytical methods described above. The six 1993 Brazilian trials on Valencia and Pera Coroa oranges with a CE formulation (*c*.1-1.7 g ai/tree) were typical. Six trees/trial were treated, and 4 oranges/tree or 24 oranges/trial sample were taken. Duplicate samples were analysed separately in each trial and both results are tabulated. All trials were according to GAP (a maximum of 2 foliar applications at 0.9-1.7 g ai/tree, the first after full bloom and the 2nd approximately 50 days later). Sprays were to run-off and the 7-day GAP PHI was observed. Sampling, transport and storage were adequate to provide confidence in sample integrity. Analytical results were not corrected for recoveries. At the 7-day GAP PHI the maximum residues were carbosulfan <0.01-0.03 mg/kg, carbofuran 0.02-0.06 mg/kg, and 3-hydroxycarbofuran <0.01-0.03 mg/kg. The 3-ketocarbofuran metabolite occurred in only one trial, at 0.02 mg/kg. Total phenols were up to 0.02 mg/kg and dibutylamine up to 0.15 mg/kg.

A 7-day GAP PHI was also observed in the 7 Mexican trials on Valencia and other oranges with an LE formulation (250 g ai/ha). Residues from application according to GAP, corrected for recoveries, were <0.01-0.08 mg/kg carbosulfan, 0.08-0.26 mg/kg carbofuran, <0.01-0.14 mg/kg 3-hydroxycarbofuran, <0.01-0.04 mg/kg 3-ketocarbofuran, and <0.01-0.14 mg/kg 3-hydroxycarbofuran. Residues of total phenols (uncorrected) were 0.01-0.12 mg/kg and of DBA up to 0.14 mg/kg.

In four 1994 Spanish trials according to GAP with an LE formulation (*c*.3 g ai/tree) both mature (112-day PHI) and immature (28-day PHI) Valencia oranges were analysed. No residues (<0.01 mg/kg) of carbosulfan were detected at either PHI. In the mature oranges carbofuran residues (corrected for recovery) were <0.01-0.36 mg/kg, 3-ketocarbofuran <0.01-0.05 mg/kg, and 3-hydroxycarbofuran 0.02-0.14 mg/kg. The residues of total phenols (uncorrected) were up to 0.25 mg/kg and of DBA up to 0.14 mg/kg. Not unexpectedly, residues (except of 3-ketocarbofuran) were substantially higher in the immature oranges with a corrected maximum of 0.82 mg/kg carbofuran, <0.01 mg/kg 3-ketocarbofuran, and 0.39 mg/kg 3-hydroxycarbofuran. Maximum (uncorrected) residues of total phenols were 0.63 mg/kg and of DBA 0.29 mg/kg.

Additional Spanish trials according to GAP were conducted in 1993 and 1994 with high-volume applications of an EC formulation (937.5 g ai/ha, 3000 l/ha). Sampling was not only at the harvest GAP PHI (84-147 days), but also at days 0, 30, 45, 60...147. Analyses were only for carbosulfan, carbofuran, and 3-hydroxycarbofuran. Because these compounds are those that the Meeting recommended for inclusion in the definitions of the residues arising from the use of carbosulfan and carbofuran (see below), the results can be used to estimate maximum residue levels and STMRs. The JMPR had previously recommended that all field trials should also include analyses for 3-ketocarbofuran. The Meeting upheld that recommendation with respect to future submissions of data on commodities other than citrus but concluded that, because a number of trials had demonstrated that the compound occurs at relatively low levels in citrus, the data on 3-ketocarbofuran were adequate for citrus fruit.

No residues of carbosulfan were detected at these extended PHIs (84-147 days), but residues of carbosulfan at day 0 (corrected for recoveries) were as high as 3.3 mg/kg. It was seldom

detectable after 30 days and even then only in the peel. Carbofuran and especially 3-hydroxycarbofuran were present in some cases after 30 days, and even at harvest after the lengthy PHIs. Generally 3-hydroxycarbofuran was the higher of the two at this stage.

In the six 1993 trials residues at harvest (110-147 days) were <0.01-0.04 mg/kg carbofuran (mostly <0.01) and 0.05-0.13 mg/kg 3-hydroxycarbofuran. Peel and pulp samples were also analysed at 45 days in two of the trials: carbosulfan was not detected in the peel or pulp (<0.01 mg/kg) and carbofuran residues were about 0.27 or 0.37 mg/kg in the peel and <0.01 mg/kg in the pulp, giving 0.02-0.17 mg/kg in whole oranges. 3-hydroxycarbofuran was at a similar level in the peel and 0.01 mg/kg in the pulp.

In the seven 1994 studies (PHIs 84-140 days) residues in whole oranges were calculated from those in the peel and pulp and the measured peel/pulp weight ratios (24/76, 27/73, 28/72 or 30/70 at harvest, depending on the type of orange). The calculated residues were <0.01 mg/kg carbosulfan, <0.01-0.06 mg/kg carbofuran and 0.04-0.13 mg/kg 3-hydroxycarbofuran. At day 0 the maximum residues in the peel and pulp (uncorrected for recovery) were 0.9 and <0.01 mg/kg carbosulfan, 0.63 and <0.01 mg/kg carbofuran and 0.64 and 0.05 mg/kg 3-hydroxycarbofuran.

The Meeting concluded that MRLs for citrus fruits should be established both for carbosulfan defined as carbosulfan and for carbofuran defined as the sum of carbofuran and 3-hydroxycarbofuran, expressed as carbofuran. The Meeting examined the distribution of data from trials complying with GAP according to these definitions in order to estimate MRLs and STMRs, and observed (not surprisingly) the absence of detectable carbosulfan residues in the Spanish trials with PHIs of 84-147 days compared with the measurable but low levels after 7 days in the Mexican and Brazilian trials. There is much less variation in the sum of carbofuran and 3-hydroxycarbofuran residues however, even with the wide divergence of national PHIs.

Duplicate samples were analysed in most of the trials and the results recorded separately. In order to avoid averaging problems in cases where one of two duplicate results was below the level of detection and to avoid the possibility of over-estimating the median residue, the Meeting decided to treat all the results separately for the estimation of MRLs and STMRs, and included estimated levels for residues between the limits of detection and determination.

The Meeting had two options for the estimation of STMRs for carbosulfan and carbofuran in oranges. One was to use the residues found in the pulp in four 1994 Spanish trials in which carbosulfan was undetected (<0.01 mg/kg) in all four trials and carbofuran + 3-hydroxycarbofuran was undetected in three and at a level of 0.02 mg/kg in the fourth. Since residues were detectable and estimated to be 0.01 mg/kg in each of two 45-day pulp samples in Spanish trials, the residue of 0.02 mg/kg found in the one trial according to GAP is not likely to be aberrant.

The second option was to estimate STMRs for residues of carbosulfan and carbofuran + 3-hydroxycarbofuran in whole oranges from the much larger database of 30 trials. Because of the greater uncertainty associated with the database of only four trials, the Meeting took the second option.

The low or undetectable residues found in the limited number of orange pulp samples and the results of the orange metabolism study described above which showed ≤0.2% and ≤0.3% of the

TRR in the pulp and juice respectively give added assurance that residues of carbosulfan and carbofuran + 3-hydroxycarbofuran in the edible portions of oranges, if present, are likely to be very low.

The residues of carbosulfan from all the treatments according to GAP (counting duplicate samples separately) were 0.08, 0.04, 0.03 (3), 0.02 (7), 0.01 (2), and <0.01 mg/kg (39) in a total of 53 samples. If the Spanish trials are excluded, the residues of carbosulfan were 0.08, 0.04, 0.03 (3), 0.02 (7), 0.01 (2), and <0.01 mg/kg (12): 26 samples. From these results, the Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.01 mg/kg for carbosulfan in oranges. The STMR is at the limit of detection.

The residues of the simple sum of carbofuran + 3-hydroxycarbofuran were 0.5, 0.4 0.39, 0.33, 0.26, 0.22 (2), 0.19, 0.17 (2), 0.15, 0.14 (2), 0.13 (2), 0.12 (4), 0.11 (6), 0.10, <0.10, 0.09 (3), 0.08 (3), 0.07 (4), <0.07, 0.06 (4), 0.05 (4), 0.04, <0.04, 0.03 (3), and 0.02 (2) mg/kg (53 samples).

On the basis of this distribution, recognizing that the residues would be only very slightly lower if an adjustment were made for the molecular weight of 3-hydroxycarbofuran (about 7% higher than carbofuran), the Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.1 mg/kg for the sum of carbofuran and 3-hydroxycarbofuran, expressed as carbofuran, in oranges. The Meeting concluded that the STMR for the total carbamate residues would be essentially the same as for carbofuran + 3-hydroxycarbofuran because of the low proportion of carbosulfan in the total carbamate residue.

The Meeting also received information on GAP (without labels) from Thailand for carbosulfan uses on rice, asparagus and watermelons together with what appeared to be an incomplete report of field trials. Although fairly detailed information was provided on the conduct of the trials, no analytical results were included. The information on GAP for these crops was recorded in the evaluation in case the results of the trials become available in the future and provided the GAP is confirmed by approved labels. However, the two trials apparently completed on each of these crops would not be sufficient to estimate maximum residue levels.

Summary information on GAP for German uses on rape, maize and hops was also received but no labels or residue data were provided. Official information on GAP for several commodities was also received from the UK, but again without data on residues. The information on GAP should be re-submitted, together with relevant labels, with any future reports of residue trials.

Feeding studies. Holstein dairy cows were dosed at levels equivalent to 0, 1, 3, 10 and 50 ppm carbosulfan in the diet for 28 days. Milk, kidney, liver, muscle and fat were analysed for carbosulfan, carbofuran, 3-hydroxycarbofuran, 3-ketocarbofuran, the 7-phenol, 3-keto-7-phenol and 3-hydroxy-7-phenol metabolites and dibutylamine. Selected cows were held for an additional 3 or 6 days for recovery studies. The residues in the milk and tissues were generally in the decreasing order 3-hydroxycarbofuran, 3-ketocarbofuran, carbofuran and carbosulfan, although in some samples of milk carbosulfan residues were of the same order as those of carbofuran.

No carbamate residues, except one of 7 ìg/kg 3-hydroxycarbofuran in the milk of one of

three cows at the 10 ppm feeding level after four days, were detected in any samples at the 1, 3 or 10 ppm feeding levels. Phenols were detected at the 10 ppm level, but only in kidney (max. 57 ìg/kg 7-phenol and 12 ìg/kg 3-hydroxy-7-phenol). Dibutylamine was found at the 10 ppm feeding level up to 54 ìg/kg in milk and in all the tissues (highest in kidney at 106 ìg/kg). Carbamates were found in the milk and tissues from the 50 ppm feeding level. In summary, the maximum and mean residues at the 50 ppm feeding level were as shown below.

	Maximum/mean residue, ìg/kg						
Compound	Milk	Skimmed milk	Cream	Kidney	Liver	Muscle	Fat
carbosulfan	12/7	ND	45/28	ND	ND	ND	76/44
carbofuran	8/4	ND	16/8	ND	ND	ND	ND
3-hydroxycarbofuran	30/19	20/10	ND	133/112	60/54	30/25	ND
3-ketocarbofuran	11/5	ND	ND	ND	23/14	ND	ND
7-phenol	8/4	8/6	20/11	400/358	ND	ND	14/10
3-keto-7-phenol	42/27	39/23	17/14	74/66	ND	ND	ND
3-hydroxy-7-phenol	26/19	14/12	ND	173/163	34/32	12/9	11/8
dibutylamine	119/77	---	---	890/590	294/222	58/48	47/36

where ND = 5 ìg/kg in milk and 10 ìg/kg in the other substrates, with limits of determination of 25 ìg/kg and 50 ìg/kg respectively.

At the 50 ppm feeding level carbosulfan was found in milk up to 12 ìg/kg, cream up to 45 ìg/kg, and fat up to 76 ìg/kg, but not in kidney, liver or muscle. At this feeding level carbofuran was found only in milk (up to 8 ìg/kg in one cow) and in cream up to 16 ìg/kg in a different cow after a 3-day withdrawal period. 3-ketocarbofuran was detected only at the 50 ppm feeding level and then only in the milk and liver at maximum levels (in the same cow) of 11 and 23 ìg/kg respectively. No residues were detected in either milk or liver after 3- or 6-day withdrawal periods.

Most of the carbamate residue at the 50 ppm level consisted of 3-hydroxycarbofuran, except in cream and fat. In milk the mean and maximum residues of 3-hydroxycarbofuran were 19 ìg/kg after 7 days and 30 ìg/kg after 2 days respectively, gradually decreased to 11 ìg/kg after 27 days, and were undetectable after a 3-day withdrawal period. There was some reduction of carbosulfan and dibutylamine in fat during the 3- and 6-day recovery periods and no 7-phenol was detected in fat during these periods. The total carbamate residues in milk were fairly constant at approximately 30 ìg/kg after the first day of sampling through the dosing period. The 3-hydroxycarbofuran metabolite was up to 133 ìg/kg in kidney, ≤60 ìg/kg in liver and ≤30 ìg/kg in muscle. It was not detected in fat.

Both carbosulfan and carbofuran were found in cream (at mean levels of 28 and 8 ìg/kg respectively) but not in skimmed milk (<5 ìg/kg). 3-ketocarbofuran was not found in either, and 3-hydroxycarbofuran in skimmed milk (mean level 10 ìg/kg) but not in cream, not unexpectedly in view of the polarity afforded by the hydroxyl group.

In the milk, the residues of total phenols were fairly constant over the test period after the first day, with the 3-keto-7-phenol generally predominating. The highest average residues were 3-keto-7-phenol 27 ìg/kg, 3-hydroxy-7-phenol 19 ìg/kg and 7-phenol 4 ìg/kg. These were all

undetectable (<5 ìg/kg) after 3 or 6 days withdrawal. The highest phenolic residues in the tissues were in the kidney with mean levels of the 7-phenol of 358 ìg/kg, the 3-hydroxy-7-phenol of 163 ìg/kg and the 3-keto-7-phenol of 66 ìg/kg. In the liver and muscle only the 3-hydroxy-7-phenol was detected, at mean levels of 32 and 9 ìg/kg respectively, and in fat only the 7-phenol (10 ìg/kg) and 3-hydroxy-7-phenol (8 ìg/kg).

Apparent dibutylamine was reported in most controls at maximum levels of about 50 ìg/kg in both milk and tissue samples, and the residues in treated groups did not correlate well with the dose rates. Its apparent natural occurrence made reliable estimates of the DBA derived from carbosulfan difficult in all samples from animals at the 1 to 10 ppm feeding levels, and in muscle and fat at the 50 ppm level. The mean residues of 590 ìg/kg dibutylamine in the kidneys and 222 ìg/kg in the livers of the 50 ppm group clearly arose mainly from the treatment however.

Since the highest carbamate residues likely to result from the use of carbosulfan in an animal feed item would be about 2 mg/kg from dry citrus pulp with an STMR of 0.29 mg/kg and this is likely to constitute no more than 20-25% of a cattle diet, and since there were no significant residues at the 10 ppm feeding level and relatively low levels even at 50 ppm, the Meeting concluded that no MRL was required for carbosulfan or its metabolites in milk or tissues to accommodate the use of carbosulfan on citrus. Any residues that might occur would be covered by the maximum residue levels estimated for animal products to accommodate the use of carbofuran (see Section 4.5).

Processing

The Meeting examined reports of two processing studies, one on grapefruit and one on oranges, although data on supervised trials were available only for oranges.

Washing the fruit reduced residues of carbosulfan in grapefruit and oranges by about 67% and 53% respectively. Both carbofuran and total carbamates were reduced by about 21% in grapefruit, but there was no reduction in oranges. The loss of carbosulfan from oranges appears to be offset by increases in carbofuran and 3-hydroxycarbofuran. This situation is analogous to the finding of low or undetectable residues of carbosulfan in harvest samples of oranges although total carbamate residues remain relatively constant over long periods. Because the oranges were processed on the day of the last application instead of after the normal pre-harvest interval, the Meeting decided to consider the total carbamate levels as a measure of the residue in evaluating the processing study. To omit carbosulfan, which would have been largely converted to carbofuran and 3-hydroxycarbofuran at harvest, would underestimate the residues.

No residues (<0.01 mg/kg) of carbosulfan were found in orange juice, so no processing factor could be calculated. Because the residue of 0.17 mg/kg carbosulfan in the whole unwashed oranges is similar to or slightly above the maximum residue found in field trials according to GAP, there would be no real expectation of finding carbosulfan in orange juice. An STMR-P of 0 for carbosulfan *per se* in orange juice would be reasonable. The residue of 0.73 mg/kg total carbamates is also slightly higher than the residues found from GAP applications in field trials. There was no concentration of any carbosulfan metabolite in the juice, although carbofuran was detected at low levels. A processing factor of about 0.01 for total carbamates applied to an STMR of 0.1 mg/kg for the sum of carbofuran and 3-hydroxycarbofuran would give an STMR-P

of 0.001 mg/kg for carbofuran + 3-hydroxycarbofuran in orange juice. Although no MRL for either carbosulfan or the sum of carbofuran and 3-hydroxycarbofuran would appear to be needed since the residues would be expected to be below the limit of detection of 0.01 mg/kg, an MRL of 0.05 mg/kg, at the limit of determination, would be reasonable if one is needed.

The processing factor for carbosulfan on processing unwashed orange fruit to molasses was approximately 0.12. A worst-case STMR-P for carbosulfan in orange molasses would be the STMR for oranges, 0.01 mg/kg, x 0.12 = 0.0012 mg/kg. The processing factor for total carbamate residues was 1.1, and this multiplied by the STMR of 0.1 mg/kg for the sum of carbofuran and 3-hydroxycarbofuran in unwashed whole fruit gives an STMR-P of 0.11 mg/kg. If an MRL for carbosulfan in molasses is needed, a value of 0.05 mg/kg, at the limit of determination, would be appropriate (the maximum expected residue being 0.012 mg/kg). Because there is no significant concentration, the residues of carbofuran + 3-hydroxycarbofuran would not be expected to exceed the maximum residue level of 0.5 mg/kg estimated for whole fruit.

The processing factor for carbosulfan from unwashed oranges to dry pulp was 0.82, so the STMR-P = the STMR for oranges, 0.01 mg/kg, x 0.82 = 0.0082 mg/kg. The STMR-P for the sum of carbofuran and 3-hydroxycarbofuran = STMR 0.1 x processing factor 2.9 = 0.29 mg/kg. On the basis of the 0.82 processing factor and the recommended MRL of 0.1 mg/kg for carbosulfan in whole oranges, 0.1 mg/kg would also be sufficient as an MRL for carbosulfan in dry citrus pulp. The processing factor of 2.9 and the recommended MRL for carbofuran + 3-hydroxy-carbofuran in oranges of 0.5 mg/kg, indicate that 2 mg/kg should be the MRL for the sum of carbofuran and 3-hydroxycarbofuran in dry citrus pulp.

Orange oil. The processing factor for carbosulfan was 7.2 and that for the sum of carbofuran and 3-hydroxycarbofuran was 7.1. Since the STMR levels in oranges were 0.01 and 0.1 mg/kg respectively the corresponding STMR-Ps for orange oil would be 0.072 and 0.71 mg/kg. The same processing factors applied to the recommended MRLs of 0.1 mg/kg for carbosulfan and 0.5 mg/kg for carbofuran in oranges would lead to recommended MRLs of 1 and 5 mg/kg respectively for the oil.

The results of these estimates are summarized below.

Sample	Carbosulfan				Carbofuran + 3-hydroxycarbofuran			
	Processing factor	Max. res. level[1], mg/kg	Orange STMR, mg/kg	Processed fraction STMR-P, mg/kg	Processing factor	Max. res. level[1], mg/kg	Orange STMR, mg/kg	Processed fraction STMR-P, mg/kg
Whole oranges	--	0.1	0.01	--	--	0.5	0.1	--
Juice	NF[2]	<0.01 (0.05*)	0.01	0.0	0.01	0.005 (0.05*)	0.1	0.001
Molasses	0.12	0.012 (0.05*)	0.01	0.0012	1.1	0.55 (0.5)	0.1	0.11
Dry Pulp	0.82	0.08 (0.1)	0.01	0.0082	2.9	1.5 (2.0)	0.1	0.29
Oil	7.2	0.72 (1.0)	0.01	0.072	7.1	3.5 (5.0)	0.1	0.71

[1] The first number is the estimated maximum residue based on the processing factor and the maximum residue level for whole oranges. The numbers in parentheses are the recommended MRLs. If the estimated maximum residue level is less than the 0.05 mg/kg limit of determination, the limit of determination is recommended as the MRL.

[2] No factor could be estimated because no residues were detected in the juice

FURTHER WORK OR INFORMATION

Desirable

1. Information on residues of carbosulfan in food in commerce or at consumption

2. The final report on the studies of the stability of carbosulfan and its metabolites in oranges and their processed products during frozen storage (final version of Interim Report P-3154)

4.7 CHLORMEQUAT (015)

TOXICOLOGY

Chlormequat was evaluated by the Joint Meeting in 1970, 1972, and 1994. In 1972, an ADI of 0-0.05 mg/kg bw was established on the basis of the NOAEL in a study of reproductive toxicity in rats. In 1994, the ADI was withdrawn owing to the inadequacy of the database in comparison with acceptable contemporary standards. The compound was reviewed at the present Meeting in response to a request from the manufacturer. New data on the absorption, distribution, excretion, and biotransformation of chlormequat and on its long-term toxicity in rats and dogs, carcinogenicity in mice and rats, reproductive toxicity in rats, and skin sensitization potential in guinea-pigs were reviewed.

In experiments with ^{14}C-labelled chlormequat in rats, absorption was rapid and elimination was essentially complete within 24 h, occurring almost entirely via the urine mainly as unmetabolized chlormequat. Less than 1% of the administered dose remained in the tissues. Accumulation of ^{15}N-labelled material in the kidneys was reported, but the experimental details were incomplete and detailed evaluation was not possible. Studies of the biotransformation of chlormequat suggested that the only metabolites found in rat urine may have been salts of chlorocholine. A polar, unidentified metabolite was found in faeces.

Pharmacological tests in mice, rats, rabbits, and cats given chlormequat intravenously revealed a stimulatory effect on the parasympathetic nervous system and a myoneural blocking action. Further work showed that chlormequat is a partial agonist of the nicotinic acetylcholine receptor; the affinity for muscarinic receptors was low and relatively unselective.

Chlormequat was of moderate acute oral toxicity in rats, mice, hamsters, guinea-pigs, and monkeys (LD_{50} = 200-1000 mg/kg bw), but rabbits and dogs appeared to be more sensitive (LD_{50} = 50-80 mg/kg bw) than the other species. The signs of toxicity may have been due to pharmacological activity, and there were no consistent treatment-related findings at autopsy. WHO has classified chlormequat as slightly hazardous.

In a four-week study of toxicity in rats at dietary concentrations of 0, 500, 1500, 3000, or 4500 ppm, the NOAEL was 1500 ppm, equal to 140 mg/kg bw per day, on the basis of reduced body-weight gain and depression of serum creatinine concentration. These results are largely in agreement with those of older studies in rats of up to 90 days' duration. In a 12-month study of

toxicity in dogs at dietary concentrations of 0, 150, 300, or 1000 ppm, the NOAEL was 150 ppm, equal to 4.7 mg/kg bw per day, on the basis of diarrhoea, vomiting, and salivation.

In a 110-week study of toxicity and carcinogenicity in mice at dietary concentrations of 0, 150, 600, or 2400 ppm, the NOAEL was 150 ppm, equal to 21 mg/kg per day, on the basis of tubular down-growth in the ovaries and endometrial hyperplasia.

In a 78-week study of toxicity and carcinogenicity in rats at dietary concentrations of 0, 280, 940, or 2800 ppm, the NOAEL was 940 ppm, equal to 43 mg/kg bw per day, on the basis of reduced body weight. Tumour incidences were not enhanced.

The potential carcinogenicity of chlormequat was investigated in a 104-week study in rats at dietary concentrations of 0, 280, 940, or 2800 ppm. No carcinogenicity were observed. The NOAEL was 940 ppm, equal to 42 mg/kg bw per day, on the basis of reduced body weight.

In a multigeneration study of reproductive toxicity in rats at dietary concentrations of 0, 300, 900, or 2700 ppm, the NOAEL for reproductive toxicity was 900 ppm, equal to 69 mg/kg bw per day, on the basis of reduced numbers of pregnancies and of delivered pups and retarded growth and development of the pups.

The developmental toxicity of chlormequat has been investigated in mice after administration by intraperitoneal injection, gavage, or via the diet, in rats by dietary administration, and in hamsters and rabbits by gavage. Many of the study reports were available only in summary form. In a study in mice at dietary concentrations of 0, 1000, or 10 000 ppm on days 1-15 of gestation or 25 000 ppm on days 11-15 of gestation, the number of malformations in animals fed 10 000 ppm or 25 000 ppm was reported to be slightly higher than that in controls; however, the significance of this observation was difficult to assess. In hamsters receiving chlormequat at levels of 0, 25, 50, 100, 200, 300, or 400 mg/kg bw once on day 8 of gestation or 100 mg/kg bw per day on days 7-9 of gestation, malformations and evidence of delayed development were seen after three doses of 100 mg/kg bw per day on days 7-9 of gestation or a single dose of 200, 300, or 400 mg/kg bw on day 8. Evidence of maternal and fetal toxicity was also seen at these doses. The study in hamsters could not be fully evaluated, owing to lack of detail in the publication. A full report of a well-conducted study in which rabbits were dosed orally with 0, 1.5, 3, 6 or 12 mg/kg bw per day on days 6-18 of gestation was available. Signs of maternal toxicity were seen at the highest dose, but there was no evidence of developmental toxicity.

Chlormequat has been adequately tested for genotoxicity *in vitro* and *in vivo* in a range of assays. The Meeting concluded that it was not genotoxic.

Chlormequat was not irritating to the skin or eye in rabbits. It did not cause delayed contact hypersensitivity when tested in albino guinea-pigs by the method of Buehler or by the method of Magnusson and Kligman.

An ADI of 0-0.05 mg/kg bw was allocated on the basis of the NOAEL of 4.7 mg/kg bw per day for diarrhoea, vomiting, and salivation in a one-year study of toxicity in dogs, and using a safety factor of 100.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 150 ppm, equal to 21 mg/kg bw per day (110-week study of toxicity and carcinogenicity)

Rat: 940 ppm, equal to 42 mg/kg bw per day (104-week study of toxicity and carcinogenicity)
900 ppm, equal to 69 mg/kg bw per day (two-generation study of reproductive toxicity)

Rabbit: 6 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
12 mg/kg bw per day (fetotoxicity and teratogenicity in a study of developmental toxicity)

Dog: 150 ppm, equal to 4.7 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.05 mg/kg/bw

Studies that would provide information useful for the continued evaluation of the compound

Developmental toxicity study in rodents that meets current scientific standards.

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to chlormequat

Human exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	Dermal irritation, rabbit	Not irritating
	Eye irritation, rabbit	Not irritating
	Skin sensitization, guinea-pig	Non-sensitizing
	Inhalation toxicity, rat	LC_{50} > 5 mg/l air
	Dermal toxicity, rabbit	LD_{50} = 1300 mg/kg bw
	Oral toxicity, rabbit	LD_{50} = 70 mg/kg bw
	Oral toxicity, cat	LD_{50} = 7-50 mg/kg bw
Medium-term (1-26 weeks)	Repeated oral, reproductive toxicity, rabbit	NOAEL = 6 mg/kg bw per day: maternal toxicity, no reproductive toxicity
Long-term (≥ one year)	Repeated oral, one year, dog	NOAEL = 4.7 mg/kg bw per day: diarrhoea, vomiting and salivation

4.8 CHLOROTHALONIL (081)

RESIDUE AND ANALYTICAL ASPECTS

Chlorothalonil is a non-systemic protectant fungicide. It was first evaluated for residues in 1974 and has been reviewed several times since, most recently as a periodic review in 1993. The 1993 JMPR required additional residue data from supervised trials on different types of melons, residue data on grapes treated according to GAP in Australia and animal transfer studies.

At the 27th (1995) Session of the CCPR the manufacturers indicated that they would provide information on GAP and residue data to the 1997 JMPR for some crops. The representative of the EU was invited to submit residue trials data and information on GAP for the use of chlorothalonil on tomatoes to the JMPR, to support extrapolation and to establish an MRL for peppers (ALINORM 95/24A, paras 107-111). The 1996 CCPR was informed that additional data would be provided for peaches, and decided to keep the MRL for peach at Step 7B.

The fate of residues has been studied with [^{14}C]chlorothalonil in lactating goats, laying hens and *in vitro* in bovine tissues.

Lactating goats. In goats dosed at a level equivalent to 3 ppm in the daily diet, the total radioactive residue (TRR, calculated as chlorothalonil equivalents) in milk and meat were extremely low with residues of 0.009 mg/kg in the milk and 0.004 mg/kg in the meat. The organs with the highest TRR were the liver and kidney which averaged 0.08 mg/kg and 0.22 mg/kg respectively, the residues being complex mixtures. The 4-hydroxy metabolite, SDS-3701 (4-hydroxy-2,5,6-trichloroisophthalonitrile) was identified in milk, liver and kidney. The metabolite was quantified in a group at 30 ppm at levels up to 0.05 mg/kg in the milk and liver and 0.08 mg/kg in the kidneys. The other major components of the residue that could be characterized were conjugates of chlorothalonil with glutathione. There were no detectable residues of the parent compound in the milk or tissues.

In similar metabolism and transfer studies with SDS-3701 this compound was the only terminal residue. After doses equivalent to 0.2 ppm it was found in muscle and fat at 0.01 to 0.02 mg/kg, in heart at 0.04 to 0.05 mg/kg, in liver at 0.07 mg/kg, in milk at 0.09 to 0.15 mg/kg and in kidney at 0.17 to 0.26 mg/kg.

Poultry. Laying hens were dosed once daily at levels equivalent to 2, 6 or 20 ppm of chlorothalonil in the diet for 21 days. The TRR was calculated as chlorothalonil equivalents. No radioactivity (<0.04 mg/kg) was detectable in egg whites at the 2 or 6 ppm levels at any sampling interval. The high dose yolks showed a maximum total radioactivity of 0.047 mg/kg from day 13 of dosing. Since no activity was detectable in the egg whites, the residues in whole eggs would be ≤50% of those in the yolks. Analysis of the tissues revealed the only detectable TRR to be present in the liver. The maximum TRR of 0.098 mg/kg was present in the livers of the mid-dose group within 6 hours after the final dose (2 ppm dose <0.04 mg/kg; 20 ppm dose 0.05 mg/kg).

Similar metabolism and transfer studies were conducted with SDS-3701 at dose levels equivalent to 0.1, 0.3 and 1 ppm. The TRR were calculated as SDS-3701 equivalents. No radioactivity (<0.04 mg/kg as SDS-3701) was detectable in egg whites at any dose level. In egg yolks the TRR in the low-dose group reached a plateau at approximately 0.04 mg/kg on day 21. The TRR in the mid- and high-dose yolks reached plateaus of 0.12 mg/kg at day 21 and 0.42 mg/kg at day 16 respectively. The residue in the egg yolks was shown to be unchanged SDS-3701. No activity was detectable in the fat or cardiac tissue of the low-dose group. The cardiac tissue from the mid- and high-dose groups showed maximum activities of 0.055 mg/kg and 0.15 mg/kg. The low-dose livers contained maximum residues of 0.06 mg/kg within 6 hours after the final dose. The highest TRR levels in the mid- and high-dose livers were 0.27 and 0.78 mg/kg respectively.

Studies of *in vitro* reactions of chlorothalonil with ruminant tissue systems as well as freezer storage stability studies with meat tissues and milk demonstrated that chlorothalonil was not stable in these substrates. It reacts extremely rapidly with components of bovine tissue homogenates with a maximum half-life of 1 minute, giving rise to polar metabolites and bound residues.

A multi-residue analytical method is used for the determination of chlorothalonil in fatty and non-fatty foods by gas chromatography with electron-capture or ion trap detection, with an LOD of 0.01 mg/kg and recoveries of 89-104%.

Chlorothalonil residues are lost quite rapidly at room temperature during such sample preparation as the comminution of fruits and vegetables (e.g. 95% loss from lettuce and 80% from broccoli), but subsequent losses were minimal during storage in the freezer. The losses have important implications, as analytical results could seriously underestimate chlorothalonil residues. The Meeting wishes to draw the attention of enforcement and monitoring laboratories to the need for sample preparation to be carried out under frozen conditions and followed by immediate extraction. The manufacturer confirmed that the data on residues in the samples from supervised trials evaluated by the present Meeting were valid because the samples were kept frozen throughout sample preparation.

Definition of the residue for animal products. Because the metabolite SDS-3701 is considered to be of toxicological importance, the Meeting recommended its inclusion in the definition of the residue for the risk assessment of residues in products of animal origin.

Definition of the residue in animal products for compliance with MRLs: chlorothalonil.

Definition of the residue in animal products for risk assessment: sum of chlorothalonil and 4-hydroxy-2,5,6-trichloroisophthalonitrile, expressed as chlorothalonil.

Chlorothalonil is not fat-soluble (log P_{ow} = 2.87).

Supervised residue trials gave the following results.

Citrus fruits. The use of chlorothalonil is registered in Spain (2 x 1.25 kg ai/ha, PHI 28 days). Whole fruits were analysed in six Spanish trials (one on mandarins, five on oranges). After two applications of 1.25 kg ai/ha the residues of chlorothalonil at 26-28 days ranged from 0.26 to 1.9 mg/kg. No information was received on residues in the pulp.

The Meeting concluded that the residue data were insufficient to estimate a maximum residue level for a major crop and confirmed the recommendation of the 1993 JMPR to withdraw the CXL.

Peaches. Chlorothalonil is registered in Italy and Spain (4 x 1.5 kg ai/ha). The Italian PHI is 14 days, and in Spain the last treatment should be not later than nut size of the fruit (PHI about 60 days).

Six residue trials were carried out in Italy and Spain at the GAP application rate (4 x 1.5 kg ai/ha), but the PHI was three weeks. The residues ranged from 0.54 to 1.4 mg/kg.

In six Italian trials with 3 applications of 1.25-1.5 kg ai/ha, the last with the fruit at nut size (PHI 64 or 66 days) the residues were <0.01 (5) and 0.04 mg/kg, and four Spanish trials (3 or 4 x 1.25-1.5 kg ai/ha) showed residues of <0.01 (82 days), 0.01 (69 days), 0.03 (87 days) and 0.15 (87 days) mg/kg. As one of the results at 87 days is higher than the Italian residues at 66 days, all these results should be included in the assessment. All the residues in the ten trials carried out in Italy and Spain (with PHIs of 64, 66, 69, 82 and 87 days) in rank order were <0.01 (6), 0.01, 0.03, 0.04 and 0.15 mg/kg.

The JMPR was informed that the reported residues were in the fruit without stone, not calculated for the whole commodity, and that the pulp represented 95% of the total weight. The Meeting concluded that a reduction in the residue values by 5% was not significant and did not recalculate the results.

The Meeting estimated a supervised trials median residue level of 0.01 mg/kg, and a maximum residue level of 0.2 mg/kg, based on Spanish GAP, to replace the draft MRL for peach (1 mg/kg) recommended by the 1993 JMPR.

Grapes. The 1993 JMPR listed as desirable additional residue data on grapes treated according to GAP in Australia (multiple treatments of 1.3-1.65 kg ai/ha, 0.12-0.15 kg ai/hl). The PHIs are 7 days for table grapes and 14 days for wine grapes.

Two trials according to GAP were reported to the 1983 and 1993 Meetings. In the first trial (7 x 0.11 kg ai/hl) residues were 8.6 mg/kg after 10 days. In the second (6 x 0.13 kg ai/hl) they were 0.6 mg/kg after 7 days and 2.9 mg/kg after 18 days.

In the five Australian trials reported to the current Meeting, grapes were treated 1-4 times at rates of 1.9-4.6 kg ai/ha. In two of them, residues of chlorothalonil were 4.8 and 5.2 mg/kg in two samples taken 7 days after a single treatment of 1.9-2.25 kg ai/ha (0.125-0.15 kg ai/hl). In the other trials, samples were taken from 60 to 96 days after the last treatment. Thus the trials were with fewer treatments or longer PHIs than the recommended GAP.

The Meeting agreed that the Australian residue data suggest the need for a higher MRL, but the data were not sufficient to support a recommendation to replace the current CXL (0.5 mg/kg).

Blackberries. Chlorothalonil is registered in the UK (4 x 2.5 kg ai/ha, 28-day PHI). One trial on blackberries in Sweden at the lower rate of 1 x 1.25 kg ai/ha was reported. No residues higher than the LOD of 0.01 mg/kg were found 7-28 days after treatment.

The Meeting noted that insufficient data were submitted and could not estimate a maximum residue level. The recommendation of the 1993 JMPR to withdraw the CXL was confirmed.

Currants. Chlorothalonil is registered in the UK (4 x 2.5 kg ai/ha, 28-day PHI). Six trials on black currants in the UK with 3 x 2.5 kg ai/ha, PHI 28 days, were reported. The chlorothalonil residues in rank order were 0.83, 0.94, 1.5, 1.9, 3.3 and 3.8 mg/kg.

The Meeting agreed to extrapolate from black to white and red currants and estimated a supervised trials median residue level of 1.7 mg/kg and a maximum residue level of 5 mg/kg for black, red and white currants.

Bananas. Registered uses exist with multiple treatments and PHIs of 1 or 0 days in Australia (1.1-2.16 kg ai/ha) and Latin America (aerial application, 0.88-1.63 kg ai/ha).

Two Australian trials on unbagged bananas reported to the 1993 JMPR were according to Australian GAP (10 x 1.1 or 2.2 kg ai/ha, 1-day PHI) and resulted in residues of 0.6 and 2.0 mg/kg.

In three of the four Latin American trials evaluated by the 1993 JMPR the residues were below 0.01 mg/kg; it was not stated whether the bananas were bagged or unbagged. In the fourth trial on unbagged fruit carried out in Costa Rica in 1985 (10 x 1.75 kg ai/ha, aerial application) the maximum residue in 6 field samples was 0.12 mg/kg 6 days after treatment.

Six Latin American supervised trials carried out in 1993 according to GAP (10-15 x 1.7 kg ai/ha, aerial application) were reported to the present Meeting. Samples of bagged bananas taken on the day of treatment showed residues below the LOD (<0.01 mg/kg).

On the basis of the residues in bagged bananas, the Meeting estimated an STMR of 0 and a maximum residue level of 0.01* mg/kg as a practical limit of determination.

Broccoli. Chlorothalonil is registered in the UK (2 x 1.5 kg ai/ha, 7-day PHI) and in the USA (1.7 kg ai/ha, 7-day PHI, number of treatments not specified). The Meeting re-evaluated the two US residue trials according to GAP reported to the 1993 JMPR (4 or 8 x 1.3 kg ai/ha, PHI 7 days) and reviewed two new trials (2 x 1.5 kg ai/ha, PHI 7 days).

The residues from the four trials show a median value of 2.25 mg/kg (rank order 1.5, 2.2, 2.3 and 2.6 mg/kg).

The Meeting estimated a supervised trials median residue level of 2.25 mg/kg and a maximum residue level of 5 mg/kg for broccoli.

Gherkins. The residues in four plot samples from one indoor Dutch trial were 0.64-1.1 mg/kg (median 0.78 mg/kg) three days after one treatment with 2.2 kg ai/ha.

As there were too few treatments to comply with Dutch GAP, which specifies 3-5 applications of 0.75-2.25 kg ai/ha, the Meeting could not estimate a maximum residue level.

Peppers. In response to a referral from the 1995 CCPR, the Meeting agreed that an extrapolation from tomatoes to peppers was inappropriate because of the large difference in the surface-to-weight ratio.

Chlorothalonil is registered in Australia, where multiple treatments of 1.3-1.65 kg ai/ha with a PHI of one day are recommended. In Latin America, multiple treatments of 1.8 kg ai/ha and a PHI of seven days are registered.

A total of 15 residue trials were carried out on bell peppers. Eight trials were conducted in Australia with 6 to 8 applications at 1.65-3.3 kg ai/ha, but samples were taken at the 1-day PHI in only two of them. The residues of chlorothalonil one day after treatment with 1.65 kg ai/ha were 0.43 and 5.3 mg/kg. Residues of 0.04 mg/kg were found in one Brazilian trial (3 x 1.75 kg ai/ha) 7 days after treatment. The residues in five trials carried out in 1996 (7-12 x 1.74-1.92 kg ai/ha) in Mexico, Honduras, Chile and Costa Rica 7 days after treatment were 0.05, 1.4, 1.6, 4.1 and 5.4 mg/kg. These were of the same order as the Australian residues and support the conclusion that a maximum residue level higher than 5 mg/kg is appropriate. All the results in rank order were 0.04, 0.05, 0.43, 1.4, 1.6, 4.1, 5.3 and 5.4 mg/kg (median 1.5 mg/kg).

The Meeting estimated a supervised trials median residue level of 1.5 mg/kg and a maximum residue level of 7 mg/kg for sweet peppers.

Mushrooms. Results of four field trials and one indoor trial reflecting Dutch GAP for cultivated mushrooms were reported by The Netherlands. The maximum residue was 0.78 mg/kg seven days after two treatments with 22 kg ai/ha.

The data were insufficient to estimate a maximum residue level.

Sweet corn (corn-on-the-cob). Registered uses of chlorothalonil exist in Australia (multiple treatments, 1.3-1.65 kg ai/ha, 1-day PHI) and the USA (multiple ground or aerial treatments, 0.7-1.6 kg ai/ha, 14-day PHI).

Four trials were carried out in the USA with 8 x 1.3 kg ai/ha. No residues above the LOD of 0.01 mg/kg were found in the cobs or the grain 14 days after treatment. Forage samples from three of the trials showed residues from 8.2 to 58 mg/kg at day 14. The difference between the residue levels in the cobs and the forage shows that surface residues of chlorothalonil would not be expected to translocate into the grain.

The Meeting estimated a supervised trials median residue level of 0.01 mg/kg and a maximum residue level of 0.01* mg/kg as a practical limit of determination.

Beans (dry). Chlorothalonil is registered in the UK with 2 x 1.5 kg ai/ha, and in the USA with multiple treatments of 1.2-1.75 kg ai/ha. The last treatment should be at end of flowering.

Residues from 24 trials with treatments near UK GAP (2 x 1.5 -1.8 kg ai/ha) at 49-71 days after treatment ranged from <0.01 to 0.1 mg/kg.

Chlorothalonil residues in trials according to US GAP (2-6 x 1.2-1.8 kg ai/ha) were <0.04 (2), 0.04 and 0.05 mg/kg at 40 to 43 days after treatment.

Combining the UK and US data gave residues in rank order of <0.01 (10), 0.02 (7), <0.04 (2), 0.04 (2), 0.05, 0.06, 0.07, 0.08 and 0.1 (3) mg/kg. The Meeting estimated a supervised trials median residue level of 0.02 mg/kg.

The Meeting also estimated a maximum residue level of 0.2 mg/kg for beans (dry), and confirmed the recommendation of the 1993 JMPR to withdraw the CXL for lima bean (dry).

Celeriac. A single trial in The Netherlands approximated Dutch GAP of 3-5 x 1.88 kg ai/ha, PHI 28 days. The maximum residue in four field samples was 2.8 mg/kg 28 days after two treatments with 1.8 kg ai/ha.

The data were insufficient to estimate a maximum residue level.

Wheat. Four field samples were taken in each of two trials in The Netherlands at 1 x 1.2 kg ai/ha with a 41-day PHI which approximated Dutch GAP of one treatment at 1 kg ai/ha and a PHI of 42 days.

The residues in the straw ranged from 0.03 to 4.1 mg/kg. No change of the current CXL of 20 mg/kg is proposed. The highest residue in the grain was 0.12 mg/kg. The Meeting agreed that the data suggested that a higher MRL than the current CXL of 0.1 mg/kg was needed, but the two trials were not sufficient to support a new recommendation.

Fresh herbs. Chlorothalonil is registered for outdoor use in the Netherlands an parsley and celery leaves (3-5 x 1.87 kg ai/ha, 28-day PHI). One trial on parsley, one on celeriac leaves and two on celery leaves (3-4 x 1.8-1.9 kg ai/ha, PHI 27-28 days) were reported.The maximum residues of the four replicates from each trial in rank order were 0.13, 1.6, 2.3 and 2.4 mg/kg.

The Meeting estimated supervised trials median residue levels of 1.95 mg/kg and maximum residue levels of 3 mg/kg for parsley and celery leaves (fresh).

Determination of metabolites and impurities in plants. Samples of selected crops were analysed for the metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile (SDS-3701), and the technical impurities hexachlorobenzene (HCB) and pentachlorobenzonitrile (PCBN). In sweet peppers the highest residue of SDS-3701 was 0.04 mg/kg. SDS-3701 and HCB residues in bananas and sweet corn cobs were below the LODs of 0.01 and 0.00025 mg/kg respectively. SDS-3701, HCB and PCBN were not detected in dry beans (<0.03, <0.004 and <0.01 mg/kg respectively).

Animal products. Animal metabolism and transfer studies with [^{14}C]chlorothalonil on lactating goats and laying hens showed very little or no transfer of the pesticide from animal feed to milk, fat, tissues or eggs. Chlorothalonil *per se* absorbed from the gastrointestinal tract would be very short-lived and could not be transmitted as a residue to food items such as meat, liver, milk or edible offal.

Animal transfer studies on cattle were carried out for 28 days at levels of 1.5 ppm chlorothalonil plus 0.1 ppm SDS-3701, 3 ppm chlorothalonil plus 0.2 ppm SDS-3701, 9 ppm chlorothalonil plus 0.6 ppm SDS-3701 and 30 ppm chlorothalonil plus 2 ppm SDS-3701, to represent potential dietary levels of residues in livestock feeds. The median residue levels of chlorothalonil in such feed items as sugar beet and cereal straw found in supervised trials reported to the 1993 JMPR demonstrate that a level of 3 ppm chlorothalonil plus 0.2 ppm SDS-3701 should be realistic for residues in potential feed items and appropriate for estimating the transfer of chlorothalonil to animal products. The residues of the metabolite SDS-3701 were 0.1 mg/kg in milk (reaching a plateau after day 9), 0.02 mg/kg in muscle, 0.04 mg/kg in liver and 0.28 mg/kg in kidney at the end of the study (day 28).

Since the full details of the studies were not reported, the Meeting could not estimate maximum residue levels for animal products.

Data on residues of chlorothalonil in foods in commerce in 1995 were reported from The Netherlands. Of 4282 samples analysed, 4228 (98.7%) were without residues (<0.01 mg/kg). Residues above the Dutch MRLs were found in 14 samples (0.33 %).

FURTHER WORK OR INFORMATION

Desirable

1. Additional residue data on table grapes and sweet corn treated according to GAP in Australia.

2. Additional residue data from supervised trials on different types of melons (from 1993).

4.9 CLETHODIM (187)

RESIDUE AND ANALYTICAL ASPECTS

Clethodim was first evaluated by the 1994 JMPR which recommended a number of MRLs. At the 28th Session of the CCPR opinions were expressed that the 1994 monographs were unclear and over-summarized. Detailed written comments were submitted by some governments, to which the manufacturer has provided an item-by-item response.

In response to the submitted comments, the Meeting evaluated the previously reviewed data in more detail. The comments and the responses of the Meeting are given below.

Metabolism

(i) "*There are no data on the kinds and quantities of metabolites in the goat study. Therefore, it cannot be established whether the definition of residues for cattle kidney, liver, meat, milk is acceptable*."

The study was re-evaluated. Milk contained 0.02-0.05 mg/kg clethodim equivalents and the highest tissue concentrations were found in the liver (0.414 mg/kg clethodim equivalents) and kidney (0.378 mg/kg). In milk, the extracted radioactivity was mostly associated with lactose and clethodim sulfoxide. In the blood and tissues the major compounds were clethodim sulfoxide (33-52% of the substrate radioactivity) and *S*-methyl-clethodim sulfoxide (6-37%). Clethodim was only found above 4% of the substrate radioactivity in blood (28%) and liver (28%).

(ii) "*There are no data on quantities concerning the metabolism in plants, i.e. there are no data indicating the determined quantities of the metabolites referred to*."

The metabolism studies on carrots, soya beans and cotton have been re-evaluated and information on the quantities of individual metabolites is provided in the monograph. The identified metabolites were clethodim sulfoxide, clethodim sulfone, the imine sulfoxide and sulfone, and 5-hydroxyclethodim sulfoxide and sulfone. Clethodim was not present or was found at very low levels. Clethodim sulfoxide and the imine sulfoxide were the major metabolites in both leaves and edible parts.

Methods of analysis

(iii) "*According to the method of residue analysis referred to, two compounds have to be determined simultaneously, therefore it is doubtful whether a determination limit of 0.05 mg/kg for both compounds is practicable, also in view of the dissolution of isomers into several peaks which is possible under certain circumstances.*"

In the "common moiety" method referred to, clethodim and its metabolites containing the 2-cyclohexen-1-one moiety are determined as dimethyl 3-[2-(ethylsulfonyl)propyl]pentanedioate (DME) and its 3-hydroxy analogue (DME-OH) as described in the 1994 monograph. The manufacturer has supplied several typical chromatograms which showed two resolved peaks

with some tailing, for labelled DME and DME-OH standards in clean solvent at concentrations of 0.5 ìg/ml and 0.75 ìg/ml or 10 or 25 ng. The reports of the trials included data showing acceptable recoveries (generally 70-110%) for a range of crop commodities; these were usually at fortification levels above 0.2 mg/kg each of clethodim, clethodim sulfoxide and 5-hydroxyclethodim sulfone. Some acceptable recoveries of clethodim sulfoxide and sulfone at 0.05 mg/kg were submitted, e.g. for dried peas. Some of the residue trials (e.g. on succulent beans) reported “limits of quantification” of 0.1 mg/kg.

A revised confirmatory method was submitted to the present Meeting. The recovery data for the revised method, which is necessary to differentiate clethodim from related compounds such as sethoxydim, indicated that 0.05 mg/kg could not be achieved routinely. The Meeting noted that the lowest fortification level at which acceptable individual recoveries could be achieved was generally about 0.5 mg/kg. Acceptable recoveries were obtained from sugar beet, potatoes and liver at 0.1, 0.2 and 0.2 mg/kg respectively however. The Meeting agreed that it will be necessary for monitoring and enforcement laboratories to use the amended confirmatory method to differentiate residues of clethodim from those of sethoxydim if measurable residues are found with the "common moiety" method reviewed by the 1994 Meeting. The Meeting also agreed that the limit of determination appropriate for routine monitoring and enforcement should be that of the confirmatory method.

On the basis of the information on the revised confirmatory method, the Meeting concluded that the practical limit of determination appropriate for routine monitoring and enforcement should be 0.5 mg/kg, with lower levels only for sugar beet, fodder beat, potatoes, liver, kidney and milk. For milk a practical limit of determination of 0.1 mg/kg was considered appropriate. Accordingly the Meeting recommended that some of the low maximum residue levels estimated by the 1994 Meeting be raised to 0.5* mg/kg and that these should be recommended as MRLs.

(iv) "*The method of analysis referred to does not make it possible to distinguish between residues from sethoxydim and a clethodim treatment. A verification method for the determination of clethodim and its metabolites has not been published and is thus not available for food inspection purposes.*"

The revised confirmatory method mentioned above is evaluated in the monograph. It is specific for the determination of clethodim and its metabolites in crops, animal tissues, milk and eggs, and can distinguish residues of clethodim from those of sethoxydim. The Meeting expressed concern that details of the revised confirmatory method were not currently in the public domain, but was informed that the manufacturer would make full details of the method available to monitoring and enforcement laboratories on request.

Supervised trials

(v) "*The residue trials for beans (dry), field peas (dry), potatoes and sugar beets are summarized too strongly. Obviously, in some cases only summaries of trials have been available to the JMPR; we hold the view that an evaluation on such a basis should be refused.*"

The trials data for dry beans, dry peas, potatoes and sugar beets reviewed by the 1994 Meeting are given in more detail in the monograph. The Meeting agreed that summaries of data should not be used when not accompanied by the full study reports, but full study reports were

available to the Meeting on all the trials about which concern had been expressed except two potato trials, one each in the Ukraine and Belgium, for which only summaries were available.

(vi) "*It cannot be understood in all cases on which GAPs (use pattern) and which residue data the proposed MRLs are based. We hold the view that the residue data for potatoes are insufficient, irrespective thereof they do not justify an MRL of 0.2 mg/kg since the data from Canada cannot be used as a basis of comparison with the treatment in Belgium, Ecuador, Peru and Switzerland for climatic reasons.*" In addition, it was stated that "*The data is only available in summarized form. The number of trials that are within GAP is rather limited. The proposal is based on Canadian trials.*"

The Meeting agreed that outdoor trials data in Canada would not normally be related to GAP in Europe or South America. Additional information was provided to the current Meeting on GAP for potatoes in Australia, Belgium, Bulgaria, Canada, Czech Republic, Dominican Republic, Ecuador, Germany, Israel, Peru, Poland, Russia, Switzerland and Yugoslavia. This indicated slight changes from the GAP reported in 1994 for Belgium and Switzerland. The maximum application rates are 0.12-0.36 kg ai/ha with PHIs of 7-60 days. Canadian GAP was reported to the current Meeting. Although the Meeting agreed that the data were rather limited, a number of trials were available which indicated that residues resulting from a number of use patterns were low and often below the LOD. The Meeting confirmed that the previously estimated maximum residue level of 0.2 mg/kg was appropriate.

(vii) "*The MRL for sugar beet seems to be based on two Italian trials the results of which deviate from all other trials without any explanation being given.*"

GAP for sugar beet in Belgium, Morocco, Spain and Switzerland was reported to the 1994 Meeting. The maximum application rates were 0.20-0.36 kg ai/ha with PHIs from 50-90 days or not specified.

Nine French trials and one German trial were considered comparable to the German GAP reported to the current Meeting, with residue levels of <0.03 (9) and 0.05 mg/kg. Four Italian trials reported to the 1994 Meeting had originally been considered to comply with Spanish GAP, with reported residue levels of 0.06 (2) and 0.17 (2) mg/kg at 59 or 60 days. However, the Meeting was informed that treatment of sugar beet was at about the 2-8 leaf stage and that the minimum PHI was "about 90 days in practice."

In view of this new information the Meeting agreed to revise the previous recommendation and estimated a maximum residue level of 0.1* mg/kg, based on the trials according to German GAP. The Meeting concluded that the limit of determination in sugar beet was 0.1 mg/kg because acceptable recovery data for the revised confirmatory method had been submitted at this level.

(viii) "*The MRLs of 0.1 mg/kg cattle kidney and liver are obviously based on a dosage of 10 mg/kg feed. But there are no reports on residues in potential feeding stuffs which would lead to such residues in everyday feed. Soya beans (MRL 10 mg/kg) usually only reach a percentage of 25-30 % in everyday feed: for cotton seed and rape seed an MRL of only 0.5 mg/kg has been envisaged. The MRL of 0.1 mg/kg cattle kidney, liver thus is unnecessarily high.*"

The Meeting observed that the highest residues (DME, S-methyl-DME and DME-OH) found in cows at the lowest dosing level were 0.059, <0.05 and <0.05 mg/kg, and 0.051, <0.05 and <0.05 mg/kg in liver and kidney respectively. Since clethodim residues are calculated by the summation of the DME and DME-OH peaks in the common moiety method, the Meeting agreed that the maximum residue levels of 0.1 mg/kg estimated for cattle liver and kidney by the 1994 Meeting had been appropriate. However, in view of the new information provided on the limit of determination of the revised confirmatory method, the Meeting agreed to increase the estimates to 0.2* mg/kg. The Meeting recognised that acceptable data on recoveries from kidney by the revised confirmatory method were not available but considered that the limit of determination in kidney was likely to be similar to that in liver, from which recoveries were satisfactory at 0.2 mg/kg.

(ix) The comment was made for beans (dry) "*The data is only available in summarized form. The number of trials is not specified. There are only trials from one country (Brazil) where clethodim is not registered. The trials are in accordance with GAP of other countries in the region. The proposal is based on a PHI of 65 days (pp. 358, 1994 Evaluations). Taking this PHI into account, 0.05 mg/kg is more appropriate.*"

In response, the supervised trials data for dry beans reviewed by the 1994 Meeting are given in more detail in the monograph. The Meeting reassessed the data which were available to the 1994 Meeting, concluded that they were insufficient to estimate a maximum residue level, and withdrew the previous recommendation for an MRL.

(x) "*Although a minor point, the table on pp 346 (1994 Evaluations) does not specify the levels in refined oil, and clarification is sought on the statement in the text (pp 347) that processing reduces levels to 10% in refined oil.*"

Additional information is provided in the monograph. The residue in the refined oil was <0.08 mg/kg and in the unprocessed cotton seed 0.8 mg/kg. A processing factor of <0.1 for cotton seed to refined oil is therefore appropriate.

(xi) Comments on dry field peas were that "*There is only registered use in Australia. The proposal is based on a PHI of 50-110 days (pp 358, 1994 Evaluations). On the basis of the Australian trial data (number of trials not specified, dosage 0.06-0.24 kg ai/ha, PHI 110 days) a limit of 0.05 mg/kg is sufficient. Also UK data (0.36 kg ai/ha [six times Australian registered dose], PHI 53 and 85 days) and Belgium data (up to three times registered dose in Australia, PHI 41 days) support this latter level. Only the French trials (0.18 kg ai/ha, PHI 67-82 days) points to a level of 0.1 mg/kg, but this is not in accordance with GAP.*"

A re-evaluation of the data on dry field peas has been carried out (see below), since new information on GAP and data from residue trials were reported to the present Meeting.

(xii) "*The proposal for sunflower seed is based on data from Argentina taking into account a PHI of 106 days. However, such a long PHI is not in accordance with the PHI reported for Argentina and other countries in table 4 of the Evaluations. The Netherlands therefore reserves its position for these proposals. For oil, crude and oil edible 0.05 mg/kg are reasonable when 0.2 mg/kg is a appropriate level for sunflower seed.*"

GAP for sunflower in Argentina, Bolivia, Ecuador, Israel, Morocco, Paraguay and Spain was reported in the 1994 monograph, where the maximum application rate in Spain was stated to be 0.2 kg ai/ha with an unspecified PHI. The manufacturer informed the Meeting that the use was post-emergence and that the Spanish PHI was "60 days in practice". Residues from applications 60-74 days before harvest were 0.03-0.13 mg/kg in three Italian trials.

The maximum application rate in South America was 0.12-0.34 kg ai/ha with PHIs of 5-56 days or not specified. The PHIs in all of the Argentinean trials were longer at 102-106 days. The manufacturer stated that "although the PHI from the Argentina trials exceeded the GAP of 75 days, we believe that we would not detect any greater than what we have observed at a 75 day PHI." The Meeting concluded that there were insufficient data from trials according to GAP to estimate a maximum residue level and withdrew the previous estimate.

GAP for such broad categories as "fruit" or "vegetables" has been ignored in evaluating the results of the other supervised trials reviewed below.

Peaches. Conflicting information on GAP in Spain had been reported, with application rates of 0.096-0.192 or 0.036-0.24 kg ai/ha. The timing of the application was also unclear. The Meeting was informed that the application was directed around the base of the tree.

GAP for “fruit trees” was reported for Chile, Ecuador and Saudi Arabia and for “orchard crops” for New Zealand. The maximum application rates were 0.06-0.24 kg ai/hl and 0.18-0.72 kg ai/ha with PHIs ranging from 15-60 days or not specified.

The Meeting noted that although all the residues in the trials on peaches were below the limit of determination of 0.03 mg/kg, only one trial included a PHI longer than 21 days. Since longer intervals between treatment and harvest might lead to determinable residues owing to uptake, and in view of the conflicting information on GAP, the Meeting concluded that there were insufficient data to estimate a maximum residue level.

Onions and garlic. Information on GAP for garlic in Saudi Arabia, Spain and the USA was reported. The maximum application rates were 0.192- 0.28 kg ai/ha with PHIs of 30, 45 or 60 days. The maximum number of applications was not stated for any country.

Only two trials on garlic were considered to comply with US GAP. Although the DME-OH residue levels were described by the manufacturer as “not considered to be clethodim-related, due to matrix interference peak” this could not be confirmed by the Meeting and the results were therefore included; the residues (sum of DME and DME-OH) were 0.36 and 0.1 mg/kg.

GAP for onions was reported for Australia, Belize, Dominican Republic, Guatemala, Honduras, Israel, New Zealand, Russia, Saudi Arabia, Turkey, the USA and Uzbekistan, and pending GAP in Brazil. The maximum application rates were 0.12-0.28 kg ai/ha (0.108 kg/ha in the pending Brazilian GAP) with PHIs of 7-65 days.

The residues in trials considered to comply with US GAP were <0.05, ≤0.1(4), 0.13 and 0.15 mg/kg. The residues in trials considered to be in accord with GAP in New Zealand or pending GAP in Brazil were all below the limit of determination, as were other residues from exaggerated application rates in some of these trials. The residues from the trials according to GAP were

<0.01, <0.02, <0.03 (4) and <0.05 (6) mg/kg. Only one trial accorded with Australian GAP, with a residue of 0.05 mg/kg.

The Meeting agreed that the results of the garlic and onion trials could be combined, but noted that the US residues formed a different population from those in the Brazilian and New Zealand trials. The combined US residues in rank order were <0.05, <0.1 (4), 0.1, 0.13, 0.15 and 0.36 mg/kg. The Meeting estimated maximum residue levels of 0.5 mg/kg and STMRs of 0.1 mg/kg, based on US GAP, for both onion and garlic.

Cabbage. GAP was reported for Australia and Poland. The maximum application rates are 0.12 and 0.24 kg ai/ha with PHIs of 7 and 60 days respectively.

Only one residue trial was considered to comply with Australian GAP and one with Polish. The residues were 0.07 and 0.15 mg/kg respectively. There were insufficient data to estimate a maximum residue level.

Cauliflower. GAP was reported only for New Zealand, with a maximum application rate of 0.24 kg ai/ha and a PHI of 35 days. Only one trial was considered to comply with this, with a residue of 0.28 mg/kg. There were insufficient data to estimate a maximum residue level.

Cucumber. GAP for cucumbers was reported only for Poland, with a maximum application rate of 0.24 kg ai/ha and a PHI of 60 days, and for cucurbits in Paraguay with the same maximum application rate and an unstated PHI.

A single trial was considered to be comparable to Polish GAP, because although the PHI was shorter the residue level was <0.05 mg/kg. In six US trials all residues were <0.14 mg/kg at the short PHI of 13-14 days, but none of the trials was according to GAP. There were insufficient data to estimate a maximum residue level.

Summer squash. GAP for cucurbits was reported for Paraguay, but none of the three trials in the USA were considered to conform to it. There were insufficient data to estimate a maximum residue level.

Tomatoes. GAP for tomatoes was reported for Belize, Bulgaria, Dominican Republic, Israel, Italy, Nicaragua, Spain and the USA, and pending GAP for Brazil. The maximum application rates are 0.12-0.28 kg ai/ha (0.108 kg/ha for the pending GAP) with PHIs of 7-30 days, “unrestricted” or unstated.

The residues in two trials considered to comply with the pending Brazilian GAP were <0.05 mg/kg.

The residues in trials considered to comply with Spanish GAP were <0.03 (5), 0.03, 0.08 and 0.13 mg/kg, and with US GAP <0.1 (3), 0.11, 0.12, 0.15 (2), 0.16, 0.17, 0.21, 0.27, 0.34, 0.35 (2), 0.43, 0.46, 0.50, 0.52, 0.54, 0.65, 0.71, 0.76 (2) and 0.82 mg/kg. The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.35 mg/kg, based on the trials according to US GAP.

Lettuce. GAP was reported for Australia and Israel. The maximum application rates are 0.12 kg

ai/ha with PHIs of 28 days and unstated respectively.

The residues in trials considered to comply with Australian GAP were 0.04 and 0.21 mg/kg. There were insufficient data to estimate a maximum residue level.

Beans (fresh). GAP was reported for beans for Belgium, Bolivia, Bulgaria, Paraguay, Peru, Spain and Turkey, for mung and fava beans for Australia and for legumes for Chile. The maximum application rates are 0.06-0.48 kg ai/ha with PHIs of 0-65 days or unstated.

The residues in fresh beans from trials considered to comply with Belgian GAP were <0.025 and <0.05 (4) mg/kg. Although some of the Belgian results were at shorter PHIs than GAP, the residues were all below the limit of determination. In addition one trial on "green beans" with a residue of 0.21 mg/kg and one on "French beans" with a residue of <0.03 mg/kg were considered to comply with Spanish GAP. Although data on a number of US trials were also submitted, no GAP was reported for the North American continent. A trial on broad (fava) beans in Spain did not conform to reported GAP.

The Meeting estimated a maximum residue level of 0.5* mg/kg and an STMR of 0.05 mg/kg for beans, except broad bean and soya bean, based on the trials according to Belgian GAP.

Lentils. GAP for lentils was reported to the current Meeting for Canada, New Zealand and Turkey, and to the 1994 Meeting for New Zealand and Spain. GAP for beans and legumes would presumably cover lentils.

Although two Spanish trials were reported, they could not be evaluated against the Spanish GAP recorded in 1994 because the GAP did not include the PHI. Neither of the trials was considered to comply with relevant GAP. There were insufficient data to estimate a maximum residue level.

Lupins. GAP for lupins was reported for Australia, with a maximum application rate of 0.12 kg ai/ha; no PHI was specified.

Only one trial was considered to comply with Australian GAP with a residue of <0.1 mg/kg. The Meeting could not estimate a maximum residue level.

Carrots. GAP for carrots was reported for Israel and Russia, and pending GAP for Brazil. The maximum application rates were 0.108 (Brazil) - 0.24 kg ai/ha with PHIs of 40-75 days.

The residues in two trials which complied with the pending Brazilian GAP were <0.05 mg/kg. None of the other trials were considered to accord with any other reported GAP. There were insufficient data to estimate a maximum residue level.

Celery. GAP for celery was reported for Australia. The maximum application rate is 0.12 kg ai/ha with a PHI of 9 weeks.

The only trial which complied with Australian GAP showed a residue of 0.04 mg/kg. There were insufficient data to estimate a maximum residue level.

Linseed (flax). GAP was reported for Canada, Russia and the Ukraine. The maximum application rates were 0.09-0.24 kg ai/ha. PHIs were 60-80 days or not specified.

One trial was considered to be in accord with Russian GAP, with a residue of <0.01 mg/kg. Several Canadian trials were reported in which exaggerated rates had been used with all residues below the limit of determination at PHIs of 84-119 days, but since no samples were taken at the Canadian PHI of 60 days the Meeting concluded that there were insufficient data to estimate a maximum residue level.

Peanuts. GAP was reported for Argentina, Australia, Bolivia, Israel, Taiwan and the USA. The maximum application rates were 0.09-0.336 kg ai/ha with PHIs of 40-70 days or not specified. GAP for "vegetables" was also reported for Chile, Ecuador, New Zealand, Paraguay and Peru.

The residues in trials considered to comply with US GAP were <0.05, 0.34, 0.56, 0.79, 1.3 (2), 1.8, 2.7 and 3.5 mg/kg in the kernels and 0.17, 0.20, 0.24, 0.24, 0.3, 0.60, 0.75 and 0.81 mg/kg in the hulls. The Meeting estimated a maximum residue of 5 mg/kg and an STMR of 1.3 mg/kg for peanut.

Alfalfa. GAP was reported for Argentina, Canada, Chile, Ecuador, Israel, Peru and the USA. The maximum application rates were 0.09-0.48 kg ai/ha with PHIs of 15-30 days or not specified.

Trials according to national GAP were carried out in Canada and the USA with residues of <0.02 (7) and 0.02 mg/kg in Canada, and 0.27, 0.53, 0.61, 0.62, 0.67, 0.85, 1.2, 1.4 (3), 1.5, 1.6, 1.9, 2.0, 2.6, 2.7 (2), 3.0, 4.4, 4.5, 5.4 and 8.9 mg/kg in the USA. The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 1.6 mg/kg, based on US GAP.

White Clover. GAP for clover was reported for Israel and New Zealand. The maximum application rates are both 0.12 kg ai/ha with a PHI of 63 days in New Zealand and not specified in Israel. GAP for "vegetables" was reported for Chile, Ecuador, New Zealand, Paraguay and Peru

The two residues in trials considered to comply with New Zealand GAP were 0.07 and 0.26 mg/kg. The samples analysed were described as "young plants" and "silage". There were insufficient data to estimate a maximum residue level.

Field peas (dry). GAP for field peas was reported for Australia and Canada. The maximum application rate in Canada is 0.09 kg ai/ha with a PHI of 75 days. The maximum rate reported by the Australian government, supported by a product label, was 0.06 kg ai/ha and differed from that reported by the manufacturer.

All the residues in six trials in Australia were <0.1 mg/kg after 110 days even at exaggerated doses. The residues in several further trials which were considered to comply with Canadian GAP were <0.02 (4), 0.06, 0.08, <0.10, 0.18 (2), 0.31, 0.65 and 1.8 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.08 mg/kg, based on Canadian GAP.

Peas. GAP for peas was reported for Belgium, the Czech Republic, Israel, New Zealand and Spain, and for "proteaginous peas" for France. The maximum application rates are 0.06-0.36 kg

ai/ha with PHIs of 30 or 60 days, or not specified. No trials were considered to comply with relevant GAP and no maximum residue level could be estimated.

Fodder beet. GAP was reported for Belgium, the Czech Republic, Germany, Italy, Russia and Switzerland. The maximum application rates are 0.14-0.36 kg ai/ha with PHIs of 60-90 days or not specified. The Meeting was informed that application is at about the 2-8 leaf growth stage.

The residues in three trials in France which were considered to comply with Belgian GAP were all below the LOD of 0.03 mg/kg in both roots and tops. In additional trials at the same sites with exaggerated application rates the residues were also all below 0.03 mg/kg. The Meeting estimated a maximum residue level of 0.1* mg/kg and an STMR of 0.03 mg/kg. The Meeting established the limit of determination for fodder beet at 0.1 mg/kg because acceptable recovery data for the revised confirmatory method had been submitted for sugar beet at this level.

Other commodities. Residue trials data were also submitted for leeks, spinach, artichokes, sweet peppers and "non-bell peppers" but no specific GAP was reported to the present or the 1994 Meeting. The Meeting agreed that it would be appropriate to evaluate these trials against a general GAP for vegetables in the case of this compound, since it is a post-emergence herbicide, but there were no trials on any of these commodities according to GAP from which to estimate maximum residue levels.

FURTHER WORK OR INFORMATION

Desirable

Data on residues occurring in commerce and/or at consumption (from 1994 Meeting).

4.10 2,4-D AND ITS SALTS AND ESTERS

EVALUATION OF EFFECTS ON THE ENVIRONMENT

2,4-D, 2,4-dichlorophenoxyacetic acid, is a selective herbicide available as the free acid, salts and esters. 2,4-D has low volatility and is not expected to be lost by evaporation after application. Amine salt formulations of 2,4-D are less volatile than butyl, ethyl, or isopropyl ester formulations.

The 2-ethylhexyl (EH) ester is hydrolysed under alkaline conditions (half-life 48 days at pH 7 and 2.2 days at pH 9). 2,4-D may be degraded slowly by photolysis. The half-life of 2,4-D in aqueous solution was 4.5 days under aerobic conditions and 312 days under anaerobic conditions. The major breakdown product was CO_2, with 2,4-dichlorophenol, 2,4-dichloroanisole, and 4-chlorophenoxyacetic acid also being formed as intermediates. The half-lives of 2,4-D determined in natural waters after aerial application of its dimethylamine (DMA) salt ranged from 1.1 to 20 days. 2,4-D formulations were found to be rapidly hydrolysed or biodegraded in ponds and lakes.

There was no evidence of bioaccumulation of 2,4-D in aquatic organisms.

The behaviour of 2,4-D salts and esters in soils is greatly influenced by the organic matter content and pH. 2,4-D is more strongly adsorbed in soils with higher organic matter content and/or lower pH. The rapid biodegradation of 2,4-D in soil prevents significant downward movement under normal field conditions. Run-off from treated soil has been estimated at between 0.01 and 1% of the applied 2,4-D; the maximum recorded concentrations following run-off were about 0.2 ìg/l. Under non-sterile conditions various esters of 2,4-D are hydrolysed very rapidly in soils (>72% within 72 h). A number of microbial organisms rapidly degrade 2,4-D, which has half-lives of 1.25 h to 40 days, usually between 3 and 10 days. The DMA salt rapidly dissociates, leaving 2,4-D which then undergoes further degradation.

Field trials in the USA using the DMA salt or the EH ester at 2.24 kg acid-equivalent/ha on grass resulted in maximum initial residues at day 0 of 120 or 153 mg acid-equivalent/kg, respectively. These initial residues decreased by a half to a third by day 7.

In general, populations of aerobic bacteria, actinomycetes, and fungi in soils were not affected by 2,4-D at 25 ppm. At an application rate of 0.95 kg/ha, populations of bacteria, fungi, and actinomycetes were reduced by 26.3%, 19.5% and 30%, respectively, by the iso-octyl (IO) ester, but approximately half as much by the DMA salt.

2,4-D at the maximum recommended application rate has a growth-stimulating effect (10%) on *Skeletonema costatum*, whereas it inhibits the growth of *Navicula pelliculosa*, (24%) and *Lemna gibba* (75%). The 5-day EC_{50} for the acute toxicity of 2,4-D and its salts and esters differs widely among algal species and compounds, ranging from 0.23 mg ai/l (EH ester for *Skeletonema costatum*) to 153 mg ai/l (DMA salt for *Anabaena flosaquae*). The acute toxicity of 2,4-D to the aquatic higher plant *Lemna gibba* also depended upon the salt or ester used, with 14-day EC_{50} values of 3.3, 0.58 and 0.5 mg/l for 2,4-D, the DMA salt and the EH ester respectively.

At concentrations ranging from 0.001 to 100 mg/l, 2,4-D had no effect on chlorophyll production in several algal species. *Anabaenopsis raciborskii* was found to tolerate up to 800 ìg/ml of 2,4-D in liquid culture media.

Many studies have been performed on invertebrate fresh water and estuarine or marine species, including *Daphnia*, *Gammarus*, *Macrobranchium*, *Crassostrea*, *Palaemonetes*, *Panaeus*, and *Uca*. Many forms of 2,4-D have been evaluated: 2,4-D itself, the DMA, diethanolamine (DEA), isopropylamine (IPA), tri-isopropanolamine (TIPA), and sodium salts, and the EH, butoxyethyl (BE), and isopropyl (IP) esters. 2,4-D and its salts are generally less toxic to these organisms than the ester forms. Acute toxicity (48-h LC_{50} values) to *Daphnia magna* ranged from 5.2 mg ai/l (IO ester) to 184 mg ai/l (DMA salt) and 21 day NOECs ranged from 0.0015 mg ai/l (EH ester) to 27.5 mg ai/l (DMA salt) and 79 mg ai/l (acid).

At concentrations of 1.0 and 10.0 mg BE ester/l, grass shrimp were observed to avoid water containing these levels. In a life-cycle study on *Daphnia magna*, the NOEC was 23.6 mg ai DEA salt/l. In a chronic toxicity study on *Daphnia magna* using the BE ester, the Maximum Acceptable Toxicant Concentration (MATC) ranged between 0.70 mg/l and 0.29 mg/l.

Frog and toad tadpole 96-hour LC_{50} values ranged from 8 mg/l for the free acid to 477 mg/l for the DMA salt.

Many data were available on the effects of 2,4-D and its salts and esters on various growth stages of fish such as *Oncorhynchus, Lepomis*, *Pimephales*, *Gambusia*, *Micropterus*, and *Salm*o. Generally, 2,4-D and its salts are less toxic to fish than are the esters. Typical 96-h LC_{50} values for adult fish ranged from 5 to 10 mg a.i./l for the IO ester, from 200 to 400 mg a.i./l for 2,4-D, and from 250 to 500 mg a.i./l for the DEA salt, although lower figures have been reported. Early life stages appear to be more sensitive, with 32-day NOECs ranging from 0.12 mg a.i./l (EH ester) to 17.1 mg a.i./l (DEA salt) and 63.4 mg a.i./l (acid).

Embryos and larvae of the fathead minnow (*Pimephales promelas*), were exposed to up to 416.1 ìg/l of the BE ester for 32 days. The NOEC was 80.5 ìg/l, with the MATC estimated to be 96.0 ìg/l. The sodium salt of 2,4-D had no inhibitory effect on the hatching of carp eggs at 25 mg/l, but at a concentration of 100 mg/l none hatched. At 50 mg a.i./l the sodium salt was not harmful to carp embryos but induced behavioural changes, some morphopathological changes, and ultimately death in carp larvae.

Honeybee oral and contact LD_{50} values for the DMA salt and EH ester were all >100 ìg/bee. Toxic effects have not been noted for bees in the field.

2,4-D (in combination with MCPA) did not harm *Trichogramma cacoeciae* at 1.5% in water or *Aleochara bilineata* at the label recommended rate. 2,4-D mixed amine salts and mixed isopropyl esters were toxic to coccinellid larvae and to sawflies. No reproductive effects were observed in European cockroaches reared on food containing 1000 mg/kg of 2,4-D (unspecified).

Application of 2,4-D at 1250 g a.i./l in field crops did not affect staphylinids, carabids, or spiders during a 20-month observation period. Mortality of adult millipedes exposed to 2,4-D at a rate of 33.6 kg/ha was noted on the first day and exceeded 50% of control mortality by day 7.

The 14-day LC_{50} for earthworms exposed to the DMA salt was 350 mg/kg soil, with no mortality noted at concentrations less than or equal to 100 mg a.i./kg. A 48-hour LC_{50} of 61.6 $ìg/cm^2$ has been reported for earthworms exposed on filter paper.

Acute avian LD_{50} values range from 200 to >2000 mg/kg bw for mallards, bobwhite quail, Japanese quail, pheasants, chukar partridges, and rock doves. Dietary LC_{50} values exceed 4640 mg/kg diet for mallards, bobwhite quail, Japanese quail, and pheasants for the acid, salt, and ester. At doses greater than the recommended application rate, the acid, salt, and ester did not adversely affect the reproductive performance of pheasants, quail, partridges, or chickens.

Oral LD_{50} values for rats and rabbits range from 699 to 2322 mg/kg bw for the acid and its salts and esters. Dermal LD_{50} values for the rabbit exceed 2000 mg/kg bw and inhalation LC_{50} values range from 1.8 to 10.7 mg/l.

Risk assessment

The information on use and application rates used for this risk assessment is derived from the

agricultural use of 2,4-D within the European Union and the USA. It should be noted that 2,4-D can be formulated as a variety of different salts (e.g. DMA, sodium, DEA, TIPA, and IPA) and esters (EH, IO, and BE). However of all these different forms, the DMA salt and EH ester account for approximately 95% of the global use of 2,4-D. This risk assessment is therefore restricted to the use of these compounds. It should be noted that both of them are rapidly hydrolysed to 2,4-D. The major uses of 2,4-D include application to cereals, corn, sorghum, soya beans, sugar cane, rice, pasture, top fruit, turf, non-cropland, fallow, forestry, and aquatic weeds. Applications can be made by either conventional tractor-mounted or drawn hydraulic sprayers or by aerial application (e.g. in forestry use) at rates varying from 0.25-4.48 kg acid-equivalent/ha.

This risk assessment is based on the principle of calculating Toxicity:Exposure Ratios (TERs) and follows the EPPO/CoE Environmental Risk Assessment models and trigger values.

Aquatic environment

The main risk to aquatic organisms from the use of 2,4-D is from overspray during aerial use, spray drift from ground-based hydraulic applications, or use to control aquatic weeds.

The EPPO/CoE risk assessment scheme for aquatic organisms showed a low acute risk (TERs >10) to fish, aquatic invertebrates, and algae from both spray drift contamination arising from ground-based hydraulic applications and from overspray contamination arising from aerial applications. A potential acute risk (TERs <10) to both aquatic higher plants and amphibians from overspray contamination during aerial applications was identified. The use of 2,4-D to control aquatic weeds also presented a potential acute risk (TERs <10) to algae as well as amphibians and aquatic higher plants. However, the risk to algae and aquatic higher plants can be ignored as these organisms are the targets when 2,4-D is used in this way. A potential acute risk to amphibians still remains from the use for aquatic weed control. It should be noted, however, that such a risk to amphibians needs to be balanced against the risks associated with alternative aquatic weed control practices such as not conducting weed control (e.g. algal bloom leading to water deoxygenation) or the potential damage caused by manual weed control, both of which may pose a higher risk to fish and other aquatic organisms. The EH ester is not recommended for aquatic weed control.

Owing to the very rapid degradation of the salts and esters of 2,4-D in water, the long-term risk to aquatic organisms from these compounds was considered to be low. However the primary breakdown product, 2,4-D acid, is more persistent in water and therefore the long-term risk assessment is based on it. Measured levels of 2,4-D in surface waters associated with approved uses (ranging from 0.00008 mg/l in small watersheds in Saskatchewan to 0.0021 mg/l in ground and surface waters in the UK) indicate that the long-term risk to fish and water-column- and sediment-dwelling invertebrates is low (TERs >10).

Terrestrial environment

Micro-organisms

The most significant routes of exposure of soil micro-organisms to 2,4-D are likely to be from its use by ground or aerial applications. Data from laboratory studies indicate that the risk to soil micro-organisms from the use of 2,4-D should be low at application rates of 7.5 and 18.75 kg

2,4-D/ha, which are higher than the maximum recommended application rates. In another study, application of the DMA salt and the IO ester at rates corresponding to 0.95 kg 2,4-D/ha resulted in 10-30% reductions in populations of soil bacteria, fungi, and actinomyces, with the ester producing greater reductions. As the trigger for concern in the CoE/EPPO micro-organism risk assessment scheme is an effect of >30%, it can be concluded that the risk to soil micro-organisms from the use of 2,4-D should be low.

Plants

2,4-D is a translocated selective herbicide that is used to control a variety of broad-leaved weeds. Consequently, although 2,4-D may pose a risk to broad-leaved non-target plants, this is to be expected from its mode of action and consequent use.

Invertebrates

Bees

Bees may be exposed to 2,4-D by foraging flowering weeds present in treated crops. At the maximum individual application rate of 4.48 kg acid-equivalent/ha, the hazard quotients for both contact and oral toxicity were >45 for both the DMA salt and the EH ester. As the EPPO/CoE trigger for concern is a hazard quotient of >50, the acute risk to honeybees from the use of 2,4-D at this application rate should be low. This is supported by the fact that 2,4-D has never been implicated in any honeybee poisoning incidents in the UK Wildlife Incident Investigation Scheme (WIIS).

Other arthropods

Arthropods may be exposed to 2,4-D from its many agricultural and non-agricultural uses. On the basis of the EPPO/CoE triggers for concern with regard to effects on non-target arthropods in laboratory studies (effects >30%), 2,4-D may pose a risk to arthropods at high application rates, but the laboratory data were either generated with a joint formulation with MCPA, or were old and may be unreliable. Limited field data at the lower and more typical range of application rates (up to 1.25 kg/ha) indicate that this risk may not be realized in the field.

Earthworms

Earthworms may be exposed from either single or multiple applications of 2,4-D to a wide variety of crops but in particular from its use on grass, fallowland, and stubble. The TER from a maximum application rate of 5.37 kg DMA salt/ha is above the EPPO/CoE trigger value of 10, which indicates that the acute risk to earthworms from the use of 2,4-D should be low.

Vertebrates

Vertebrates are likely to be exposed to 2,4-D either from grazing on treated or contaminated vegetation or consuming contaminated insects. For this risk assessment the estimation of residues on food items represents the maximum value determined immediately after application and does not take into account the rapid degradation in the environment. It further assumes that all food consumed contains 2,4-D at the level of the MRL.

Birds

The short-term dietary TERs based on measured initial residues on short grass arising from the application of 2.24 kg acid-equivalent/ha, indicate a potential medium risk (10 <TER <100) to grazing birds from both aerial and ground-based applications. The initial residues declined to a half or a third by 7 days after application. It should be noted that 2,4-D has never been implicated in any bird-poisoning incidents as a result of normal use. This suggests that the risk to grazing birds from 2,4-D is unlikely to be high. The short-term dietary TERs based on initial residues on large insects predicted by the EPPO/CoE vertebrate risk assessment scheme indicate a low acute risk (TER >100) to small insectivorous birds from both aerial and ground applications (4.48 kg acid-equivalent/ha and 2.24 kg acid-equivalent/ha respectively). Large insects are likely to constitute a higher proportion of both bird and mammalian diets than small insects during early growth stage or pre-emergence use.

Mammals

The acute oral TERs based on measured initial residues on short grass arising from application at 2.24 kg acid-equivalent/ha indicate a potential high risk (TER <10) to grazing mammals from both aerial and ground-based applications, but the initial residues declined to a half or a third by 7 days after application. The acute oral TERs based on predicted initial residues on large insects however indicate a medium acute risk (10 <TER <100) from aerial applications, and a low acute risk (TER >100) from ground-based applications, to small insectivorous mammals. It should be noted however that 2,4-D has never been implicated in any mammal-poisoning incidents as a result of normal use. This suggests that the risk to mammals from 2,4-D is unlikely to be high.

4.11 ETHEPHON (106)

TOXICOLOGY

Ethephon was last reviewed toxicologically by the 1993 JMPR, which established an ADI of 0-0.05 mg/kg bw. At that time, the Meeting noted that ethephon is an unesterified phosphonic acid and therefore is unlikely to phosphorylate hydrolases at the serine residue. Inhibition of plasma and erythrocyte, but not brain, cholinesterase activity has however been seen *in vivo*. Studies of cholinesterase inhibition with pure or technical grade ethephon *in vitro* were not available. The Meeting considered that the effects on cholinesterase required clarification and recommended re-evaluation of the compound in 1995.

The 1995 JMPR was informed that pure ethephon, technical-grade ethephon, and six manufacturing impurities in technical-grade ethephon were each being tested for anticholinesterase activity in rat plasma and erythrocytes *in vitro*. The Meeting recommended re-evaluation of ethephon in 1997.

The present Meeting was informed that ethephon did not inhibit cholinesterase activity in these preparations and that an investigative research programme to address this issue was being undertaken. The Meeting recommended that the results of these studies be reviewed when they become available.

The ADI of 0-0.05 mg/kg bw was maintained.

No toxicological monograph was prepared.

4.12 FENAMIPHOS (085)

TOXICOLOGY

Fenamiphos was first evaluated for toxicological effects by the JMPR in 1974, at which time an ADI of 0-0.0006 mg/kg bw was established. In 1985, following a direct request for re-evaluation by a Member State, additional data were reviewed and the ADI was reduced to 0-0.0003 mg/kg bw and made temporary because of concern about fetotoxicity seen in a study in rabbits. The 1985 JMPR requested submission of the results of an ongoing study of oncogenicity in rats, a full, legible report and raw data from the study of developmental toxicity in rats, and a new study of developmental toxicity in rabbits to clarify the observation of fetotoxicity at low dietary levels. The results of these studies were considered by the 1987 JMPR, which established an ADI of 0-0.0005 mg/kg bw. Fenamiphos was evaluated at the present Meeting within the CCPR periodic review programme.

In rats, fenamiphos was rapidly excreted, with over 96% of the administered dose eliminated within 48 h. Excretion was primarily in the urine, with less than 4% of the dose eliminated in the faeces. At 48 h the levels of tissue residues were below the limit of quantification except after a high dose (3 mg/kg bw), when the maximal tissue levels observed were 3.5-8.4 ìg/kg in the liver, 1.6-2.1 ìg/kg in the kidney, and 1.6-3.5 ìg/kg in the skin. Fenamiphos was completely metabolized in rats. Metabolites retaining anticholinesterase activity, such as fenamiphos sulfoxide and desisopropyl-fenamiphos sulfoxide, were seen in variable but generally low proportions (rarely greater than 3%). Most of the products were dephosphorylated phenol, phenol sulfoxide, or phenol sulfone metabolites and their corresponding sulfates.

Fenamiphos is extremely hazardous after single oral doses to rats, mice, rabbits, cats, dogs, and chickens (LD_{50} values 2.4-23 mg/kg bw) and highly hazardous after dermal administration to rats and rabbits (LD_{50} values 75-230 mg/kg bw). It is moderately hazardous after inhalation in rats and mice (LC_{50} values ≤ 100 ìg/l, 4 h). WHO has classified fenamiphos as “extremely hazardous”.

The sulfoxide, sulfone, and desisopropylated sulfone metabolites of fenamiphos are similarly toxic to rats after oral administration (LD_{50} values 1.4-4.1mg/kg bw). The phenol sulfoxide and sulfone metabolites are only slightly toxic to rats after oral administration, with LD_{50} values ranging from 1200 to 1900 mg/kg bw.

Fenamiphos inhibited plasma cholinesterase more effectively than erythrocyte acetylcholinesterase, both *in vitro* and *in vivo*. Fenamiphos sulfoxide, fenamiphos sulfone, desisopropyl fenamiphos, desisopropyl fenamiphos sulfoxide, and desisopropyl fenamiphos sulfone inhibited plasma and erythrocyte cholinesterase *in vitro* more effectively than fenamiphos itself.

In evaluating the following studies, inhibition of erythrocyte acetylcholinesterase activity was not used as an indicator of adverse effects in the nervous system when information on brain acetylcholinesterase activity was also available. In the absence of this information, NOAELs were determined on the basis of inhibition of erythrocyte acetylcholinesterase (of ≥ 20%). Statistical significance was used as a criterion for considering depression of brain acetylcholinesterase activity to be adverse.

In a three-week study in which rats were exposed by inhalation to atmospheres containing 0, 0.03, 0.25, or 3.5 ìg fenamiphos/litre for 6 h/d, five days per week, the only finding was inhibition of plasma cholinesterase at the highest dose. Erythrocyte and brain acetylcholinesterase were unaffected. The no-observed-adverse-effect concentration (NOAEC) was 3.5 ìg/litre.

In a three-month study in rats, fenamiphos given at dietary concentrations of 0, 0.37, 0.57, or 0.91 ppm inhibited plasma cholinesterase activity only at the highest dose. No treatment-related changes in erythrocyte or brain acetylcholinesterase activity were seen at any dose. In a second study of short-term toxicity, rats were fed diets containing 0, 4, 8, 16, or 32 ppm fenamiphos for three months. Erythrocyte acetylcholinesterase activity was inhibited at doses of 16 ppm (equivalent to 0.8 mg/kg bw per day) and above. This was considered an adverse effect as brain acetylcholinesterase was not measured in this study. The overall NOAEL was 8 ppm, equivalent to 0.4 mg/kg bw per day.

Rabbits received fenamiphos by dermal application at doses of 0, 0.5, 2.5, or 10 mg/kg bw per day for three weeks (6 h/d, five days per week). Body-weight gain was slightly reduced in animals of each sex at 10 mg/kg bw per day. In females, reductions in cholinesterase activity in the brain (by 20%) and plasma were noted at 2.5 mg/kg bw per day and above. Erythrocyte acetylcholinesterase activity, however, was affected only at 10 mg/kg bw per day. In males, the only findings were decreased plasma and erythrocyte cholinesterase activity at 10 mg/kg bw per day. The NOAEL was 0.5 mg/kg bw per day.

In a series of studies, dogs were fed diets containing 0, 0.5, 0.6, 1, 1.7, 2, 3, 5, 6, 10, 12, or 18 ppm fenamiphos for periods ranging from three months to two years. In dogs treated at 18 ppm (equivalent to 0.45 mg/kg bw per day) for three months, muscle tremors were seen. In dogs treated at 12 ppm (equal to 0.31 mg/kg bw per day) for one year, brain acetylcholinesterase activity was inhibited in females (by 17%), and males showed slight anaemia. Erythrocyte acetylcholinesterase activity was inhibited at doses of 3 ppm (equal to 0.083 mg/kg bw per day) and above for one year. Plasma cholinesterase activity was inhibited at doses of 1.7 ppm (equivalent to 0.042 mg/kg bw per day) and above in a three-month study. No other parameters were affected. Since no information on brain acetylcholinesterase activity was available at doses between 3 and 12 ppm, the Meeting considered 3 ppm (equal to 0.083 mg/kg bw per day) to be the overall NOAEL in dogs.

In mice fed diets containing 0, 2, 10, or 50 ppm fenamiphos for 20 months, there were marginal decreases in survival and body-weight gain at 50 ppm (equal to 7.4 mg/kg bw per day). The relative ovarian and spleen weights were reduced at 10 ppm (equal to 1.4 mg/kg bw per day) and above. There were no non-neoplastic changes that could be attributed to treatment, and fenamiphos was not carcinogenic at any dose. Cholinesterase activity was not measured at any

dose. The NOAEL was 2 ppm, equal to 0.3 mg/kg bw per day.

In rats fed diets containing 0, 3, 10, or 30 ppm fenamiphos for two years, the only treatment-related effects were inhibition of erythrocyte acetylcholinesterase activity throughout the study and behavioural changes during the first six weeks of the study at 30 ppm. Brain acetylcholinesterase activity was not measured. The NOAEL was 10 ppm, equal to 0.56 mg/kg bw per day.

Rats were fed diets containing 0, 1.7, 7.8, or 37 ppm fenamiphos for two years. At 37 ppm, equal to 2.5 mg/kg bw per day, body-weight gain in both males and females was decreased. Erythrocyte acetylcholinesterase activity was inhibited at 7.8 ppm (equal to 0.46 mg/kg bw per day) and above. Brain acetylcholinesterase activity was inhibited only at 37 ppm; inhibition was 25% in animals of each sex killed after one year, and 14% in males at study termination. Animals of each sex at 37 ppm also had an increased frequency of non-neoplastic inflammatory lesions of the nasal, laryngeal, and lung tissues and increased relative weights of the brain, heart, and lungs. Fenamiphos was not carcinogenic at any dose. The NOAEL was 7.8 ppm, equal to 0.46 mg/kg bw per day.

Fenamiphos was adequately tested in a battery of tests for genotoxicity. It was found to be mildly clastogenic at cytotoxic doses *in vitro* but not *in vivo*. It did not cause reverse or forward mutation, unscheduled DNA synthesis, or sister chromatid exchange *in vitro*. The Meeting concluded that fenamiphos is not genotoxic.

In a two-generation study of reproductive toxicity, rats were treated with 0, 2.5, 10, or 40 ppm fenamiphos. Parental toxicity was characterized by reduced weight gain in F_0 and F_1 dams at 40 ppm (equal to 2.8 mg/kg bw per day) during lactation, and in F_1 males at 10 ppm (equal to 0.64 mg/kg bw per day) and above before mating. Pathological changes in the salivary gland were seen in F_0 males and females at 40 ppm. Erythrocyte acetylcholinesterase activity was consistently inhibited at 10 ppm and above in females but only at 40 ppm in males. Brain acetylcholinesterase activity was inhibited at the highest dose in adult F_0 and F_1 females (by 21-29%) and in F_1 males (by 6%) but not in pups of either sex. In pups at 40 ppm, erythrocyte acetylcholinesterase activity was inhibited only on day 21 of lactation. The only reproductive effect was decreased weight gain of F_1 and F_2 pups at 40 ppm, beginning on day 7 of lactation. The NOAEL for systemic toxicity was 2.5 ppm, equal to 0.17 mg/kg bw per day. The NOAEL for reproductive toxicity was 10 ppm, equal to 0.64 mg/kg bw per day.

In a study of developmental toxicity, mated rats were treated with 0, 0.3, 1, or 3 mg/kg bw per day on days 6-15 of gestation. Maternal toxicity was seen at the highest dose, characterized by mortality, tremors, and reduced weight gain. The fetuses were not affected at any dose. Cholinesterase activity was not measured in this study. The NOAELs were 1 mg/kg bw per day for maternal toxicity and 3 mg/kg bw per day for developmental toxicity.

Fenamiphos was also administered to mated rats at doses of 0, 0.25, 0.85, or 3 mg/kg bw per day on days 6-15 of gestation. The highest dose resulted in maternal deaths, tremors, salivation, lacrimation, urine staining, and hypoactivity. Body-weight gain and food consumption were also significantly reduced. Erythrocyte acetylcholinesterase activity was reduced at this dose, but the changes in brain acetylcholinesterase activity were not statistically significant or dose-related. The fetuses were unaffected at 3 mg/kg bw per day. The NOAELs were 0.85 mg/kg bw per day

for maternal toxicity and 3 mg/kg bw per day for developmental toxicity.

In a study of developmental toxicity in rabbits, animals received 0, 0.1, 0.3, or 1 mg/kg bw per day on days 6-18 of gestation. At 0.3 mg/kg bw per day and above, fenamiphos was maternally toxic, resulting in decreased body-weight gain, bloody nasal discharge, and white ocular discharge. Fetotoxicity, characterized by chain fusion of the sternebrae, was seen only at 1 mg/kg bw per day. The NOAEL for maternal toxicity was 0.1 mg/kg bw per day, and that for developmental toxicity was 0.3 mg/kg bw per day. Cholinesterase activity was not measured in this study.

In a second study, mated rabbits were treated with 0, 0.1, 0.5, or 2.5 mg/kg bw per day on days 6-18 of gestation. Clear signs of maternal toxicity seen at the highest dose included mortality, salivation, dyspnoea, ataxia, diarrhoea, and decreased weight gain and food consumption during treatment. Although some questions remain about the doses that were actually administered (because of uncertain homogeneity), no embryotoxic or teratogenic effects were seen at the maternally toxic dose of 2.5 mg/kg bw per day.

A single dose of 25 mg/kg bw fenamiphos had no effect on neuropathy target esterase activity in the brains or spinal cords of hens under atropine protection.

Fenamiphos did not induce delayed neuropathy in three studies in hens, when tested at doses of 0, 2, 5, 16, or 26 mg/kg bw per day for 30 days or when given once at doses of 0 or 25 mg/kg bw.

Fenamiphos was minimally irritating to rabbit skin and moderately irritating to rabbit eyes and was a mild skin sensitizer in guinea-pigs.

In a study of acute neurotoxicity, rats were given single doses of 0, 0.37, 1.5, or 2.3 mg/kg bw fenamiphos by gavage. Erythrocyte acetylcholinesterase activity was inhibited at the lowest dose tested in males only, and in both males and females at higher doses. At 1.5 mg/kg bw, males showed unco-ordinated gait and muscle fasciculation. At the highest dose, decreased motor activity was also seen in males, and clinical signs, decreased grip strength, and deaths were observed in rats of each sex. There was no effect on brain acetylcholinesterase activity at any dose. The NOAEL was 0.37 mg/kg bw per day.

In another study of neurotoxicity rats were fed diets containing 0, 1, 10, or 50 ppm fenamiphos for 13 weeks. At 10 ppm and above, erythrocyte acetylcholinesterase activity was inhibited in animals of each sex. At the highest dose brain acetylcholinesterase activity was inhibited (by 12%) in females only. A battery of functional observational and motor activity tests revealed no treatment-related effects. The NOAEL was 10 ppm, equal to 0.61 mg/kg bw per day.

An ADI of 0-0.0008 mg/kg bw was established on the basis of an overall NOAEL of 0.083 mg/kg bw per day in the dog, using a safety factor of 100.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including relevant summaries from the previous monograph and monograph addenda on fenamiphos.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 2 ppm in the diet, equal to 0.3 mg/kg bw per day (20-month study of toxicity and carcinogenicity)

Rat: 0.37 mg/kg (single doses, study of neurotoxicity)
10 ppm, equal to 0.61 mg/kg bw per day (three-month study of neurotoxicity)
2.5 ppm, equal to 0.17 mg/kg bw per day (parental toxicity in a study of reproductive toxicity)
10 ppm, equal to 0.64 mg/kg bw per day (study of reproductive toxicity)
0.85 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
3 mg/kg bw per day (developmental toxicity in a study of developmental toxicity)
7.8 ppm, equal to 0.46 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rabbit: 0.1 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
0.3 mg/kg bw per day (fetotoxicity in a study of developmental toxicity)

Dog: 3 ppm in the diet, equal to 0.083 mg/kg bw per day (overall assessment)

Estimate of acceptable daily intake for humans

0-0.0008 mg/kg bw

Estimate of acute reference dose

The available data did not permit the Meeting to establish an acute reference dose different from the ADI (0-0.0008 mg/kg bw). Although the results of a study of neurotoxicity in rats given single doses were available, the dog was found to be the more sensitive species. Information on acute effects in dogs may allow the establishment of an acute reference dose in the future.

Studies that would provide information useful for the continued evaluation of the compound

1. Effects of single doses in dogs (with appropriate evaluation of functional changes in the cholinergic nervous system, including brain acetylcholinesterase activity).

2. Observations in humans.

Toxicological criteria for estimating guidance values for dietary and non-dietary exposure to fenamiphos

Human exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	Oral neurotoxicity, rat	NOAEL = 0.37 mg/kg bw per day: effects observed during battery of functional observational tests
	Oral toxicity, rat (fasted)	LD_{50} = 2.4-6 mg/kg bw
	Inhalation toxicity, 4 h, rat	LC_{50} = 91-100 ìg/l
	Inhalation toxicity, 5 days, rat	NOAEL = 4 ìg/l
	Dermal toxicity, rat	LD_{50} = 72-92 mg/kg bw
	Dermal irritation, rabbit	Minimally irritating
	Ocular irritation, rabbit	Moderately irritating
	Dermal sensitization, guinea-pig	Mildly sensitizing
Medium-term (1-26 weeks)	Repeated inhalation toxicity, 3 weeks, rat	NOAEL = 3.5 ìg/l (highest dose tested)
	Repeated dermal toxicity, 3 weeks, rabbit	NOAEL = 0.5 mg/kg bw per day: inhibition of brain acetylcholinesterase activity
	Repeated oral, reproductive toxicity, rat	NOAEL = 0.17 mg/kg bw per day: parental toxicity
		NOAEL = 0.64 mg/kg bw per day: reproductive toxicity
	Repeated oral, developmental toxicity, rabbit	NOAEL = 0.1 mg/kg bw per day: maternal toxicity
		NOAEL = 0.3 mg/kg bw per day: developmental toxicity
Long-term (≥ 1 year)	Repeated oral, 1 - 2 years, dog	NOAEL = 0.083 mg/kg bw per day: inhibition of brain acetylcholinesterase activity, anaemia

4.13 FENBUCONAZOLE (197)

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

Fenbuconazole is a triazole fungicide intended for use as an agricultural and horticultural fungicide spray for the control of leaf spot, yellow and brown rust, powdery mildew and net blotch on wheat and barley and apple scab, pear scab and apple powdery mildew on apples and pears. It was considered for the first time by the present Meeting.

TOXICOLOGY

Fenbuconazole is rapidly absorbed and eliminated, mainly in the faeces through significant biliary excretion; there was no evidence of significant retention in tissues. The compound was also extensively metabolized with phase I oxidation or hydroxylation at a number of sites in the molecule, followed by phase II sulphate and glucuronide conjugation (predominantly glucuronidation). Dermal absorption of fenbuconazole (technical material and a formulation) constituted 2-13% of the administered dose over 24 h, the absorption over 10 h being <5%.

Fenbuconazole was of low acute toxicity when administered orally (LD_{50} > 2000 mg/kg bw), dermally (LD_{50} > 5000 mg/kg bw), or by inhalation (LC_{50} > 2.1 mg/litre air). It was not irritating to the skin or eyes and was not a sensitizer in a Buehler test, but was a weak sensitizer in a maximization test. WHO has not yet classified fenbuconazole for acute toxicity.

After dietary administration, hepatomegaly with associated effects on clinical chemistry, such as changes in cholesterol and triglyceride levels and increases in the serum activity of hepatic enzymes, were seen in mice, rats, and dogs. In a 13-week study of toxicity in mice with dietary levels of 0, 20, 60, 180, or 540 ppm the NOAEL was 60 ppm (equal to 11 mg/kg bw per day) on the basis of hepatic effects at higher doses. In a three-month study of toxicity in rats with dietary levels of 0, 20, 80, 400, or 1600 ppm the NOAEL was 20 ppm (equal to 1.3 mg/kg bw per day) on the basis of hepatic effects and hypertrophy of the thyroid gland follicular cells at higher doses. In a 13-week study of toxicity in dogs with dietary levels of 0, 30, 100, 400, or 1600 ppm the NOAEL was 100 ppm (equal to 3.3 mg/kg bw per day). In a one-year study in dogs with dietary levels of 0, 15, 150, or 1200 ppm the NOAEL was 150 ppm (equal to 5.2 mg/kg bw per day). The NOAELs in the studies in dogs were based on decreased body-weight gain and increased incidence of hepatic hypertrophy with associated effects on clinical chemistry at higher doses.

In a 78-week study of toxicity and carcinogenicity in mice, with dietary levels of 0, 10, 200, or 650 ppm in males and 0, 10, 650, or 1300 ppm in females, there was clear evidence of treatment-related hepatomegaly, with dose-related hepatocytic hypertrophy and vacuolation and limited evidence of treatment-related hyperplasia and tumorigenicity in the liver at the highest dose. The NOAEL was 10 ppm (equal to 1.3 mg/kg bw per day). In a two-year study in rats with dietary levels of 0, 8, 80, or 800 ppm, the predominant effects were hepatocytic hypertrophy, thyroid follicular-cell hypertrophy and an increase in thyroid follicular-cell adenomas; in addition thyroid carcinomas were seen at the high dose. The NOAEL was 80 ppm, equal to 3 mg/kg bw per day.

The aetiology of the hepatic and thyroidal effects in rats was further investigated in a 4-13-week study which illustrated the biological feedback mechanism in rats: hepatomegaly leading to increased metabolism and excretion of thyroxine, increased levels of thyroid stimulating hormone and thyroid hypertrophy/hyperplasia. The effects seen after four weeks in this study were reversible. In studies designed to investigate the hepatotoxicity of fenbuconazole, hepatic effects were seen in rats and mice that were similar to those induced by phenobarbital. Increased cytochrome P450 activity (CYP2B form) was observed, with hepatocellular hypertrophy and proliferation. The NOAEL in mice after treatment for 13 weeks was 60 ppm (equal to 14 mg/kg

bw per day).

Fenbuconazole was adequately tested for genotoxicity *in vitro* and *in vivo*. The Meeting concluded that fenbuconazole is not genotoxic.

Fenbuconazole was not teratogenic in either rats (at doses of 0, 30, 75, or 150 mg/kg bw per day) or rabbits (at doses of 0, 10, 30, or 60 mg/kg bw per day) but fetotoxicity was seen in both studies with an NOAEL of 30 mg/kg bw per day. The NOAELs for maternal toxicity were 30 mg/kg bw per day in rats and 10 mg/kg bw per day in rabbits. No effects on reproductive parameters were seen in a multigeneration study in rats at dietary levels of 0, 8, 80, or 800 ppm, but fetotoxicity was again seen at high doses together with maternal toxicity. The NOAEL was 80 ppm, equal to 5.8 mg/kg bw per day.

An ADI of 0-0.03 mg/kg bw was allocated, on the basis of the NOAEL of 3 mg/kg bw per day in the two-year study in rats using a safety factor of 100. The Meeting noted that the NOAEL in the 13-week study in rats and in the 78-week study in mice was 1.3 mg/kg bw per day, but it concluded that this figure should not be used to derive the ADI. The NOAEL from the 13-week study in rats was not considered to be relevant in the light of the results of the larger, two-year study. The Meeting concluded that the overall NOAEL in mice was 14 mg/kg bw per day. This figure was taken from the 13-week study which included detailed investigations of hepatotoxicity. Hepatotoxicity was the critical effect in the long-term study in mice and the NOAEL in the 13-week study was lower than the lowest dose causing hepatotoxicity in the long-term study.

A toxicological monograph was prepared summarizing the data that were reviewed at the present meeting.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 60 ppm, equal to 14 mg/kg bw per day (13-week study of hepatotoxicity)
10 ppm, equal to 1.3 mg/kg bw per day (78-week study of toxicity)

Rat: 20 ppm, equal to 1.3 mg/kg bw per day (13-week study of toxicity)
80 ppm, equal to 3.0 mg/kg bw per day (two-year study of toxicity)
30 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
80 ppm, equal to 5.8 mg/kg bw per day (two-generation study of reproductive toxicity)

Rabbit: 10 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Dog: 150 ppm, equal to 5.2 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.03 mg/kg bw

Studies that would provide information useful for the continued evaluation of the compound

Observations in humans

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to fenbuconazole

Human exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	Oral toxicity, rat	LD_{50} > 2000 mg/kg bw
	Dermal toxicity, rat	LD_{50} > 5000 mg/kg bw
	Inhalation toxicity, rat	LC_{50} > 2.1 mg/l
	Dermal irritation, rabbit	Not irritating
	Ocular irritation, rabbit	Not irritating
	Dermal sensitization, guinea pig	Not sensitizing in Buehler test, weakly sensitizing in maximization test
Medium-term (1-26 weeks)	Repeated oral, 1-year, toxicity, dog	NOAEL = 5.2 mg/kg bw per day: hepatic effects
	Repeated dermal, 4 weeks, toxicity, rat	NOAEL = 1000 mg/kg bw per day (highest dose tested)
	Repeated oral, reproductive toxicity, rat	NOAEL = 5.8 mg/kg bw per day: maternal and fetal toxicity
	Repeated oral, developmental toxicity, rabbit	NOAEL = 10 mg/kg bw per day: maternal toxicity
Long term (≥1 year)	Repeated oral, 2 years, toxicity and carcinogenicity, rat	NOAEL = 3 mg/kg bw per day: hepatic and thyroid effects

RESIDUE AND ANALYTICAL ASPECTS

Fenbuconazole is a white solid with low solubility in water and low vapour pressure. It has a log P_{ow} of 3.22 and is reasonably soluble in fat. It is a triazole fungicide formulated mainly as an EC or an EW.

Fenbuconazole was rapidly absorbed and eliminated, mainly in the faeces with significant biliary excretion, in rats; there was no evidence of any retention in the tissues. The compound was also extensively metabolized with oxidation and hydroxylation at a number of sites in the molecule, followed by conjugation to form sulfates and glucuronides, mainly the latter.

Metabolism and distribution were investigated in lactating goats and chickens. In goats dosed at levels equivalent to 1, 10 and 100 ppm in the feed, less than 0.5% of the TRR remained in the milk and less than 1.6% in the tissues. Two major metabolites were identified in the milk as 1,2,4-triazole (0.24 mg/kg fenbuconazole equivalents at the highest dose) and triazolylalanine (TA, 0.15 mg/kg at the highest dose), with very low levels of the parent compound. At the highest dose, the levels of the TRR in the liver, kidney, muscle and fat were 12.4, 0.97, 0.22 and 0.11 mg/kg respectively. In the liver five major components were identified: the parent compound (0.95 mg/kg), 4-(4-chlorophenyl)-2-hydroxymethyl-2-(phenyl)butanenitrile (RH-7968, 0.95 mg/kg), the glucuronide of the 4-hydroxy derivative (1.23 mg/kg), the triazole (1.79 mg/kg) and TA (4.95 mg/kg). A further phenol metabolite was present in the kidney.

When chickens were dosed with the equivalent of 100 ppm in the feed, less than 0.7% of the TRR was found in the eggs and less than 0.8% in the tissues (0.04% in the lean meat, 0.01% in the fat, 0.02% in the liver and 0.02% in the kidneys). Three major components were identified in the eggs: the parent (0.89 mg/kg), two isomeric lactones (0.29 mg/kg) and the triazole (0.54 mg/kg). In the liver the glucuronide (3.69 mg/kg) and the triazole (1.25 mg/kg) were the major metabolites. In the fat the parent was the major component (0.43 mg/kg) with several low-level metabolites identified.

Plant metabolism was studied in peaches, wheat and peanuts. Metabolism occurs by oxidation at the benzylic carbon adjacent to the chlorophenyl ring.

In the wheat study, phenyl- and triazole-labelled [^{14}C]fenbuconazole were foliar-applied at a rate of 2 x 0.4 kg ai/ha. At harvest the total ^{14}C residues (expressed as fenbuconazole equivalent) were 0.04-0.44 mg/kg in the grain and 9.8-10.6 mg/kg in the straw. The predominant components in the grain were TA and triazolylacetic acid (TAA) which were present at levels of 0.25 and 0.11 mg/kg respectively. The parent compound was present in the grain, but at less than 0.01 mg/kg. In the straw fenbuconazole was the main component at levels of 8.8-11.8 mg/kg. Three other components were identified in the straw as the lactones found in chickens (1.1-1.4 mg/kg), a ketone (the 4-oxo derivative, 0.59-0.62 mg/kg) and a glucoside conjugate of the 4-(4-chloro-3-hydroxyphenyl) analogue (0.43 mg/kg).

In the peach study, phenyl- and triazole-labelled [^{14}C]fenbuconazole were foliar-applied five times, at a rate of 0.2 kg ai/ha. At harvest the total ^{14}C residues in the peaches expressed as fenbuconazole equivalent were 0.08-0.12 mg/kg. TA and fenbuconazole predominated, at levels of 0.06 and 0.02-0.04 mg/kg respectively. The lactones and TAA were also identified, plus 5 unknowns which were not individually above 0.01 mg/kg.

In the third study, peanuts were treated four times with phenyl- and triazole-labelled [^{14}C]fenbuconazole at a rate of 0.57 kg ai/ha. The major component in both the vine and the shells was fenbuconazole (48 and 34% respectively), with TA, the glucoside conjugate, and the ketone the main remaining components. In the nut no fenbuconazole was present and 92% of the residue was TA.

In a study of metabolism and distribution in rotational crops, wheat, turnips and collards were planted in soil which had been treated bare with either phenyl- or triazole-labelled fenbuconazole at the exaggerated rate of 8.96 kg ai/ha. At harvest TA and TAA were by far the predominant components of the TRR in the crops. In a further study, phenyl-labelled fenbuconazole was applied to soil at 3 x 0.07 or 4 x 0.28 kg ai/ha and lettuce, radishes, sorghum, carrots or barley were planted 35-260 days after treatment. The total residues in all crop samples at harvest were ≤0.04 mg/kg.

The lactones and ketone formed in plants were identified in the rat metabolism studies; TA and TAA were not identified in rats but are common metabolites of all triazoles. In several of the residue trials the levels of the lactones and ketone were determined but were generally at low concentrations compared with fenbuconazole.

Fenbuconazole was found to be persistent in soil, although degradation varied greatly, with half-lives of 38-367 days in the laboratory and 28-425 days (DT90 >1 year) in the field. The compound was immobile in column leaching studies and showed K_{oc} values of 2185-9042. Neither photolysis nor hydrolysis of fenbuconazole occurred in aqueous media, and in sediment/water systems it partitioned rapidly into the sediment where it persisted.

Several methods of analysis were reported for various commodities, most of them by GLC with NP detection. Most of the methods also allow determination of metabolites (e.g. the lactones) and have limits of determination of 0.01-0.05 mg/kg with recoveries of about 80%. The Meeting agreed that 0.05 mg/kg was an appropriate practical limit of determination of parent fenbuconazole in most commodities for routine monitoring and the enforcement of MRLs.

Residues of fenbuconazole and the lactones, the ketone in plant products and the 2-hydroxymethyl derivative in animal products were stable in apples, wheat grain and straw stored at –10°C and products of animal origin stored at –4°C for at least 18 months and 2-4 months respectively. Residues of fenbuconazole and the lactones (and the ketone in some commodities) were also stable when stored at –10°C for 54 months in peaches and pecans, 12 months in almonds, and about 31 months in hen and cow muscle. There was some decrease in total fenbuconazole residues in some cereal fractions that had been stored for about 56 months.

The Meeting agreed that the residue should be defined as fenbuconazole both for compliance with MRLs and the estimation of dietary intake.

The Meeting concluded that although the solubility of the residue in fat was intermediate the enforcement of MRLs could best be carried out on a whole-product basis; this conclusion is supported by the data on animal metabolism. Accordingly the Meeting agreed not to describe the residue as fat-soluble.

Supervised trials

In listing the residue results, values at or above 0.1 mg/kg have been given to two significant figures and those below 0.1 mg/kg to one significant figure.

Grapefruit and oranges. The only reported GAP was pending in the USA where the maximum application rate for both commodities is 0.28 kg ai/ha with a PHI of 0 days. Residues of fenbuconazole from trials on grapefruit complying with this GAP were 0.02, 0.10, 0.12, 0.13, 0.16, 0.16, 0.19, 0.34 and 0.49 mg/kg in the whole fruit and <0.01 (5) and 0.02 mg/kg in the pulp.

The residues in oranges were 0.18 (2), 0.19 (2), 0.28, 0.30, 0.34, 0.44 and 0.52 mg/kg in the whole fruit and <0.01 (4) and 0.01 mg/kg in the pulp. Because GAP was only pending the Meeting was unable to estimate a maximum residue level for either fruit.

Pome fruit. GAP for apples was reported for France, Israel, Italy, Portugal, South Africa, Turkey and the UK and for pears for Greece, Israel, Italy, Portugal, South Africa and the UK, and was reported to be pending for apples in the USA and Greece and for pears in France. The maximum application concentrations are 0.002-0.004 kg ai/hl except in the UK and the USA where the application rates were reported as 0.068 and 0.14 kg ai/ha respectively. PHIs were either 14 or 28 days.

Residues of fenbuconazole in apples from trials complying with the pending US GAP were 0.01, 0.02, 0.04, 0.05 (2), 0.06 (2), 0.07 (2), 0.08, 0.09 (2), 0.12 (4), 0.13 (2), 0.15, 0.16 (2), 0.17, 0.18, 0.20 (2), 0.27 and 0.28 mg/kg. Many of the results from these trials had been corrected for the average recovery. Because the GAP was pending the Meeting could not use these results to estimate a maximum residue level.

Residues of fenbuconazole in apples from trials according to UK GAP were <0.02, 0.02 (3), 0.03 (3), 0.04 (2), 0.05 and 0.06 mg/kg, those from trials complying with Southern European GAP (France, Greece, Italy and Portugal) were <0.005, <0.01, 0.01, 0.02 and 0.03 mg/kg, and the residues in pears from trials complying with Southern European GAP were 0.01 (2), 0.02 (2), 0.05 and 0.06 mg/kg.

The residues from the trials on apples and pears according to GAP appear to be from similar data populations. The combined residues were <0.005, <0.01, <0.02, 0.01 (3), 0.02 (6), 0.03 (4), 0.04 (2), 0.05 (2) and 0.06 (2) mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.025 mg/kg for fenbuconazole in pome fruit.

Cherries. GAP was reported only for the USA. The maximum application is 0.105 kg ai/ha with a PHI of 0 days.

The residues in the trials complying with the maximum US GAP were 0.20, 0.21, 0.31, 0.33, 0.34, 0.36 (2), 0.42 and 0.51 mg/kg. Four other trials with an exaggerated application rate (33% higher than GAP) showed residues of 0.43, 0.47, 0.53 and 0.55 mg/kg at day 0. In addition, trials at the maximum US application rate with residues of <0.01, 0.12, 0.22, 0.25, 0.43 and 0.47 mg/kg at a PHI of 7 days were considered to be within the range of GAP. All of the above residues at day 0 had been corrected for average recoveries. Some of the trial samples were stored frozen for 3.5 to 4 years before analysis. Since the data on the storage stability of fenbuconazole residues in peaches indicated that they were stable up to 54 months the Meeting agreed to use these results, but emphasized that the storage of trial samples for long periods before analysis was undesirable.

The Meeting agreed that an STMR should be estimated from the residues on day 0, including those from the exaggerated rate: 0.20, 0.21, 0.31, 0.33, 0.34, 0.36 (2), 0.42, 0.43, 0.47, 0.51, 0.53 and 0.55 mg/kg. The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.36 mg/kg for fenbuconazole in cherries.

Apricots and peaches. GAP for apricots was reported for Israel and the USA, and pending GAP for France. The maximum application rates are 0.0025 kg ai/hl in Israel, 0.0075 kg ai/hl in France, and 0.105 kg ai/ha in the USA, with PHIs of 0-14 days.

The residues in the trials on apricots considered to comply with US GAP were 0.12, 0.16, 0.21, 0.25 and 0.27 mg/kg. All of these results had been corrected for average recoveries and referred to the residue in the fruit without stone. The trials complying with the pending French GAP with the highest application rate (0.0075 kg ai/hl) gave residues of 0.06, 0.17, 0.26, 0.21 and 0.33 mg/kg. Some of these were in the fruit without stone.

GAP for peaches was reported for Israel and the USA, and pending GAP for France and South Africa. The maximum application rates are 0.002-0.005 kg ai/hl or 0.105 kg ai/ha, with PHIs ranging from 0 to 14 or 60 days: the pending French GAP was originally reported by the company as having a 60-day PHI, but the Meeting was informed that the PHI would be 3 days. Based on a 3-day PHI the residues in trials complying with the pending French GAP were 0.07 (3), 0.09, 0.10 (2), 0.11, 0.13 and 0.21 mg/kg. Some of these results were for the fruit without stone. The residues in the trials considered to comply with US GAP were 0.19, 0.25 (2), 0.28, 0.37, 0.46 and 0.51 mg/kg, corrected for average recoveries, in the fruit without stone.

The Meeting agreed that the US residues in apricots and peaches were mutually supportive and could be combined, giving residues in rank order of 0.12, 0.16, 0.19, 0.21, 0.25 (3), 0.27, 0.28, 0.37, 0.46 and 0.51 mg/kg. The Meeting noted that these results had been corrected for recovery and that the residues were in the fruit without stone, and estimated maximum residue levels of 0.5 mg/kg and STMRs of 0.25 mg/kg for fenbuconazole in peaches and apricots.

Plums (including prunes). GAP was originally reported for Israel and the USA, with pending GAP for France, but the Meeting was informed that the US GAP was actually pending. The maximum application rates are 0.002-0.0075 kg ai/hl in Israel and France and 0.105 kg ai/ha in the USA. PHIs are 0-14 days.

The residues in trials considered to comply with the pending French GAP were 0.05, 0.06, 0.07, 0.16, 0.20, 0.23, 0.27, 0.30, 0.36 and 0.38 mg/kg, and those in the trials complying with the pending US GAP were <0.01, 0.01, 0.02, 0.03 (2), 0.04 (2), 0.06 and 0.07 mg/kg. Three further residues were reported in dried prunes: 0.08, 0.14 and 0.16 mg/kg. All of the US results had been corrected for average recoveries and the residue was in the fruit without stone. As both the French and US GAP is pending, the Meeting could not estimate a maximum residue level.

Grapes. GAP was reported for France, Israel, Italy, Portugal, Spain and Turkey, and pending GAP for Greece. The maximum application rates are 0.002–0.0075 kg ai/hl or 0.03–0.04 kg ai/ha, with PHIs of 7-28 days.

The residues in the trials considered to comply with Italian and pending Greek GAP were 0.04 (2), 0.05 (2) and 0.17 mg/kg and those in the trials complying with French and Spanish GAP were 0.02, 0.05, 0.10, 0.12, 0.16, 0.2, 0.3 (3), 0.35, 0.4 (2) and 0.5 mg/kg. Since the French product labels specified a rate of 0.03-0.0375 kg ai/ha, the Meeting agreed that it was not appropriate to use four German trials in which the application rates were 0.056-0.075 kg ai/ha in the evaluation.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.3 mg/kg for fenbuconazole in grapes, based on the trials complying with French and Spanish GAP. Although the highest residue in the trials was only 0.5 mg/kg, the Meeting noted that there were several residues close to 0.5 mg/kg and that the median residue was relatively high.

Strawberries. GAP was reported for Israel. The maximum application rate is 0.075 kg ai/ha with a PHI of 14 days.

Only one trial was considered to comply with Israeli GAP, with a residue of 0.17 mg/kg. Although additional data were available from Spain, the climatic and agricultural practices were not considered to be comparable to those in Israel and these data have not been used in the evaluation. There were therefore insufficient data to estimate a maximum residue level.

Bananas. GAP was reported for Columbia, Costa Rica, Ecuador, Guatemala, Honduras, Mexico, Panama, Venezuela, Philippines and the USA. GAP in all of these countries was the same with a maximum application rate of 0.105 kg ai/ha and a PHI of 0 days.

The residues in the trials with bagged fruit considered to comply with GAP were <0.01 (4) and 0.01 mg/kg in pulp, <0.01 (4) and 0.03 mg/kg in peel, and <0.01 (3) mg/kg in whole fruit. Those in the trials with unbagged fruit which complied with GAP were <0.01 and 0.02 mg/kg in pulp, 0.09 mg/kg in peel, and <0.01 (3), 0.01 and 0.02 mg/kg in whole fruit. The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.01 mg/kg for bananas. Although only 6 trials were reported for bagged bananas, the Meeting considered that there were sufficient data to estimate a maximum residue level since all the residues were well below the practical limit of determination of 0.05 mg/kg.

Melons (except watermelons). GAP for melons was reported for France, Israel, Italy, Portugal and Turkey, and pending GAP for Spain and Morocco. The maximum application rates are 0.0375-0.2 kg ai/ha or 0.005-0.01 kg ai/hl. PHIs are 3-7 days. The Meeting was informed that the PHI in France was 7 days and not the 3 days reported in the original company submission.

The residues in trials considered to comply with Italian GAP were <0.005, 0.009, 0.02 and 0.05 mg/kg, and those in the trials complying with French GAP with a 7-day PHI were <0.02, 0.02 (2), 0.03, 0.07, 0.09, 0.1 and 0.13 mg/kg. The residues all appear to be within the same population and can be combined, giving <0.005, 0.009, <0.02, 0.02 (3), 0.03, 0.05, 0.07, 0.09, 0.1 and 0.13 mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.025 mg/kg for melons.

Watermelons. GAP was reported for Israel, Italy, Portugal, Spain and Turkey, and pending GAP for Morocco. The maximum application rates are 0.0375-0.2 kg ai/ha or 0.005 -0.01 kg ai/hl, with PHIs of 3 or 7 days. There is no French GAP for watermelons.

Only one trial was considered to comply with Italian GAP, with a residue of <0.005 mg/kg. There were insufficient data to estimate a maximum residue level.

Cucumbers. GAP was reported for Israel, Spain and Turkey, and pending GAP for France and Morocco. The maximum application rates are 0.0375-0.1 kg ai/ha or 0.005-0.01 kg ai/hl, with PHIs of 3 or 7 days.

One Spanish and two Italian field trials, all with residues of 0.02 mg/kg, and five indoor trials in Spain and Greece with residues of <0.01, 0.02, 0.03 (2) and 0.11 mg/kg were considered to comply with Spanish GAP. One trial in Israel complied with Israeli indoor GAP with a residue of 0.1 mg/kg.

The Meeting concluded that the residues in all the trials according to GAP were in a single population and agreed to combine them to give <0.01, 0.02 (4), 0.03 (2), 0.1 and 0.11 mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.02 mg/kg for cucumbers.

Summer squash (courgettes, zucchini). GAP was reported for Israel, Spain and Turkey, and pending GAP for France and Morocco. The maximum application rates are 0.0375-0.2 kg ai/ha or 0.005-0.01 kg ai/hl with PHIs of 3 or 7 days.

The residues in trials considered to comply with the pending French GAP were <0.02, 0.03, 0.03 and 0.08 mg/kg; the trial with the residue of 0.03 mg/kg also complied with Turkish GAP. The residues from trials complying with the pending Moroccan GAP were <0.02, 0.03, 0.04, 0.04, 0.06 and 0.08 mg/kg. Because French and Moroccan GAP is pending the Meeting could not use the results to estimate a maximum residue level.

The outdoor trials considered to comply with Spanish GAP showed residues of <0.01 (2), 0.01, <0.02 (3) and 0.02 mg/kg. Some of these trials were also considered to comply with Israeli GAP. The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.02 mg/kg for summer squash, based on Spanish GAP.

Tomatoes. GAP for Israel was reported as 0.0075 kg ai/hl (glasshouse) and 0.05 kg ai/ha (field) with PHIs of 7 days in both cases. Pending GAP for Morocco is 0.01 kg ai/hl with a PHI of 3 days for both field and glasshouse applications.

The residues in trials considered to comply with the pending Moroccan GAP were 0.02, 0.03 (2), 0.05 (2), 0.08, 0.10, 0.13, 0.14, 0.16, 0.18, 0.31 and 0.38 mg/kg, but as the GAP was pending the Meeting could not use them to estimate a maximum residue level.

The residues in trials which complied with Israeli glasshouse GAP were 0.08, 0.19 and 0.21 mg/kg and in those complying with the field GAP <0.02 and 0.02 (2) mg/kg.

The Meeting agreed that the Israeli glasshouse use appeared to lead to higher residues than the field use. Since only three trials were available for each of these uses, the Meeting concluded that there were insufficient data to estimate a maximum residue level.

Peppers. GAP was reported for Israel (field use only), and pending GAP for Morocco. The maximum application rates are 0.0075 and 0.01 kg ai/hl, with PHIs of 7 and 3 days respectively.

The residues in field trials which complied with the pending Moroccan GAP were 0.02 and 0.10 mg/kg and in glasshouse trials 0.18, 0.20, 0.29, 0.38 and 0.41 mg/kg. The glasshouse use appeared to lead to higher residues, but as the GAP was pending the Meeting could not use the results to estimate a maximum residue level.

Two trials in Italy and Spain complied with Israeli GAP, but the Meeting agreed that the climatic conditions and agricultural practices in Italy and Spain could not be equated with those in Israel. There was therefore no basis on which the Meeting could estimate a maximum residue level.

Egg plant. GAP was reported only for Morocco, and only one residue trial was reported which complied with it. There were insufficient data to estimate a maximum residue level.

Sugar beet. GAP was reported for Italy and pending GAP for the USA. The maximum application rates are 0.1 and 0.14 kg ai/ha with PHIs of 14 days.

The residues in the trials which complied with US GAP were <0.01, 0.02 (3), 0.03 (3), 0.04 (4), 0.06, 0.07 (2), 0.08, 0.09 and 0.20 mg/kg in the roots and 0.51, 0.55, 0.80, 0.85, 0.95, 1.0, 1.2, 1.2, 1.4, 2.6 (2), 3.1, 4.2, 4.5, 5.0 and 8.9 mg/kg in the tops. As the GAP was pending the Meeting could not estimate a maximum residue level from these trials.

Only two trials complied with Italian GAP, with residues in the roots of 0.02 and 0.03 mg/kg. There were insufficient data to estimate a maximum residue level.

Wheat. GAP was reported for Belgium, France, Germany, Israel, Morocco, Portugal, South Africa and the UK, and pending GAP for the USA. The maximum application rates are 0.07-0.125 kg ai/ha with PHIs of 35–90 days or expressed as “before beginning of flowering growth stage 59”.

The residues in trials which complied with the pending US GAP were 0.005, 0.007, <0.01 (17), 0.01 (3), 0.02 (3) mg/kg in the grain and <0.05 (2), 0.08, 0.10, 0.11, 0.12, 0.23, 0.27, 0.28, 0.41, 0.45, 0.57, 0.58, 0.70, 0.75, 0.76, 0.77, 0.80, 1.4 (2), 1.6, 1.9, 2.4, 3.0 and 4.5 mg/kg in the straw. A number of other US trials complied with the pending GAP, but the samples were stored for 3.5-4 years before analysis. Since data on storage stability indicated that fenbuconazole residues were stable in wheat for at least 36 months the Meeting agreed to regard these results as valid, but emphasized that the storage of trial samples for long periods before analysis was undesirable. As the GAP was pending however the results could not be used to estimate a maximum residue level.

The residues in trials which complied with German GAP were <0.02 (9) and 0.06 mg/kg in the grain and 0.14, 0.17, 0.27, 0.41, 0.51, 0.61, 0.84, 0.91, 1.0, 1.3 and 2.5 mg/kg in the straw.

The residues in trials which complied with Portuguese GAP were <0.01 (3) and <0.02 (3) mg/kg in the grain. The straw was not analysed.

The residues in trials which complied with UK GAP were <0.02 (5), <0.02* (7) and 0.06* mg/kg in the grain and 0.11*, 0.17*, 0.39*, 0.75*, 0.79, 0.85, 0.89*, 0.95*, 1.05* and 1.26* mg/kg in the straw. The residues marked with an asterisk were from trials which also complied with German GAP.

The Meeting agreed that the residues in the trials according to German, UK and Portuguese GAP appeared to be from the same population of data and could be combined to give <0.01 (3), <0.02 (17) and 0.06 mg/kg in the grain and 0.14, 0.17, 0.27, 0.41, 0.51, 0.61, 0.79, 0.84, 0.85, 0.91, 1.0, 1.3 and 2.5 mg/kg in the straw. The Meeting estimated maximum residue levels of 0.1 mg/kg for wheat grain and 3 mg/kg for straw, and STMRs of 0.02 mg/kg for grain and 0.79 mg/kg for straw.

Barley. GAP was reported for France, Germany, South Africa and the UK. The maximum application rates are 0.072–0.125 kg ai/ha with PHIs of 35–45 days or expressed as “before beginning of flowering growth stage 59”.

The residues in trials which complied with German GAP were <0.02, 0.03 (5), 0.04, 0.05, 0.08, 0.09 and 0.14 mg/kg in the grain, and 0.21, 0.25, 0.28, 0.35, 0.55, 0.56, 0.68, 1.2, 1.7, 1.9 and 2.1 (2) mg/kg in the straw. Those from trials complying with UK GAP were <0.02 (2), <0.02*, 0.02*, 0.03 (3), 0.03* (2), 0.04 and 0.04* (3) mg/kg in the grain and 0.17*, 0.27*, 0.44*, 0.55, 0.55*, 0.67, 1.13*, 1.2, 1.8, 2.1*, 2.07*, 2.2 and 2.4 mg/kg in the straw. The residues marked with an asterisk were from trials which also complied with German GAP.

The Meeting agreed that the results of the UK and German trials could be combined to give <0.02 (3), 0.03 (8), 0.04 (2), 0.05, 0.08, 0.09 and 0.14 mg/kg in the grain and 0.21, 0.25, 0.28, 0.35, 0.55 (2), 0.56, 0.67, 0.68, 1.2 (2), 1.7, 1.8, 1.9, 2.1 (2), 2.2 and 2.4 mg/kg in the straw. The Meeting estimated maximum residue levels of 0.2 mg/kg for barley grain and 3 mg/kg for straw, and STMRs of 0.03 mg/kg for grain an 0.94 mg/kg for straw.

Maize. GAP was reported to be pending in France, with an application rate of 0.075 kg ai/ha and a PHI of 45 days.

The residues in trials which complied with the pending French GAP were ≤0.02 (5) mg/kg in maize ears and 0.10, 0.12, 0.15 0.21, 0.26 (2) and 0.27 mg/kg in the fodder. As the GAP was pending the Meeting could not estimate a maximum residue level.

Rye. GAP was reported for Germany, with an application rate of 0.075 kg ai/ha and a PHI of 35 days.

The residues in trials which complied with German GAP were <0.02 and 0.03 mg/kg in the grain, and 0.49 and 1.4 mg/kg in the straw. The Meeting concluded that the residues in wheat grain, resulting from similar GAP, could be used to support those in rye and estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.02 mg/kg for rye grain.

Triticale. Two trials were reported, but there was no information on GAP.

Almonds. GAP was reported for Israel and pending GAP for the USA, with application rates of 0.004 kg ai/hl and 0.105 kg ai/ha and PHIs of 160 and 14 days.

The residues in trials which complied with the pending US GAP were <0.01 (5) in the kernels and 0.13, 0.45, 0.51 and 0.77 mg/kg in the hulls. As the GAP was pending the Meeting could not estimate a maximum residue level or an STMR for almonds or almond hulls.

Pecans. GAP was reported for the USA, with an application rate of 0.14 kg ai/ha and a PHI of 28 days.

The residues in ten trials which complied with US GAP were all <0.01 mg/kg in pecan kernels. The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.01 mg/kg for pecans.

Oilseed. GAP for sunflowers was reported only for France. The application rate is either 0.060 or 0.075 kg ai/ha depending on the product, with a PHI of 80 days.

The residues in the seed in trials on sunflowers which complied with French GAP were <0.01 and <0.02 (5) mg/kg. Residues in two further trials with a shorter PHI (34 days) were all <0.02 mg/kg. The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.02 mg/kg for sunflower seed.

GAP for rape was also reported only for France, with an application rate of 0.060 kg ai/ha and a PHI of 30 days or 0.075 kg ai/ha and a PHI of 45 days.

The residues in two trials on rape which complied with French GAP were both <0.05 mg/kg. In two other trials with longer PHIs the residues were also <0.05 mg/kg. The Meeting took into account the data on sunflower seed in which no measurable residues were found and estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.05 mg/kg for rape seed.

Animal products. Animal transfer studies were carried out on dairy cattle and hens. Cattle dosed at a level equivalent to 6.5 ppm in the feed, showed total fenbuconazole residues of 0.01 mg/kg in one sample of muscle and up to 0.09 mg/kg in 3 samples of liver. No quantifiable residues were found in the milk, fat or kidney. At a dose level equivalent to 19.5 ppm in the feed the only residues were 0.02 mg/kg in one sample of milk and 0.1-0.2 mg/kg in three samples of liver.

In hens dosed at the equivalent of 0.12, 0.34 or 1.13 ppm in the feed, all the residues in eggs and tissues were below the limit of determination.

The highest residues in fodder crops from trials which complied with GAP were 4.5 mg/kg in wheat straw, 2.1 mg/kg in barley straw, 1.4 mg/kg in rye straw, 0.8 mg/kg in almond hulls and <0.05 mg/kg in rape seed.

Assuming maximum incorporation rates of straw (the feed item with the most significant residues) of 20 and 50% for dairy and beef cattle respectively, the maximum feed intakes will be approximately 1 ppm and 2.5 ppm in the diet. Residues would be expected to be below a limit of determination of 0.05* mg/kg in all cattle products except liver. The Meeting estimated maximum residue levels of 0.05* mg/kg for cattle meat, cattle fat, cattle milk and cattle kidney and 0.05 mg/kg for cattle liver. The Meeting agreed that the STMR should be zero for those cattle commodities in which no measurable residues were found at the equivalent of 6.5 ppm or 19.5 ppm in the diet in the cow feeding studies. Accordingly, the Meeting estimated STMRs of 0.01 mg/kg for cattle meat, milk and liver and 0 mg/kg for cattle kidney and fat.

In poultry, the highest residues would arise from barley grain in which residues were <0.02-0.14 mg/kg. Since cereal grains can constitute up to 70% of the diet the maximum feed intakes will be approximately 0.1 ppm in the diet. The Meeting estimated a maximum residue level of 0.05* mg/kg for poultry fats, poultry meat, edible offal of poultry, and eggs. The Meeting agreed that the STMR should be zero for those poultry commodities in which no measurable residues were found at the equivalent of 1.13 ppm in the diet in the poultry feeding studies. Accordingly, the Meeting estimated an STMR of 0 mg/kg for poultry fats, meat, edible offals, and eggs.

The Meeting agreed not to estimate STMR-Ps for the processed products of apples, peaches or sugar beet since only single samples had been processed on a laboratory scale and the initial residues were low. The Meeting estimated STMR-Ps for wine and grape juice of 0.018 mg/kg (0.3 x 0.06) and 0.03 mg/kg (0.3 x 0.1) respectively. The Meeting also estimated STMR-Ps for bread, flour and bran of 0.0092 mg/kg (0.02 x 0.46), 0.005 mg/kg (0.02 x 0.25) and 0.052 mg/kg (0.02 x 2.6) respectively.

No monitoring data were provided but national MRLs were reported for the USA and several European countries.

Before MRLs can be recommended for the commodities for which GAP is pending confirmation that each proposed GAP has been registered will be required, together with copies of the product labels.

FURTHER WORK OR INFORMATION

Desirable

1. The method of analysis used for the determination of fenbuconazole in soil and water in the studies of environmental fate.

2. Data on residues in food in commerce or at consumption (i.e. monitoring or total diet data).

4.14 FENTHION (039)

TOXICOLOGY

Fenthion was reviewed by the 1995 JMPR, which established an ADI of 0-0.007 mg/kg bw on the basis of an NOAEL of 0.07 mg/kg bw per day (the highest dose tested) for the inhibition of erythrocyte acetylcholinesterase activity in a 25-day study in volunteers. The available data did not permit the Meeting to establish an acute reference dose (acute RfD) different from the ADI. A study of neurotoxicity in rats given a single dose was available to the present Meeting to assist in reviewing the acute RfD.

In rats treated by gavage with single doses of 0, 1, 50 (males), 75 (females), 150 (males), or 225 (females) mg/kg bw of technical-grade fenthion, the NOAEL for the inhibition of brain acetylcholinesterase activity and for neurobehavioural effects was 1 mg/kg bw.

In a study that was reviewed by the 1995 JMPR, the administration of 0.07 mg/kg bw to volunteers daily for about 25 days did not inhibit erythrocyte acetylcholinesterase activity.

The Meeting concluded that an acute reference dose of 0.01 mg/kg bw could be allocated by taking into account the NOAEL of 1 mg/kg bw in rats and applying a safety factor of 100.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION
RELEVANT FOR ESTABLISHING AN ACUTE RFD

Levels that cause no toxic effect

Rat: 1 mg/kg bw (single oral administration, inhibition of brain acetylcholinesterase activity)

Human: 0.07 mg /kg bw per day (four-week study in volunteers, highest dose tested)

Estimated acute reference dose for humans

0.01 mg/kg bw

4.15 FIPRONIL (198)

(±)-5-amino-1-(2,6-dichloro-á,á,á-trifluoro-*p*-tolyl)-4-trifluoromethylsulfinylpyrazole-3-carbonitrile

Fipronil was considered for the first time by the present Meeting. It has been proposed for indoor and outdoor use in the control of the mosquito that carries the malaria parasite.

Fipronil is a member of a new class of pesticide chemicals, the phenylpyrazoles. Its putative mode of insecticidal action is interference with the passage of chloride ions through the gamma-aminobutyric acid (GABA)-regulated chloride ion channel, which results in uncontrolled central nervous system activity and subsequent death of the insect. Although fipronil is selectively toxic to insects, some of the toxicity of fipronil observed in mammals also appears to involve interference with the normal functioning of the GABA receptor.

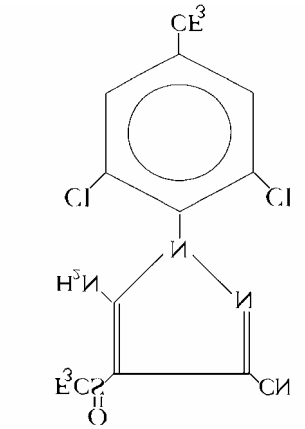
TOXICOLOGY

The toxicological profiles of fipronil, its mammalian metabolites, and two photodegradation products were considered. The Meeting concluded that the mammalian metabolites and one of the photodegradion products have similar toxicological potencies to fipronil, so they are not considered further in this report. Because the other photodegradation product, desulfinylated fipronil, appears to be more toxic than the parent compound, available data on this substance are reviewed here. The chemical structures of fipronil and the photodegradation product of toxicological concern are shown in Figure 1. The photodegradation product is designated as fipronil-desulfinyl.

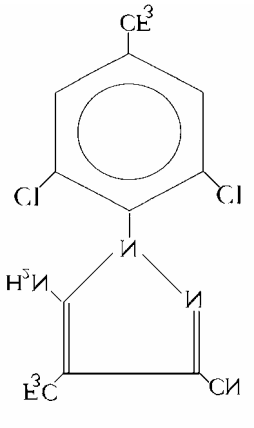
Fipronil

In a study of dermal absorption in rats, the quantity of [^{14}C]fipronil absorbed was less than 1% of the applied dose at all doses tested (0.88-48 mg fipronil/rat) and all times up to 24 h. *In vitro*, the relative extent of absorption of a formulation of [^{14}C]fipronil across rat, rabbit, or human epidermal membranes depended on the concentration of the material used. At the lowest concentration tested (0.2 g/litre), the extent of penetration was greatest for all three species, and the percentage of the dose absorbed across human and rat membranes was similar. At higher concentrations (4 and 200 g/litre), penetration was greater through rat and rabbit skin than through human skin.

Figure 1. Chemical structures of fipronil and its photodegradation product fipronil-desulfinyl



Fipronil



Fipronil-desulfinyl

There was no appreciable difference between male and female rats in the absorption, distribution, metabolism, or excretion of fipronil after oral administration. The proportion of the dose absorbed appeared to depend on the treatment regimen, being greatest with a single dose of 4 mg/kg bw of [^{14}C]fipronil (minimum absorption, 50%), intermediate with a repeated dose regimen of 4 mg/kg bw per day for 14 days followed by a single, oral labelled dose of 4 mg/kg bw (minimum absorption, 40%), and lowest (minimum absorption, about 30%) with a single dose of 150 mg/kg bw of [^{14}C]fipronil (presumably due to saturation of absorption at the high dose). Once absorbed, fipronil was rapidly metabolized and the residues widely distributed in the tissues where significant amounts of residues remained, particularly in fat and fatty tissues, one week after treatment. The levels of residues in fat and other tissues were greater with repeated low doses or a single high dose than with a single low dose. The long half-life (150-245 h in some cases) of fipronil in blood may reflect slow release of residues from fat and might suggest potential bioaccumulation of metabolic products of fipronil.

Faeces, followed by urine, were the major routes of elimination of fipronil in the rat. Its biotransformation largely involved changes in the functional groups attached to the pyrazole ring. The compounds identified in faeces and urine were the parent compound and the sulfone, the amide derived from the nitrile group, a reduction product, and a cleavage product of the sulfone and its derivatives formed by further cleavage. The sulfone was the major metabolite in fat and tissues.

Fipronil was moderately hazardous to rats (LD_{50} = 92 mg/kg bw) and mice (LD_{50} = 91 mg/kg bw) after oral administration of single doses and to rats after single exposure by inhalation (LC_{50} = 0.36 mg/litre). After a single dermal exposure, fipronil was relatively non-hazardous to rats (LD_{50} >2000 mg/kg bw) but was moderately hazardous to rabbits (LD_{50} = 354 mg/kg bw). In rats, signs of toxicity and death were delayed for up to four days after either a single oral dose or repeated oral doses of 75 mg/kg bw per day for up to five days. WHO has not yet classified fipronil for acute toxicity.

In a 13-week study of toxicity, mice were fed diets containing fipronil at doses of 0, 1, 3, 10, or 25 ppm. A dose-related increase in the incidence of liver-cell periacinar hypertrophy with cytoplasmic vacuolation was observed in males at doses of 1 ppm (equal to 0.13 mg/kg bw per day) and above. An NOAEL was not identified.

Rats were fed diets containing 0, 25, 50, 100, 200, or 400 ppm fipronil for four weeks. At 25 ppm (equal to 3.4 mg/kg bw per day), liver weights and plasma cholesterol were increased in females and thyroid follicular-cell hypertrophy of minimal severity was observed in animals of each sex. The levels of total protein and globulin were also increased in both males and females, although the changes at this and higher doses were generally small and poorly correlated with the dose. An NOAEL was not identified.

In a 13-week study of toxicity, fipronil was administered in the diet to rats at doses of 0, 1, 5, 30, or 300 ppm. At 30 ppm and above, relatively small, sometimes inconsistent changes in haematological parameters (decreased packed cell volume, mean cell volume, haemoglobin concentration and prothrombin time, increased platelet count) and clinical chemical parameters (increased total protein and globulins, decreased albumin:globulin ratio and alanine aminotransferase and aspartate aminotransferase activities) were observed, mostly in females. Some alterations were seen in plasma glucose and urea concentrations at 30 ppm; also at 30 ppm, the absolute and/or relative weights of the liver and thyroid were increased in either males or females or both, and there was evidence of thyroid follicular cell epithelial hypertrophy in males. The NOAEL was 5 ppm, equal to 0.33 mg/kg bw per day.

Fipronil was administered in gelatin capsules to dogs for 13 weeks in a study of toxicity at doses of 0, 0.5, 2, or 10 mg/kg bw per day. Inappetence and decreased body-weight gain and food consumption were noted in females at 2 and 10 mg/kg bw per day. The NOAEL was 0.5 mg/kg bw per day.

Fipronil was administered to dogs in gelatin capsules for one year in a study of toxicity at doses of 0, 0.2, 2, or 5 mg/kg bw per day. At 2 mg/kg bw per day and above, clinical signs of neurotoxicity (convulsions, twitching, tremors, ataxia, unsteady gait, rigidity of limbs, nervous

behaviour, hyper- or hypoactivity, vocalization, nodding, aggression, resistance to dosing and inappetence, and abnormal neurological responses) were observed in animals of each sex. One animal at 2 mg/kg bw per day was killed because of poor condition related to treatment. The NOAEL was 0.2 mg/kg bw per day.

In a second one-year toxicity study in dogs, fipronil was administered in the diet at doses of 0, 0.075, 0.3, 1, or 3 mg/kg bw per day. The highest dose was reduced to 2 mg/kg bw per day after 38 days because of toxicity. At 1 mg/kg bw per day, clinical signs of neurotoxicity (whole body twitching, and extensor rigidity of limbs) were noted in females. There were no effects on tri-iodothyronine or thyroxine levels. The NOAEL was 0.3 mg/kg bw per day.

In a study of carcinogenicity, fipronil was administered for 78 weeks in the diet to mice at doses of 0, 0.1, 0.5, 10, 30, or 60 ppm. Additional groups of animals were fed the same doses for 52-53 weeks and then killed. Survival was greater than or comparable to that of the control group at doses below 60 ppm. At week 10, all surviving animals at 60 ppm were killed because of excessive mortality. In animals at 10 ppm, some decrease in body-weight gain was noted in males and females, and efficiency of food utilization was decreased in males. At 53 and 78 weeks, the absolute and/or relative liver weights of males were increased, with an increased incidence of liver periacinar microvesicular vacuolation. There was no evidence of carcinogenicity at doses considered to be sufficient to measure such potential. The NOAEL for systemic effects was 0.5 ppm, equal to 0.055 mg/kg bw per day.

In a study of toxicity and carcinogenicity in rats, fipronil was administered in the diet at doses of 0, 0.5, 1.5, 30, or 300 ppm. For the carcinogenicity phase of the study, it was originally planned that the test material should be administered for two years, but excessive mortality resulted in early termination of this phase at week 89 in males and week 91 in females. This was not thought to compromise the study. For the toxicity phase and a reversibility phase of the study, additional groups of animals were fed the same doses of fipronil for one year, when some animals were killed and others were allowed to recover for 13 weeks. Some of the effects noted at the higher doses persisted into the reversibility phase of the study. During treatment, convulsive episodes (sometimes fatal) were observed in males at 1.5 ppm and in animals of each sex at higher doses. Animals at 1.5 ppm, predominantly females, showed irritability, vocalization, salivation, aggression, hyperactivity, and bruxism. Small decreases were noted in erythrocyte count, haemoglobin concentration, mean cell volume and packed cell volume in either males or females or both, and some alterations in protein level were observed in males. An apparent increase in the severity of progressive senile nephropathy was seen in animals of each sex at this dose. Thyroxine concentrations were decreased in both males and females. Thyroid-stimulating hormone levels were increased, notably in males, at doses of 30 ppm and above and in females at 300 ppm. The levels of tri-iodothyronine were elevated in females at 30 ppm, but only during the reversibility phase. At 300 ppm, fipronil induced follicular-cell adenomas of the thyroid gland in both males and females; males at this dose also had an increased incidence of follicular-cell carcinomas. Some thyroid follicular-cell adenomas were noted in male rats at lower doses, but a comparison with historical control data indicated no clear relationship to treatment. The NOAEL for systemic effects was 0.5 ppm, equal to 0.019 mg/kg bw per day.

Fipronil and its metabolites gave negative results in virtually all tests for genotoxicity.

Equivocal results were seen in assays for cytogenicity in mammalian cells *in vitro* (fipronil) and for polyploidy (not clastogenicity) in human lymphocytes (a mammalian metabolite). The weight of evidence indicates that fipronil and its metabolites are not genotoxic.

The Meeting concluded that the thyroid tumours observed in the two-year study in rats occurred by a non-genotoxic, threshold dose-effect mechanism involving continuous stimulation of the thyroid gland associated with persistently elevated thyroid-stimulating hormone levels. It was noted that the levels of this hormone were clearly elevated only at the two highest doses.

In a two-generation study of reproductive toxicity, rats received diets containing fipronil at 0, 3, 30 or 300 ppm. F_0 parental animals were mated twice to produce F_{1a} and F_{1b} litters; F_{1a} parents were mated only once to produce F_2 litters. In adult animals at 30 ppm, the thyroid and liver weights were increased and the pituitary gland weights were decreased. An increased incidence of thyroid gland follicular epithelial-cell hypertrophy was seen at this dose in males of the F_0 and F_1 generations and F_1 females. At 300 ppm, convulsions were observed in F_1 and F_2 litters; decreased litter size, decreased body weights and delays in physical development were also seen. Postnatal survival was decreased among pups in the F_2 litters. Absolute and relative ovarian weights were decreased in F_0 females. At 300 ppm, a decreased percentage of animals that mated and a reduction in the fertility index of F_1 parental animals was also observed. These effects may have been related to the systemic toxicity of fipronil at this dose. The NOAEL for parental systemic toxicity was 3 ppm, equal to 0.25 mg/kg bw per day, and the NOAEL for reproductive toxicity was 30 ppm, equal to 2.5 mg/kg bw per day.

Rats were administered fipronil by gavage at doses of 0, 1, 4, or 20 mg/kg bw per day on days 6-15 of gestation. Developmental toxicity was not observed, but there were some signs of maternal toxicity (decreased body-weight gain and food consumption) at 20 mg/kg bw per day. The NOAEL for maternal toxicity was 4 mg/kg bw per day, and that for developmental toxicity was 20 mg/kg bw per day, the highest dose tested.

Rabbits were administered fipronil by gavage at doses of 0, 0.1, 0.2, 0.5, or 1 mg/kg bw per day on days 6-19 of gestation. Developmental toxicity was not observed, but there were some signs of maternal toxicity (decreased body-weight gain, decreased food consumption, and reduced efficiency of food utilization at all doses. An NOAEL for maternal toxicity was not identified; the NOAEL for developmental toxicity was 1 mg/kg bw per day, the highest dose tested.

Two studies of primary dermal irritation in rabbits were performed. Fipronil was a slight irritant when moistened with corn oil before application but was not irritating when moistened with water before application. Fipronil was a slight irritant in two studies of primary ocular irritation in rabbits. It did not sensitize the skin of guinea-pigs when tested by the Buehler method but was a weak sensitizer in guinea-pigs tested by the Magnusson-Kligman method.

In a study of dermal toxicity, fipronil was applied in 0.5% carboxymethylcellulose to the intact skin of rabbits for 6 h per day on five days per week for three weeks at doses of 0, 0.5, 1, 5, or 10 mg/kg bw per day. No dermal irritation was observed. At 10 mg/kg bw per day, body-weight gains and food consumption were reduced in animals of each sex. Some animals showed

hyperactivity. The NOAEL was 5 mg/kg bw per day.

In a study of neurotoxicity, rats were given single doses of 0, 0.5, 5, or 50 mg/kg bw fipronil by gavage. At 5 mg/kg bw, decreased hind-leg splay was observed 7 h after treatment in both males and females. The NOAEL was 0.5 mg/kg bw.

In a 13-week study of neurotoxicity, rats received dietary doses of 0, 0.5, 5, or 150 ppm fipronil. At 150 ppm, body weights, weight gains, and food consumption were reduced early in the study in animals of each sex, possibly owing to problems of palatability. Although the findings in a battery of functional operational tests at this dose were relatively minor when taken separately, they appeared to represent a minimal effect of treatment when taken together. The NOAEL for neurotoxicity and systemic effects was 5 ppm, equal to 0.3 mg/kg bw per day.

In a study of neurotoxicity in female dogs, fipronil was administered in capsules at doses of 0 (one animal) or 20 mg/kg bw per day (four animals) until the appearance of neurotoxic signs in each animal, after which they were allowed to recover for 28 days. Severe neurotoxic signs were seen at 20 mg/kg bw per day during the treatment phase and in some animals only during the recovery phase. Most animals appeared to recover, although one had exaggerated reflex responses and was excitable at the end of the recovery period. A limited histopathological examination showed no change. No firm conclusions could be drawn about the reversibility of the effects, given the limitations of the study design. An NOAEL was not identified.

In a study of developmental neurotoxicity, rats were given fipronil in the diet from gestation day 6 through lactation day 10 at doses of 0, 0.5, 10, or 200 ppm. Maternal toxicity (reduced body weight during the treatment period, reduced body-weight gain during gestation, and reduced food consumption) was observed at 200 ppm. Developmental toxicity (reduced body weights in pups and a slight increase in the time to preputial separation) was noted at 10 ppm. An increase in motor activity in female pups at 10 ppm only on day 17 could not be definitively interpreted as an indication of developmental toxicity. Developmental neurotoxicity was clearly observed postnatally in pups at 200 ppm, with delayed swimming development on day 6, increased motor activity on day 17, abnormal auditory startle response on day 22, and impaired learning and memory on day 24. The NOAEL for maternal toxicity and developmental neurotoxicity was 10 ppm (equal to 0.9 mg/kg bw per day) and that for developmental toxicity was 0.5 ppm (equal to 0.05 mg/kg bw per day).

Mechanistic studies conducted with fipronil in rats suggest that it does not interfere with the incorporation of iodine into thyroxine but rather with the biliary clearance of this hormone. This may trigger an increase in the concentration of thyroid-stimulating hormone by interference with the feedback mechanism.

Mammalian metabolites of fipronil

Several mammalian metabolites of fipronil were tested for acute toxicity. The results indicated that their toxicity is comparable to or substantially less than that of fipronil.

Photodegradation products of fipronil

Numerous studies were performed with fipronil-desulfinyl, one of two photodegradation products of fipronil which can be formed in the presence of sunlight and could potentially be produced in the environment or on treated surfaces. Neither is a mammalian metabolite of fipronil. The available information indicates that, of the two, only fipronil-desulfinyl is highly toxic after either single-dose or long-term exposure, and is therefore of toxicological concern.

When 0.08-7.2 mg of [^{14}C]fipronil-desulfinyl was applied dermally to rats, absorption ranged fron 0.2 to 7% of the applied dose within 24 h.

The absorption, distribution, metabolism, and excretion of [^{14}C]fipronil-desulfinyl were studied in rats. Rats received either a single oral dose of [^{14}C]fipronil-desulfinyl at 1 or 10 mg/kg bw or 14 daily oral doses of unlabelled fipronil-desulfinyl at 1 mg/kg bw per day followed by a single oral labelled dose. In animals of each sex, elimination of the radiolabel was much greater in the faeces (46-70% of the dose) than in the urine with all dosing regimens. Appreciable residues were found in the tissues one week after treatment, the highest concentrations being present in the fat and fatty tissues. The long half-life in blood (183-195 h) and increased fat:plasma ratios of the radiolabel suggest potential bioaccumulation of fipronil-desulfinyl and/or its metabolites. Numerous metabolites or conjugates of fipronil-desulfinyl were present in urine and faeces. Biotransformation of fipronil-desulfinyl involved changes at the functional groups attached to the pyrazole ring. Only unchanged fipronil-desulfinyl was identified in the liver, fat, skin, and residual carcase.

In a 28-day study of toxicity in which fipronil-desulfinyl was administered in the diet to mice at doses of 0, 0.5, 3, 30, or 60 ppm, mortality, neurotoxic signs (increased motor activity, excessive jumping, irritability to touch, compulsive biting, and evidence of convulsions), decreased body-weight gain and food consumption, and an increased incidence of centrilobular hypertrophy of the liver were observed in animals of each sex at doses of 30 ppm and above. The NOAEL was 3 ppm, equal to 0.49 mg/kg bw per day.

Fipronil-desulfinyl was administered in the diet for 90 days to mice at doses of 0, 0.5, 2, or 10 ppm. At 2 and 10 ppm, clinical signs of neurotoxicity (irritability to touch, aggressiveness, and/or increased motor activity) were noted in males. The NOAEL was 0.5 ppm, equal to 0.08 mg/kg bw per day.

Rats received fipronil-desulfinyl by gavage for two weeks at doses of 0, 0.3, 1, 3, or 10 mg/kg bw per day. At 1 mg/kg bw per day, pale livers and reduced leukocyte counts were observed in females. Some rats at 3 mg/kg bw per day died or were killed because of poor condition. The NOAEL was 0.3 mg/kg bw per day.

Fipronil-desulfinyl was administered in the diet for 28 days to rats at doses of 0, 0.5, 3, 30 or 100 ppm. One male at 30 ppm died, and clinical signs of toxicity (piloerection and curling up on handling) and decreased body weights, food consumption, and bilirubin concentration were seen in males and females at this dose. Thymus weights were lower in females. The levels of thyroid-stimulating hormone were measured, but no effects were noted at any dose. All animals at 100 ppm died. The NOAEL was 3 ppm, equal to 0.23 mg/kg bw per day.

In a 90-day study of toxicity in rats, fipronil-desulfinyl was administered in the diet at 0, 0.5, 3, 10, or 30 ppm. At 3 ppm and above, clinical signs of neurotoxicity (aggressiveness, irritability to touch, and excessive vocalization) were observed in males. The levels of tri-iodothyronine and thyroxine were affected at higher doses, but the toxicological significance of these changes is probably negligible in the absence of changes in the level of thyroid-stimulating hormone at any dose. The NOAEL in the study was 0.5 ppm, equal to 0.029 mg/kg bw per day.

Dogs received fipronil-desulfinyl in the diet in a 28-day study at doses of 0, 27, 80, or 270 ppm. The groups at 80 and 270 ppm were terminated early because of mortality. In the group at 27 ppm, one male had a clonic convulsion. Reduced thymus weight and pale livers were also reported at this dose. As effects occurred at the lowest dose, an NOAEL was not identified.

In a 90-day study of toxicity, fipronil-desulfinyl was administered in the diet to dogs at doses of 0, 3.5, 9.5, or 35 ppm. The clinical findings in one female at 35 ppm (increased salivation, prostration, writhing, tremors, absence of rotular reflex, noisy breathing, dyspnoea) were attributed to arteritis and myocardial necrosis on the basis of microscopic findings; however, they may also have been indicative (at least in part) of neurotoxicity, because another female in this group exhibited excessive barking, aggressiveness, irritability, tremors, and increased salivation. On this basis, the Meeting concluded that the NOAEL was 9.5 ppm, equal to 0.29 mg/kg bw per day.

In a study of developmental toxicity in rats, fipronil-desulfinyl was administered by gavage on days 6-15 of gestation at doses of 0, 0.5, 1, or 2.5 mg/kg bw per day. Indications of maternal effects (decreased body-weight gain and hair loss in various areas) were observed at 2.5 mg/kg bw per day. Developmental toxicity (increased incidence of incomplete or reduced ossification of several bones and slightly reduced fetal body weight in animals of each sex) was also observed at this dose. The NOAEL for maternal toxicity and developmental toxicity was 1 mg/kg bw per day.

In a study of neurotoxicity in rats, fipronil-desulfinyl was administered by gavage as a single dose of 0, 0.5, 2, or 12 mg/kg bw. At 12 mg/kg bw, decreased body-weight gains and food consumption were observed during week 1 in animals of each sex. Decreased hind-foot splay, rectal temperature, and locomotor activity were also seen in animals of each sex at this dose. There were indications of a slowed righting reflex in males and decreased grip strength in males and females at the high dose. The NOAEL was 2 mg/kg bw per day.

In summary, the toxicity of fipronil-desulfinyl is qualitatively similar to that of fipronil, but the dose-effect curve for neurotoxic effects appears to be steeper for fipronil-desulfinyl than for fipronil. Also, fipronil-desulfinyl appears to have a much greater tendency than fipronil to bind to sites in the chloride ion channel of the rat brain GABA receptor. This finding appears to be consistent with the greater toxicity, relative to fipronil, of fipronil-desulfinyl in the central nervous system of mammals.

The Meeting established an ADI of 0-0.0002 mg/kg bw for fipronil on the basis of the NOAEL of 0.019 mg/kg bw per day in the two-year study of toxicity and carcinogenicity in rats

and incorporating a safety factor of 100.

The Meeting also considered that a separate ADI should be established for fipronil-desulfinyl on the basis that it could be a significant residue and that its toxicity is greater than that of the parent molecule fipronil. A temporary ADI of 0-0.00003 mg/kg bw for fipronil-desulfinyl was established on the basis of the NOAEL of 0.029 mg/kg bw per day in the 90-day study in rats and a safety factor of 1000 in view of the lack of a long-term study by oral administration in rats and a study of neurotoxicity in rats given repeated oral doses.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Fipronil

Levels that cause no toxic effect

Mouse: 0.5 ppm, equal to 0.055 mg/kg bw per day (78-week study of carcinogenicity and toxicity)

Rat: 5 ppm, equal to 0.33 mg/kg bw per day (13-week study of toxicity)

0.5 ppm, equal to 0.019 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

3 ppm, equal to 0.25 mg/kg bw per day (parental systemic toxicity in a study of reproductive toxicity)

30 ppm, equal to 2.5 mg/kg bw per day (study of reproductive toxicity)

4 mg/kg bw per day (maternal toxicity in a study of developmental toxicity by gavage)

20 mg/kg bw per day (developmental toxicity in a study of developmental toxicity by gavage; highest dose tested)

0.5 mg/kg bw (single dose, study of neurotoxicity by gavage)

5 ppm, equal to 0.3 mg/kg bw per day (repeated doses in the diet, study of neurotoxicity)

10 ppm, equal to 0.9 mg/kg bw per day (maternal toxicity and developmental neurotoxicity in a study of developmental neurotoxicity)

0.5 ppm, equal to 0.05 mg/kg bw per day (developmental toxicity in a study of developmental neurotoxicity)

Rabbit: 0.1 mg/kg bw per day (LOAEL for maternal toxicity in a study of developmental toxicity by gavage)

1 mg/kg bw per day (study of developmental toxicity; highest dose tested by gavage)

Dog: 0.3 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.0002 mg/kg bw

Fipronil-desulfinyl (fipronil photodegradation product)

Levels that cause no toxic effect

Mouse: 3 ppm, equal to 0.49 mg/kg bw per day (28-day study of toxicity)
0.5 ppm, equal to 0.08 mg/kg bw per day (90-day study of toxicity)
0.3 mg/kg bw per day (two week study of toxicity by gavage)
3 ppm, equal to 0.23 mg/kg bw per day (28-day study of toxicity)
0.5 ppm, equal to 0.029 mg/kg bw per day (90-day study of toxicity)
1 mg/kg bw per day (maternal and developmental toxicity in a study of developmental toxicity by gavage)
2 mg/kg bw per day (single dose, study of neurotoxicity by gavage)

Dog: 9.5 ppm, equal to 0.29 mg/kg bw per day (90-day study of toxicity)

Estimate of temporary acceptable daily intake for humans

0-0.00003 mg/kg bw

Acute reference dose for fipronil

The Meeting allocated an acute reference dose of 0.003 mg/kg bw for both fipronil and fipronil-desulfinyl on the basis of the NOAEL of 0.3 mg/kg bw per day in a study of neurotoxicity in rats given repeated doses of fipronil, and a safety factor of 100. The study of neurotoxicity in rats given single doses was not considered in allocating the acute reference dose because of concern about the prolonged toxicokinetics of fipronil. This acute reference dose will provide a safety factor of about 700 for the NOAEL in the study of neurotoxicity in rats given single doses of fipronil-desulfinyl.

Studies without which the determination of an ADI is impracticable, to be provided by 2000

1. Short-term study of neurotoxicity in rats with fipronil-desulfinyl in the diet.

2. Developmental neurotoxicity study in rats with fipronil-desulfinyl in the diet.

3. The results of an ongoing long-term study with fipronil-desulfinyl in rats.

Studies that would provide information useful for the continued evaluation of fipronil and fipronil-desulfinyl

1. Additional studies to investigate the reversibility of the neurotoxic effects of fipronil and its metabolites (functional, behavioural, learning/memory, cellular, and neurotransmitter/receptor effects).

2. Observations in humans exposed to fipronil and fipronil-desulfinyl.

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to fipronil and its photodegradation product fipronil-desulfinyl

Fipronil

Human exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	Skin, irritation, rabbit	Slightly irritating
	Eye, irritation, rabbit	Minor irritation
	Skin, sensitization, guinea-pig	Not a sensitizer (Buehler)
	Skin, sensitization, guinea-pig	Mild sensitizer (Magnusson-Kligman)
	Oral, toxicity, rat	LD_{50} = 92 mg/kg bw
	Dermal, toxicity, rabbit	LD_{50} = 350 mg/kg bw
	Inhalation, toxicity, rat	LC_{50} = 0.36 mg/l
	Neurotoxicity, rat (single dose by gavage)	NOAEL = 0.5 mg/kg bw per day: decreased hind-leg splay
Medium-term (1-26 weeks)	Repeated dermal, 3 weeks, toxicity, rabbit	NOAEL = 5 mg/kg bw per day: reduced body-weight gains and food consumption; hyperactivity in some animals; no dermal irritation observed
	Repeated oral, reproductive toxicity, rat	NOAEL = 0.25 mg/kg bw per day for maternal toxicity. NOAEL = 2.5 mg/kg bw per day for reproductive toxicity.
	Repeated oral, developmental neurotoxicity, rat	NOAEL = 0.9 mg/kg bw per day for maternal toxicity. NOAEL = 0.05 mg/kg bw per day for developmental toxicity.

Human exposure	Relevant route, study type, species	Results, remarks
		NOAEL = 0.9 mg/kg bw per day for developmental neurotoxicity.
Long-term (>1 year)	Repeated oral, 2 years (terminated at 89-91 weeks), long-term toxicity and carcinogenicity, rat	NOAEL = 0.019 mg/kg bw per day: convulsions and neurobehavioural clinical signs of toxicity; effects on the thyroid; thyroid follicular-cell adenomas and carcinomas.

Fipronil-desulfinyl

Human exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	Oral, toxicity, rat Dermal, toxicity, rat Neurotoxicity, rat (single dose by gavage)	LD_{50} = 15 mg/kg bw LD_{50} > 2000 mg/kg bw NOAEL = 2 mg/kg bw per day.
Medium-term (1-26 weeks)	Repeated oral (diet), 90 days, toxicity, rat Repeated oral (gavage), developmental toxicity, rat	NOAEL = 0.029 mg/kg bw per day. NOAEL = 1.0 mg/kg bw per day: maternal toxicity. NOAEL = 1.0 mg/kg bw per day: developmental toxicity.
Long-term (≥ 1 year)	Repeated oral toxicity	No data

4.16 FOLPET (041)

RESIDUE AND ANALYTICAL ASPECTS

Residue aspects of folpet were most recently reviewed in 1993 and 1994. The Meeting received information on metabolism, analytical methods, stability of samples during freezer storage, registered uses, data from supervised trials on fruit and vegetable crops, and processing studies.

The Meeting noted that folpet was scheduled for periodic review by the FAO Panel in 1998.

When the roots of tomato plants were treated with [*carbonyl*-^{14}C]folpet the ^{14}C was rapidly absorbed into the plants (85% within 1 day). After 11 days 90% of the absorbed ^{14}C was in the tops. Folpet itself was a very minor constituent (<0.1-0.2%) of the residue within the plant. The main identified components were phthalimide, phthalamic acid and phthalic acid. Unidentified polar metabolites, possibly ring-hydroxylated phthalamic acid derivatives, accounted for 15-30% of the ^{14}C in the tops.

When wheat was treated with [*phenylene*-^{14}C]folpet at a rate equivalent to 1.6 kg ai/ha and harvested 43 and 54 days after the second treatment the levels of ^{14}C were lower in the roots than in the straw or grain. Folpet was the major component of the residue in the straw (4.7 mg/kg) and grain (9.3 mg/kg) with the metabolites phthalic acid (4.3 mg/kg in straw and 6.4 mg/kg in grain) and phthalimide (1.5 mg/kg in straw and 3.1 mg/kg in grain) also significant constituents.

When Thomson Seedless grape vines were treated 3 times with [*phenylene*-^{14}C]folpet at a rate equivalent to 1.5 kg ai/ha and the grapes harvested 25 days after the final treatment, surface rinsing removed 26% of the grape residue. Folpet itself constituted 27% of the residue in or on the grapes, and phthalic acid and phthalimide 5.8% and 11% respectively. An unidentified compound in the water-soluble fraction accounted for 41% of the residue. It was very polar and yielded phthalic acid on hydrolysis, so was likely to be a conjugate or conjugates of phthalic acid.

A small avocado tree was treated with 3 foliar applications equivalent to 3.4 kg ai/ha of [*phenylene*-^{14}C]folpet and fruit were harvested at maturity 97 days after the final application. Very little residue was removed by rinsing the fruit, but most of it was extractable with ethyl acetate from the peel and pulp. The residues in or on the fruit were folpet 0.026 mg/kg, phthalimide 0.22 mg/kg and phthalic acid 4.5 mg/kg. Polar and other unidentified residues accounted for about 0.7 mg/kg. Folpet and phthalimide residues were mainly on the peel, but most of the phthalic acid residue was in the pulp.

The 1993 JMPR reviewed the Schlesinger analytical method for residues of folpet and phthalimide. The methods used in the supervised trials on apples, lettuce, melons, onions, strawberries and tomatoes were developed from the Schlesinger method. Folpet was determined in the cleaned up extract by GLC with an ECD. The recovery of folpet from various fortified commodities was commonly 70-100%, but with some excursions outside this range. In a total of 340 tests the mean and median recoveries were 87% and 86% respectively. The LOD was 0.05 mg/kg.

Folpet residues were shown to be stable during freezer storage for the intervals tested in apple juice (30 days), wet apple pomace (35 days), apples (149 days), cranberries (176 days), cucumbers (29 days), grape juice (36 days), lettuce (90 days), onions (41 days), tomato paste (30 days), tomato purée (31 days) and tomatoes (136 days).

Information was made available to the Meeting on registered uses of folpet and on supervised trials on apples, grapes, strawberries, onions, cucumbers, melons, tomatoes and lettuce. Relevant data evaluated in 1993 and 1994 were also reviewed where possible.

Folpet is registered in Argentina for use on apples with 3 applications of 3.6 kg ai/ha and

harvest 10 days after the final application. Folpet residues in apples from 2 trials according to GAP were 1.4 and 2.6 mg/kg.

Canadian GAP permits folpet to be applied 8 times to apples at 0.8 kg ai/ha with harvest 7 days after the final application. In 4 trials where the use pattern corresponded to GAP the residues were 0.43, 0.65, 1.1 and 1.4 mg/kg.

Folpet residues from 2 trials on apples in Chile where the trial conditions corresponded to the registered use (2.0 kg ai/ha, 3 applications, 7 days PHI) were 2.0 and 3.7 mg/kg.

In a Hungarian trial which complied with GAP (8 applications of 1.6 kg ai/ha and a PHI of 10 days), a Swiss trial according to GAP (4 applications of 2.0 kg ai/ha and a PHI of 21 days), and a Spanish trial complying with GAP (10 applications of 1.9 kg ai/ha and a PHI of 10 days), the folpet residues were 8.0, 3.4, and 3.1 mg/kg respectively.

Folpet may be applied 8 times at 1.6 kg ai/ha to apples in Portugal with harvest 21 days after the final application. In a trial meeting these conditions the residue was 3.2 mg/kg. In a trial reported in 1993 folpet was applied 10 times at 1.3 kg ai/ha, which is within the acceptable range for evaluation, and the resulting residue after 21 days was 1.8 mg/kg

In France folpet may be used up to 11 times on apples at 1.0-1.2 kg ai/ha with harvest 14 days later. In 4 trials in France complying with GAP the residues were 0.9, 1.4, 1.4 and 1.8 mg/kg.

In summary, the folpet residues in apples from trials according to GAP were 1.4 and 2.6 mg/kg in Argentina, 0.43, 0.65, 1.1 and 1.4 mg/kg in Canada, 2.0 and 3.7 mg/kg in Chile, 8.0 mg/kg in Hungary, 3.4 mg/kg in Switzerland, 3.1 mg/kg in Spain, 1.8 and 3.2 mg/kg in Portugal, and 0.9, 1.4, 1.4 and 1.8 mg/kg in France. The residues in rank order (median underlined) in the 17 trials were 0.43, 0.65, 0.9, 1.1, 1.4, 1.4, 1.4, 1.4, 1.8, 1.8, 2.0, 2.6, 3.1, 3.2, 3.4, 3.7 and 8.0 mg/kg.

The Meeting estimated a maximum residue level and an STMR of 10 mg/kg and 1.8 mg/kg respectively for apples.

The folpet residue in grapes was 1.6 mg/kg in a supervised trial that complied with GAP in Argentina (4 applications of 1.0 kg ai/ha and a PHI of 7 days). The residues were 2.6 and 3.0 mg/kg in 2 supervised trials in Chile according to GAP (2.0 kg ai/ha, 3 applications and 14 days PHI), and below the LOD, <0.05 mg/kg, in a Mexican trial in accordance with GAP (1.0 kg ai/ha, 7 applications and a PHI of 10 days).

Italian GAP permits 5 applications of folpet to grapes at 1.6 kg ai/ha with harvest 10 days after the final application. In an Italian trial according to GAP in 1996 and 2 Italian trials reported in 1993 where folpet was used 7 and 10 times at 1.5 kg ai/ha with a PHI of 10 days the folpet residues were 3.3, 0.58 and 0.75 mg/kg.

Four French trials (2 reported in 1993) were evaluated in terms of Italian GAP. The application rates were 1.5 and 1.6 kg ai/ha, with 7 and 8 applications and PHIs of 8 and 10 days, conditions which were acceptably close to GAP. The residues were 1.3, 2.2, 3.7 and 8.1 mg/kg.

In summary, folpet residues in grapes from trials according to GAP were 1.6 mg/kg in Argentina, 2.6 and 3.0 mg/kg in Chile, <0.05 mg/kg in Mexico, and 0.58, 0.75, 1.3, 2.2, 3.3, 3.7 an and 8.1 mg/kg in Italy and France. The residues in rank order (median underlined) in the 11 trials were <0.05, 0.58, 0.75, 1.3, 1.6, 2.2, 2.6, 3.0, 3.3, 3.7 and 8.1 mg/kg.

The Meeting estimated maximum residue and STMR levels for grapes of 10 mg/kg and 2.2 mg/kg respectively.

GAP in Mexico permits 4 applications of folpet to strawberries at 1.3 kg ai/ha with harvest 2 days after the final application, and in The Netherlands 2 applications of 1.4 kg ai/ha and a 14-day PHI. The residues in 3 Mexican and 3 Dutch trials complying with GAP were 1.6, 1.7 and 2.2 mg/kg, and 1.4, 1.6 and 1.9 mg/kg respectively.

The Meeting noted that the results of these 6 trials were in line with the current draft MRL for strawberry of 5 mg/kg, and decided that it would be preferable to estimate an STMR when all the information on residue trials and current GAP become available for the periodic review in 1998.

GAP for onions in Chile allows 3 applications of 2 kg ai/ha and in Mexico 4 applications at 1.5 kg ai/ha, both with harvest 7 days after the final application. Folpet residues in one Chilean and two 2 Mexican trials complying with GAP were 0.36, 0.41 and 0.41 mg/kg.

Two trials in Greece and four in Hungary according to national GAP gave residues of <0.05 (3), 0.07 and 0.21 mg/kg.

The folpet residues in onions in trials in Portugal (5.0 mg/kg) and Spain (2.5 mg/kg) were somewhat higher than in other European countries (<0.05-0.21 mg/kg), and probably related to the drip irrigation system used in Portugal and Spain, whereas sprinkler irrigation is used elsewhere.

In the trials in Greece, Hungary, Portugal and Spain the field sample was described as at least 2 kg consisting of 12 or more onions. The soil was removed mechanically by hand and the whole plant, including roots and foliage, was analysed. The Meeting was informed that this sampling procedure was based on a draft EU guideline, which is unfortunately in conflict with a long-established Codex procedure. Because the correct sample for bulb onions does not include roots or foliage the Meeting could not use the data, and the 3 trials in Chile and Mexico were insufficient to estimate a maximum residue level.

The folpet residue in cucumbers was 0.07 mg/kg in a Canadian trial according to Canadian GAP (8 applications of 1.0 kg ai/ha with a PHI of 7 days), and 0.11, 0.36, 0.56 and 0.70 mg/kg in four Mexican trials complying with national GAP (1.8 kg ai/ha with harvest after the last of 4 applications).

The Meeting noted that the current draft MRL for cucumbers is 0.5 mg/kg and concluded that it would be preferable to evaluate all the residue data in terms of relevant GAP at the periodic review in 1998.

In Greece folpet is registered for use on melons at 0.49 kg ai/ha with harvest 20 days after the final application (maximum 4). Folpet residues were below the LOD (<0.05 mg/kg) in melons in

4 Greek trials according to GAP and in 2 others where folpet was applied at twice the GAP rate.

Mexican GAP permits 6 applications at 1.8 kg ai/ha and harvest 7 days after the final application. The residues in 3 Mexican trials complying with GAP were 0.40, 0.89 and 2.2 mg/kg.

In two trials in Honduras according to GAP (4 applications of 0.64 kg ai/ha and a PHI of 3 days), the residues were 0.32 and 0.41 mg/kg, and in a Guatemalan trial according to GAP (6 applications of 0.48 kg ai/ha and a PHI of 3 days), the residue was 0.23 mg/kg.

In summary, folpet residues in melons from trials effectively according to GAP were <0.05 (6) in Greece, 0.40, 0.89 and 2.2 mg/kg in Mexico, 0.32 and 0.41 mg/kg in Honduras and 0.23 mg/kg in Guatemala. The residues in rank order in the 12 trials were <0.05 (6), 0.23, 0.32, 0.40, 0.41, 0.89 and 2.2 mg/kg.

As the residues in the Greek trials appear to belong to a different population from the others, the 6 trials in Mexico, Honduras and Guatemala were used to estimate an STMR.

The Meeting estimated maximum residue and STMR levels for folpet in melons of 3 mg/kg and 0.41 mg/kg respectively. The STMR in this case is for the whole melon because data were not available on residues in the edible portion.

GAP for tomatoes in Chile allows 7 applications of 1.7 kg ai/ha with a 7-day PHI, and in Mexico 5 applications at 2.0 kg ai/ha with a 2-day PHI. Folpet residues in one Chilean and 5 Mexican trials complying with GAP were 2.4 mg/kg and 0.45, 1.0, 1.3, 1.6 and 1.8 mg/kg respectively.

In Hungary folpet is registered for use on tomatoes at an application rate of 0.65 kg ai/ha with harvest 14 days after the final application (maximum of 3). In 4 Hungarian trials according to GAP and in 1 trial reported in 1993 with 5 applications at the GAP rate and PHI the residues were all below the LOD (<0.02 and <0.05 (4) mg/kg).

In one Italian and two Portuguese trials in compliance with Portuguese GAP (4 applications of 1.3 kg ai/ha and 7 days PHI) the residues were 0.34, 0.55 and 0.58 mg/kg. In a Spanish trial according to GAP (6 applications of 1.6 kg ai/ha and a 10-day PHI) the residue was 1.3 mg/kg.

In summary, folpet residues in tomatoes from trials according to GAP were 2.4 mg/kg in Chile, 0.45, 1.0, 1.3, 1.6 and 1.8 mg/kg in Mexico, <0.02 and <0.05 (4) mg/kg in Hungary, 0.55, 0.34 and 0.58 mg/kg in Portugal and Italy, and 1.3 mg/kg in Spain. The residues in rank order in the 15 trials were <0.02, <0.05 (4), 0.34, 0.45, 0.55, 0.58, 1.0, 1.3 (2), 1.6, 1.8 and 2.4 mg/kg.

The residues in the Hungarian trials appear to be in a different population from the others. The 10 trials from Chile, Portugal, Italy and Spain were used to estimate an STMR.

The Meeting estimated maximum residue and STMR levels for folpet in tomatoes of 3 mg/kg and 1.15 mg/kg respectively.

Folpet is registered in Mexico for 4 applications of 1.3 kg ai/ha to lettuce with harvest 7 days

after the final application. Folpet residues were 4.5, 9.8 and 16 mg/kg in 3 Mexican trials on head lettuce with 5 applications at the GAP rate and PHI, and 22 mg/kg in one trial on leaf lettuce under the same conditions.

Folpet residues were not detected (<0.05 mg/kg) in head or leaf lettuce in 2 trials in Greece according to Greek GAP (4 applications of 0.61 kg ai/ha and 20 days PHI), except that only 3 applications were made to head lettuce. No residue was detected (<0.05 mg/kg) in leaf lettuce in a Spanish trial according to GAP (4 applications of 0.78 kg ai/ha and 21 days PHI).

In summary, folpet residues in head lettuce were 4.5, 9.8 and 16 mg/kg in Mexico and <0.05 mg/kg in Greece, and in leaf lettuce 22 mg/kg in Mexico, <0.05 mg/kg in Greece and <0.05 mg/kg in Spain. The data populations in Mexico and Europe appear to be different. There were too few results to make a recommendation.

Processing

Field-treated apples were processed to juice and wet pomace to simulate commercial practice as closely as possible. The process included an initial washing step which removed about 40% of the residue. The processing factors for the production of wet pomace and apple juice were 2.6 and 0.035 respectively.

The STMR-Ps for the processed apple commodities calculated from the processing factors and the STMR for apples (1.8 mg/kg) are wet apple pomace 4.7 mg/kg and apple juice 0.063 mg/kg.

Grapes were treated post-harvest by dipping bunches for 30 seconds in a vat containing folpet (1.25 kg ai/hl). The grapes were allowed to dry and then processed into raisins and juice. Because folpet is a surface residue it was considered valid to treat grapes in this way.

The treated grapes were dried in the sun until the moisture level reached 12-16%. After destemming, the dried grapes were rehydrated to 18-20% moisture in an incubator at 21°C to produce raisins. Juice was produced from treated grapes by crushing, enzyme treatment, heating and filtering.

Folpet residues were not detectable (<0.05 mg/kg) in the grape juice. The calculated processing factor for juice is <0.003. Folpet residues in the dried and hydrated raisins were higher than in the original grapes, with processing factors of 3.2 and 1.9 respectively.

The Meeting estimated a maximum residue level for folpet residues in dried grapes or raisins of 40 mg/kg after rounding up, from the processing factor of 3.2 and the maximum residue level estimated for grapes (10 mg/kg).

The STMR-P levels calculated from the processing factors and the STMR for grapes (2.2 mg/kg) are grape juice 0.0066 mg/kg, dried raisins 7.0 mg/kg, and hydrated raisins 4.2 mg/kg.

In 10 trials on grapes in Germany in 1993 residues of folpet were measured in the must and wine produced from treated grapes. The processing factors for folpet transfer from grapes to must ranged from 0 to 0.97, mean 0.29. Folpet was not detected (<0.05 mg/kg) in any wine

sample, hence the processing factor for wine is 0. Phthalimide, a metabolite and breakdown product of folpet, was consistently present in both must and wine.

The STMR-P for must calculated from the mean processing factor and the STMR for grapes (2.2 mg/kg) is 0.64 mg/kg.

The Meeting noted that the use of folpet on grapes consistently results in phthalimide residues in wine at levels typically 25-50% of the folpet levels in the grapes. The metabolism study on grapes had shown the formation of a water-soluble conjugate of phthalic acid in grapes which also has the potential to reach the wine.

A tomato crop was treated 5 times with folpet at 2.2 kg ai/ha and harvested 7 days after the final application for processing. The tomatoes were treated in 0.5% sodium hydroxide and then vigorously washed before being processed to juice, purée and paste. Purée was produced from juice by evaporation, adjustment of salt and water levels, heating and canning. Paste was produced similarly, but with a higher salt level.

Folpet residues were not detected (<0.05 mg/kg) in tomato purée or paste produced from tomatoes containing 1.8 mg/kg of folpet. It is quite likely that the initial vigorous cleaning of the tomatoes would remove or destroy most of the folpet residues. The calculated processing factor for the transfer of folpet from tomatoes to purée and paste is <0.028, and the STMR-P calculated from the STMR for tomatoes of 1.15 mg/kg is 0.032 mg/kg.

4.17 GLYPHOSATE (158)

TOXICOLOGY

Glyphosate was evaluated toxicologically by the 1986 JMPR, which allocated an ADI of 0-0.3 mg/kg bw.

The primary degradation product of glyphosate in plants, soil, and water, is aminomethylphosphonic acid (AMPA), whose chemical structure is very similar to that of glyphosate. AMPA itself has no commercial use. On the basis of the low residual levels of AMPA in crops which are susceptible to glyphosate the 1986 Joint Meeting concluded that AMPA could be omitted from the definition of the residue when considering recommendations for MRLs, but recent supervised trials on the application of glyphosate to crops genetically modified to be glyphosate-resistant have shown that AMPA can be the main residue. As residues of AMPA may therefore be of toxicological concern, the compound was evaluated by the present Meeting.

After oral administration of AMPA to rats, 20% of the dose was absorbed and excreted unmetabolized in the urine within 120 h (17% of the dose within 24 h), and 73% of the dose was eliminated in the faeces. Only 0.07% of the dose was excreted as expired carbon dioxide within 24 h, and 0.06% was recovered from tissues after 120 h. Minor amounts (1-6 ìg/kg) were found in tissues after 120 h.

AMPA is slightly hazardous to rats given a single oral dose, with an LD_{50} of 8300 mg/kg bw.

In a 90-day study of toxicity, rats received AMPA in the diet at 0, 400, 1200, or 4800 mg/kg bw per day. A significant, dose-related decrease in body-weight gain was seen in males at the two highest doses and in females at the highest dose. The two highest doses also resulted in significantly increased lactate dehydrogenase activity, whereas aspartate aminotransferase activity and cholesterol levels were significantly increased only at the highest dose. Urinalysis showed a significant decrease in urinary pH and increased amounts of calcium oxalate crystals in the urine of animals at the highest dose. Dose-related irritation of the mucosal and submucosal layers of the urinary tract, corresponding to hyperplasia of the urinary bladder, was seen in rats at 1200 and 4800 mg/kg bw per day, the effect being more marked in males than in females. In addition, epithelial hyperplasia in the renal pelvis was observed at the highest dose. The NOAEL was 400 mg/kg bw per day.

In a 90-day study of toxicity in dogs receiving AMPA at 0, 10, 30, 100, or 300 mg/kg bw per day in gelatin capsules, no statistically significant treatment-related changes were observed. The NOAEL was thus the highest dose, 300 mg/kg bw per day. It should be noted that in a one-month range-finding study with groups of only two male and two female dogs, changes in some haematological parameters (e.g. decreased haemoglobin and PCVs, decreased erythrocyte counts) were seen in animals at 300 or 1000 mg/kg bw per day. These effects were not reproduced in the 90-day study.

No indication of genotoxic activity was seen in studies of gene mutation in bacteria, of DNA repair in bacteria and mammalian cells *in vitro*, or of micronucleus formation *in vivo*. No assays for gene mutation were performed in mammalian cells *in vitro*, but the structural similarity of AMPA to glyphosate and the negative results of genotoxicity assays of glyphosate, including one for gene mutation in mammalian cells *in vitro*, indicate that such an assay with AMPA would be redundant.

In a study of developmental toxicity, rats received AMPA at 0, 150, 400, or 1000 mg/kg bw per day in corn oil by gavage. Dose-related increases in the incidences of soft stools, mucoid faeces, and hair loss were seen in dams at the two higher doses. Dams at the highest dose also had short periods of decreased body-weight gain and food consumption. Fetal body weight was decreased at 1000 mg/kg bw per day. No teratogenic effects were observed. Dams at 150 mg/kg bw per day also had an increased incidence of soft stools; however,in the absence of any associated effects, such as hair loss or mucoid faeces, the Meeting considered this dose to be the NOAEL for maternal toxicity. The NOAEL for developmental toxicity was 400 mg/kg bw per day.

AMPA did not induce dermal or ocular irritation in rabbits.

No long-term study of the toxicity or carcinogenicity of AMPA has been carried out, but in the more recent of two such studies with technical-grade glyphosate in rats at dietary levels of 0.2, 0.8, or 2%, the AMPA content of the test compound was given, namely 0.68%. At the highest dose of 2% glyphosate in the diet, females showed decreased body-weight gain and males showed an increased incidence of degenerative lenticular changes. The NOAEL for technical-grade glyphosate was 0.8% in the diet, corresponding to 400 mg/kg bw per day for glyphosate and 2.7 mg/kg bw per day for AMPA. No increase in tumour incidence was seen in this study (as evaluated by the International Programme on Chemical Safety (IPCS)).

No multigeneration study of the reproductive toxicity of AMPA has been reported, but in a recent two-generation study in rats with technical-grade glyphosate at dietary levels of 0.2, 1, or 3%, the test compound contained 0.61% AMPA. At the highest dose, soft stools, decreased parental body weights, slightly decreased litter sizes, and decreased pup weights were observed. The NOAEL was 1% in the diet, corresponding to 740 mg/kg bw per day glyphosate and 4.5 mg/kg bw per day AMPA (as evaluated by IPCS[1]).

Glyphosate and AMPA have very similar chemical structures. Studies of the metabolism of glyphosate in experimental animals indicate that essentially none is biotransformed into AMPA. Toxicological data on the metabolite are therefore essential for risk assessment. The Meeting compared the toxicity profile of AMPA with that of glyphosate and concluded that the major targets of the toxicity of AMPA had been investigated. The results showed little toxicity. The Meeting concluded that the two compounds have similar toxicological profiles and considered that a full database on AMPA is unnecessary. AMPA was considered to be of no greater toxicological concern than its parent compound. The Meeting established a group ADI for AMPA alone or in combination with glyphosate of 0-0.3 mg/kg bw on the basis of the 26-month study of toxicity in rats fed technical-grade glyphosate, using a safety factor of 100 (see 1986 JMPR report and toxicological evaluations, FAO/WHO, 1986d, 1987a).

Since the last JMPR evaluation for toxicity in 1986, new data have become available on glyphosate, some of which are evaluated in EHC 159. The Meeting therefore recommended that glyphosate be re-evaluated by the JMPR.

A toxicological monograph on AMPA was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

AMPA

Rat: 400 mg/kg bw per day (90-day study of toxicity)
150 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
400 mg/kg bw per day (fetal toxicity in a study of developmental toxicity)

Dog: 300 mg/kg bw per day (highest dose in 90-day study of toxicity)

Glyphosate (from 1986 JMPR)

Mouse: 0.5% in the diet, equal to 814 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 31 mg/kg bw per day (26-month study of toxicity and carcinogenicity)

Dog: 500 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.3 mg/kg bw (sum of glyphosate and AMPA)

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to aminomethylphosphonic acid (AMPA)

Human exposure	Relevant route, study type, species	Results/remarks
Short-term (1-7 days)	Oral toxicity, rat	LD_{50} = 8300 mg/kg bw
	Skin irritation, rabbit	Not irritating
	Eye irritation, rabbit	Not irritating
	Skin sensitization	No data
Medium-term (1-26 weeks)	Repeated oral, 90 days, toxicity, rat	NOAEL = 400 mg/kg bw per day: urinary tract changes NOAEL = 150 mg/kg bw per day: maternal toxicity
	Repeated oral, developmental toxicity, rat	NOAEL = 400 mg/kg bw per day: developmental toxicity.
	Repeated oral, reproductive toxicity	No data
Long-term (≥ 1 year)	Repeated oral, toxicity	No data

RESIDUE AND ANALYTICAL ASPECTS

Glyphosate was first evaluated in 1986, and residue aspects were reviewed in 1987, 1988 and 1994. Maximum residue levels were estimated for kiwifruit and a range of vegetables, cereals, oilseeds and animal products.

The 1997 JMPR was requested to evaluate the new uses of glyphosate on cotton, maize and sorghum according to GAP. These new uses are (1) pre-harvest topical applications and (2) in-crop applications to cotton and maize crops which have been genetically modified to be resistant to glyphosate. Relevant data on metabolism and residue trials were submitted to the Meeting.

Genetic modification of crops

Glyphosate binds to and blocks the activity of 5-enolpyruvoyl-shikimate-3-phosphate synthase (EPSPS), an enzyme of the aromatic amino acid biosynthetic pathway. Glyphosate inhibition of EPSPS prevents the plant from synthesizing the aromatic amino acids essential for protein

production. Glyphosate-resistant EPSPS is derived from *Agrobacterium sp*. strain CP4 (CP4 EPSPS), and has been used to develop glyphosate-resistant (i.e. glyphosate-tolerant) crops.

While CP4 EPSPS has been successful in providing glyphosate resistance in cotton, its activity alone has been insufficient to ensure adequate resistance in other crops. In maize, a second mechanism has been developed to ensure sufficient levels of crop resistance to allow applications of glyphosate at rates necessary for effective weed control. The second mechanism is glyphosate inactivation, which effectively reduces cellular levels of glyphosate by converting it to aminomethylphosphonic acid (AMPA). The enzyme responsible for glyphosate inactivation is glyphosate oxidoreductase (*gox*). The gene encoding *gox* was isolated from a naturally-occurring bacterium, *Achromobacter sp*., and has been modified to optimize its expression in plants.

Plant metabolism

Numerous plant metabolism studies with vegetable, orchard tree, nut tree and pasture crops were reported to the 1986 JMPR. The 1986 Meeting concluded that glyphosate applied to the soil was absorbed very slightly or not at all by the crops examined and its conversion to AMPA, the primary metabolite, was not observed.

However, hydroponic administration allows sufficient uptake of glyphosate to elucidate its metabolism in plants. Metabolic studies with glyphosate in hydroponically-grown maize, wheat, cotton and soya beans have shown the conversion of glyphosate to AMPA and further degradation in plant tissues.

Metabolic studies in plants that have been genetically modified to be resistant to glyphosate show that the metabolism is the same as in susceptible plants. Glyphosate is metabolized to AMPA, which is either non-selectively bound to natural plant constituents, further degraded to one-carbon fragments that are incorporated into natural products, or conjugated with naturally-occurring organic acids to give trace-level metabolites. The metabolites are the same in resistant and susceptible crops but their relative distribution depends on the speed and extent of conversion to AMPA.

Methods of residue analysis

Glyphosate and its major metabolite AMPA can be determined by GLC or HPLC after derivatization. In the GLC method evaluated by the 1986 JMPR, clean-up on anion exchange, cation exchange and carbon columns is followed by trifluoroacetylation and methylation. The limit of determination was 0.05 mg/kg in cotton seed and hay and recoveries of glyphosate and AMPA respectively at 0.05-0.4 mg/kg fortification levels were 66.3-89.4% and 66.0-84.9% in cotton hay, and 56.7-74.8% and 63.4-93.2% in cotton seed.

HPLC methods were discussed in the 1986 and 1994 monographs. The preferred method employs two-column switched HPLC with a post-column reactor. The limit of determination was 0.05 mg/kg in all commodities and mean recoveries were 77-88% for glyphosate and 78-90% for AMPA.

Residues of AMPA in or on crops and definition of the residue

The Meeting received data on supervised trials on maize into which the *gox* gene had been introduced, which showed that residue levels of AMPA were much higher than those in normal crops.

The Meeting agreed to recommend two MRLs for residues in maize, one as glyphosate to accommodate uses on glyphosate-susceptible crops and the other as AMPA to accommodate uses on glyphosate-resistant crops. A violation would occur if either MRL were exceeded.

The current definition of the residue is “glyphosate” because residues of AMPA in crops are usually very low or undetectable, except in soya beans.

The Meeting agreed that the definition of the residue for estimations of dietary intake should include AMPA but the definition for enforcement purposes for all commodities, including genetically modified crops, should remain as "glyphosate" for the following reasons.

1. Already many commodities have CXLs based on the residue defined as glyphosate. All existing CXLs would have to be reviewed if the definition of the residue were changed.
2. It is not thought appropriate to establish a separate definition of the residue for maize.
3. The existing definition of the residue has already been incorporated into many national regulations, and a change of the definition would be likely to cause difficulties in international harmonization.

The Meeting also noted the significant residue levels of AMPA that occurred in soya beans, and recommended that their significance should be evaluated in a future periodic review even though they are not believed to pose any risk to consumers.

Supervised trials

In the following text the sum of glyphosate + AMPA expressed as glyphosate is referred to as "total glyphosate". The total glyphosate residue was evaluated to estimate STMRs for the assessment of dietary intake.

Cotton. Twelve supervised trials were carried out on glyphosate-susceptible cotton in the USA with pre-harvest application at 3.4 kg ai/ha. US GAP allows pre-emergence (crop) application (including pre-plant or at-planting applications), post-directed application (post-crop-emergence, directed at weeds), spot treatment and pre-harvest application at 4.2 kg ai/ha as the maximum for each treatment. The total application is restricted to 6.7 kg ai/ha per year.

Six of the trials were with pre-emergence and post-emergence applications before a pre-harvest application. The pre-emergence application rate (6.7 kg ai/ha) and the total applied (10-26 kg ai/ha) exceeded the GAP limits, but the Meeting concluded that these trials were comparable with GAP because the rate of the pre-harvest application (3.4 kg ai/ha), which should be most influential on the residue in the harvested crops, was within the GAP rate of 4.2 kg ai/ha and the studies of plant metabolism indicated that the uptake of glyphosate from soil would be negligible. The other six trials with only one pre-harvest application at 3.4 kg ai/ha were according to GAP.

Sixteen supervised trials, with three different application patterns in each, were carried out on

glyphosate-resistant cotton in the USA with 4 or 5 applications which included pre-emergent, post-emergent, post-directed and pre-harvest treatments. Eleven trials were with genotype 1445 cotton and five with genotype 1698 cotton but these have the same basic genetic structure and would be expected to show no differences in glyphosate metabolism.

All the application patterns slightly exceeded US GAP: post-emergence (trials: 0.84-1.26 kg ai/ha, GAP: 0.84 kg ai/ha), post-directed (trials: 1.26 kg ai/ha, GAP: 0.84 kg ai/ha), and total application (trials 7.56-8.8 kg ai/ha, GAP: 6.7 kg ai/ha), but the Meeting again concluded that the trials complied with GAP because the most influential final applications were compatible with GAP and earlier applications would be unlikely to have much effect on the residues.

In susceptible cotton seed the residues of glyphosate were 0.54-5.9 mg/kg at 5-9 days and 0.15-3.6 mg/kg at 10-14 days, and those of AMPA were <0.05-0.20 mg/kg at 5-14 days. The residues of total glyphosate were 0.62-6.0 mg/kg at 5-9 days and 0.23-3.7 mg/kg at 10-14 days, and of total glyphosate after maximum GAP treatments 0.62, 0.71, 2.4, 2.8, 3.0 and 6.0 mg/kg.

In resistant cotton seed the residues of glyphosate were 0.13-5.0 mg/kg at 6-9 days and 0.30-0.50 mg/kg at 17 days, and those of AMPA were <0.05-0.21 mg/kg at 7-9 days. The residues of total glyphosate were 0.21-5.2 mg/kg at 6-9 days and 0.38-0.58 mg/kg at 17 days. Those of total glyphosate after maximum GAP treatments were 0.21, 0.30, 0.42, 0.49, 0.51 (2), 0.52, 0.54, 0.55, 0.66, 0.68, 0.73, 0.75, 0.77 (2), 1.1 (2), 1.3, 1.4, 1.5, 1.8, 1.9, 2.1 (2), 2.2, 2.3, 2.5, 2.6 (3), 2.8, 2.9 (2), 3.2, 3.5, 3.7, 3.8, 4.2 (2), 4.4, 4.7 and 5.2 mg/kg.

Since the differences between both the median and maximum total glyphosate residues in resistant and susceptible crops were not significant, the Meeting based the STMR on the combined residues from the two sets of trials.

The total glyphosate residues from the 48 individual trials which complied with GAP (six on susceptible cotton and 42 on resistant cotton) in rank order (median underlined) were 0.21, 0.30, 0.42, 0.49, 0.51 (2), 0.52, 0.54, 0.55, 0.62, 0.66, 0.68, 0.71, 0.73, 0.75, 0.77 (2), 1.1 (2), 1.3, 1.4, 1.5, 1.8, <u>1.9</u>, <u>2.1</u> (2), 2.2, 2.3, 2.4, 2.5, 2.6 (3), 2.8 (2), 2.9 (2), 3.0, 3.2, 3.5, 3.7, 3.8, 4.2 (2), 4.4, 4.7, 5.2 and 6.0 mg/kg.

The Meeting estimated an STMR level of 2.0 mg/kg total glyphosate. Taking into account the residues of glyphosate alone in susceptible (0.54-5.9 mg/kg) and resistant (0.13-5.0 mg/kg) crops, the Meeting estimated a maximum residue level of 10 mg/kg glyphosate and recommended the withdrawal of the CXL of 0.5 mg/kg.

The residues of glyphosate in the hay from susceptible cotton were 3.8-33 mg/kg at 5-9 days and 6.3-84 mg/kg at 10-14 days, and those of AMPA were 0.10-0.46 mg/kg at 5-14 days. The residues of total glyphosate were 4.1-33 mg/kg at 5-9 days and 6.4-85 mg/kg at 10-14 days.

The glyphosate residues (3.8-84 mg/kg) were below the existing CXL for the straw and fodder (dry) of cereal grains (100 mg/kg), although cotton hay is not classified within this group of commodities. The Meeting agreed not to recommend an MRL for cotton hay in view of its insignificance in international trade.

The residues of glyphosate in the gin by-product from resistant cotton were 3.7-84 mg/kg at

6-9 days and 0.79-2.2 mg/kg at 17 days, and those of AMPA were <0.05-0.84 mg/kg at 6-9 days and <0.05 mg/kg at 17 days. The residues of total glyphosate were 3.8-85 mg/kg at 6-9 days and 0.87-2.3 mg/kg at 17 days.

The Meeting did not recommend an MRL because the commodity does not figure in international trade.

Maize. Twelve supervised trials on susceptible maize and 66 on resistant maize were carried out in the USA. The 12 trials were with one pre-harvest application (2.5 kg ai/ha). US GAP allows pre-emergence application (0.32-4.2 kg ai/ha), spot treatment (0.32-4.2 kg ai/ha) and pre-harvest application (2.5 kg ai/ha for ground, 0.84 kg ai/ha for aerial) but the Meeting considered that the trials were effectively compatible with the maximum GAP application because the residue from pre-emergence application would be expected to be negligible and spot treatment should not affect crops if carried out according to GAP.

The 66 trials on resistant maize were with 2 to 4 applications which included pre-emergent, post-emergent and pre-harvest applications; 22 of the trials were according to maximum GAP.

Grain. The residues of glyphosate, AMPA and total glyphosate in the susceptible maize were <0.05-0.54 mg/kg, <0.05-0.13 mg/kg and <0.13-0.62 mg/kg respectively at 6-7 days. The residues of total glyphosate after maximum GAP treatments were <0.13 (5), 0.13, 0.14, 0.19, 0.23, 0.25, 0.27 and 0.62 mg/kg.

The residues of glyphosate, AMPA and total glyphosate in the resistant maize were <0.05-0.34 mg/kg, <0.05-1.4 mg/kg and <0.13-2.2 mg/kg respectively at 6-8 days. The residues of total glyphosate after maximum GAP treatments were <0.13 (2), 0.22 (2), 0.23, 0.26, 0.37, 0.38 (2), 0.41, 0.42, 0.51 (2), 0.52, 0.54 (2), 0.60, 0.67, 0.78, 1.0, 1.6 and 2.2 mg/kg.

Since the total glyphosate residues in the susceptible and resistant maize clearly belonged to difference populations, the Meeting estimated an STMR of 0.47 mg/kg total glyphosate, based on the residues in the resistant maize.

On the basis of the residues of glyphosate in susceptible (<0.05-0.54 mg/kg) and resistant (<0.05-0.34 mg/kg) maize, the Meeting recommended an MRL of 1 mg/kg for glyphosate to replace the existing CXL (0.1* mg/kg). The Meeting also estimated a maximum residue level of 2 mg/kg for AMPA in maize on the basis of the residues of AMPA found in resistant maize (<0.05-1.4 mg/kg).

Fodder. The residues of glyphosate, AMPA and total glyphosate in the susceptible maize fodder were 3.7-92 mg/kg, 0.09-0.81 mg/kg and 3.8-93 mg/kg respectively at 6-7 days. The corresponding residues in the fodder from resistant maize were 1.8-41 mg/kg, <0.05-4.7 mg/kg and 2.0-48 mg/kg respectively at 6-8 days. The residues in both susceptible and resistant maize fodder were below the existing CXL for the straw and fodder (dry) of cereal grains (100 mg/kg).

The Meeting estimated a maximum residue level of 5 mg/kg for AMPA in maize fodder from the residues in fodder from resistant maize (<0.05-4.7 mg/kg).

Forage. According to GAP, the forage of susceptible crops should be cut before the pre-

harvest application of glyphosate, whereas the forage of resistant crops can be cut after the application before harvest. Trials to determine residues in forage were therefore restricted to resistant maize.

The residues of glyphosate, AMPA and total glyphosate in the maize forage were <0.05-0.52 mg/kg, 0.06-1.1 mg/kg and 0.18-1.9 mg/kg respectively after 48-65 days. Those of total glyphosate from maximum GAP treatments were 0.18, 0.23, 0.26, 0.35, 0.55, 0.61, 0.64, 0.81, 0.86, 0.92, 1.0 (2), 1.1, 1.8 and 1.9 mg/kg.

The Meeting estimated maximum residue levels of 1 mg/kg glyphosate and 2 mg/kg AMPA, which are recommended for use as MRLs, and an STMR of 0.81 mg/kg total glyphosate.

Sorghum (pre-harvest applications to susceptible plants). Eight supervised trials were carried out in the USA with one pre-harvest application at 1.7 kg ai/ha. US GAP allows pre-emergence application at 0.32-4.2 kg ai/ha, spot treatment at 0.32-4.2 kg ai/ha and pre-harvest application at 1.7 kg ai/ha. For the reasons given above, the Meeting considered the trials to be compatible with maximum GAP.

Grain. The residues of glyphosate, AMPA and total glyphosate were 1.4-13, <0.05-0.22 and 1.6-13 mg/kg respectively after 6-8 days. Those of total glyphosate in rank order were 1.6, 1.8, 1.9, 5.4, 6.2, 6.6 and 13(2) mg/kg.

The Meeting recommended an MRL of 20 mg/kg for glyphosate to replace the existing CXL (0.1* mg/kg), and an STMR of 5.8 mg/kg for total glyphosate.

Fodder and hay. Residue data said to be on sorghum hay were submitted, but the Meeting concluded that the commodity analysed in the trial should be classified as sorghum fodder.

The residues of glyphosate, AMPA and total glyphosate in fodder were 2.9-33, <0.05-0.41 and 3.0-34 mg/kg respectively at 6-8 days. The corresponding residues in ″hay″ were 3.1-37, <0.05-0.45 and 3.2-37 mg/kg at 10-15 days.

The glyphosate residues in both fodder (2.9-33 mg/kg) and hay (3.1-37 mg/kg) were below the existing CXL for the straw and fodder (dry) of cereal grains (100 mg/kg).

Processing

Cotton. Although only one study was available the Meeting agreed to calculate STMR-Ps because the processing adequately simulated industrial practice.

Processing factors from cotton seed to delinted cotton seed, cotton kernels, cotton hulls and cotton meal were 0.19, 0.084, 0.34 and 0.12 respectively. They were <0.034 for processing to crude cotton seed oil, cotton soapstock, refined cotton seed oil and bleached-deodorized cotton seed oil.

The Meeting estimated maximum residue levels of 0.05* mg/kg for crude and edible cotton seed oil, and STMR-Ps of 0.38, 0.17, 0.68 and 0.24 mg/kg for delinted cotton seed, cotton kernels, cotton hulls and cotton meal respectively, by calculation from the cotton seed STMR of

2.0 mg/kg.

Maize. Residues of glyphosate and AMPA were determined in the processed commodities but the residue of glyphosate in the raw grain was below the LOD, although AMPA was detected. Information on the conversion of glyphosate to AMPA during the processing was not available. The Meeting could not use the data to estimate STMR-Ps.

Sorghum. The mean processing factors were 4.7, 1.2, 0.36, 4.7 and 0.49 from sorghum to bran, clean grain, flour, grain dust and grits (medium) respectively and <0.028 or <0.11 for processing to germ and starch.

The Meeting estimated STMR-Ps of 0 for sorghum germ and starch because they contained negligible residues of glyphosate and AMPA individually, and 27, 7.0, 2.1, 27 and 2.8 mg/kg for bran, clean grain, flour, grain dust and grits (medium) respectively, by calculation from the sorghum STMR (5.8 mg/kg).

FURTHER WORK OR INFORMATION

Desirable

Processing studies with both susceptible and resistant maize in which the raw grain contains measurable residues of both glyphosate and AMPA.

4.18 GUAZATINE (114)

TOXICOLOGY

Guazatine was first evaluated by the Joint Meeting in 1978, when an ADI of 0-0.03 mg/kg bw was established on the basis of an NOAEL of 200 ppm (equivalent to 3 mg/kg bw per day) in a two-year dietary study in dogs. The pesticide was reviewed at the present Meeting within the CCPR periodic review programme. New data on its absorption and metabolism, the toxicity of repeated doses in mice and dogs, its long-term toxicity in rats and mice, genotoxicity, reproductive toxicity, and developmental toxicity were assessed. Data on the pesticide 1,1-iminodi(octamethylene)diguanidine, with the common name iminoctadine (BSI, draft ISO), which constitutes about 1.5% of the guazatine mixture, were also considered.

Guazatine is a preparation of the triacetates of dimeric and trimeric guanidated octane-1,8-diyldiamine which also contains a range of oligomers and reaction products. The Meeting was concerned that the production controls and specifications for guazatine were inadequate. The quoted purity of 70% is based on normalization to a component which comprises approximately 1.5% of the mixture and provides no control over the levels of the other components. Some data were provided to show that the composition of the batch used in the key toxicity studies was similar to that of other batches produced at the same time, 1990-91, but there were no data to confirm that the batches used in the studies of toxicity were representative of those currently produced.

Some components of guazatine were absorbed by rats to a limited extent after oral

administration of the ^{14}C-labelled material and then excreted rapidly. Within 24 h, faecal elimination represented 85-94% of the dose, with 3-6% in the urine and < 1% in exhaled air. The highest levels of radiolabel were found in the kidney and liver, with evidence that the salivary, pituitary and thyroid glands may also contain significant amounts of residue. A study involving treatment with 14 doses of 2 mg/kg bw showed limited potential accumulation in the liver and kidney. The results of a study by intravenous injection showed that some components of guazatine may be secreted back into the gastrointestinal tract via the stomach and salivary glands. The metabolism of guazatine has not been fully characterized, but successive conversion of the terminal guanidino groups to amino plays a significant role *in vivo*.

Guazatine produces severe local irritation, and single oral doses are of moderate toxicity, with an oral LD_{50} value in rats of 280 mg/kg bw. WHO has classified guazatine as moderately hazardous.

In a number of short-term studies in rats, guazatine was administered at doses of 0, 60, 200, 800/1200, or 1500/2000 ppm in the diet for 14 weeks. At doses of 60 and 200 ppm, the activity of serum alkaline phosphatase was slightly decreased, but no significant changes were seen in body-weight gain or in the results of pathological, haematological, or urinary examinations. At doses of 800 ppm and above, decreased body-weight gain, increased activities of alanine and aspartate aminotranferases, and decreased activity of alkaline phosphatase were found, together with pathological changes such as local irritation of the gut and hyperplasia of the epithelia of the parotid gland excretory ducts with mononuclear cell infiltration. Increased weights of the kidney, liver, and heart were seen without associated histopathological changes. The overall NOAEL was 200 ppm, equivalent to 10 mg/kg bw per day.

In a 13-week range-finding study, mice received guazatine at 0, 10, 50, 200, or 500 ppm. Significantly reduced body-weight gain was seen in animals of each sex at 200 ppm and above. Increased liver weights and alterations in centrilobular hepatocytes were seen in both males and females at 500 ppm. Alterations in erythrocyte parameters were seen in animals at doses of 200 ppm and above. Although no significant effects were reported at 10 or 50 ppm, an NOAEL was not identified in view of limited histological investigations in the study.

In a one-year study in dogs, guazatine was administered at 0, 25, 75, or 250 ppm. Reduced body-weight gain in females, increased alanine aminotransferase activity in animals of each sex, and increased aspartate aminotransferase activity in males were observed at a dietary concentration of 250 ppm. In females at 75 ppm, body-weight gain was reduced. The NOAEL was 25 ppm, equal to 0.8 mg/kg bw per day.

Guazatine has been tested in an adequate battery of assays for genotoxicity. The Meeting concluded that guazatine is not genotoxic.

Guazatine was not carcinogenic in two two-year studies in rats given doses of 0, 20, 60 or 200 ppm or 0, 50, 150, or 350 ppm. Non-neoplastic findings included reduced serum alanine and aspartate aminotranferase activities, salivary gland hyperplasia, and testicular atrophy at 350 ppm. In a two-year study of iminoctadine administered at 0,10, 100 or 300 ppm, there was no reported increase in tumour incidence. The overall NOAEL was 150 ppm, equal to 7 mg/kg bw per day.

In a study of carcinogenicity, mice received 0, 50, 120, or 300 ppm guazatine. The incidences of malignant tumours were increased at 120 and 300 ppm: haemangiosarcoma of the liver and spleen was seen in males at 120 and 300 ppm and hepatocellular carcinoma in females at 300 ppm. The incidence of renal-tubular tumours (adenoma and carcinoma) was increased in males receiving 300 ppm. These are rare tumour types in the mouse strain that was used, normally being seen in only 0-6% of animals. Although the absolute incidences of these tumours in guazatine-treated animals were low and not statistically significant, they were clearly greater than those in historical controls. No convincing information was available on the underlying mechanism of tumour production. The non-neoplastic effects seen in this study were increased incidences of lymphoid foci in the lung, bronchiole-associated lymphoid tissue, keratinized vaginal epithelium, and brain mineralisation in females receiving 300 ppm. Body weight gain was reduced by approximately 20% in animals of each sex receiving 300 ppm. In addition, an abstract describing a study on iminoctadine (0, 10, 100, or 300 ppm) reported a slight increase in the incidence of renal epithelial tumours in male mice receiving 300 ppm. The Meeting considered that the production of rare malignant tumours by an unknown mechanism is of great concern. The overall NOAEL for long-term administration to mice was 50 ppm, equal to 6.8 mg/kg bw per day, on the basis of increases in the incidence of haemangiosarcoma in males at 120 ppm, equal to 17 mg/kg bw day.

In a multigeneration study of reproductive toxicity in rats receiving guazatine at 0, 60, or 200 ppm, no significant effects were seen at the highest dose, equivalent to 12 mg/kg bw per day. In a two-generation study of reproductive toxicity in rats guazatine administered at 0, 50, 150, or 350 ppm did not affect reproductive performance at the highest dose, equal to 22 mg/kg bw per day.

In a study of developmental toxicity in rats, guazatine was administered at 0, 5, 10, or 20 mg/kg bw per day. The NOAEL for maternal toxicity, teratogenicity, and fetotoxicity was 20 mg/kg bw per day, the highest dose tested. In a range-finding study, significant mortality was seen at 40 mg/kg bw per day.

In a study of developmental toxicity in rabbits, guazatine was administered at 0, 2.8, 5.6, or 11 mg/kg bw per day. There were no signs of fetotoxicity or teratogenicity at the highest dose. The NOAEL was 5.6 mg/kg bw per day on the basis of marked decreases in maternal body-weight gain.

The Meeting concluded that it could not establish an ADI for guazatine owing to the inadequate information on its composition and concerns about the production of rare malignant tumours in mice.

A toxicological monograph summarizing the data received since the previous evaluation and relevant data from the previous monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 50 ppm, equal to 6.8 mg/kg bw per day (two-year study of toxicity and

carcinogenicity)

Rat: 350 ppm, equal to 22 mg/kg bw per day (two-generation study of reproductive toxicity)
20 mg/kg bw per day (study of developmental toxicity)
150 ppm, equal to 7 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Dog: 25 ppm, equal to 0.8 mg/kg bw per day (one-year study of toxicity)

Studies that would provide information necessary for the continued evaluation of the compound

1. Data on the levels of individual components in batches of guazatine from recent production runs.

2. Investigation of the mechanism of tumour production in mice.

3. Clarification of the extent of absorption, excretion, and metabolism of all components of guazatine.

4. Clarification as to whether the stated doses used in the studies of toxicity were expressed as free base or triacetate.

RESIDUE AND ANALYTICAL ASPECTS

Guazatine was evaluated by the JMPR in 1978 and 1980, and is now re-evaluated in the CCPR periodic review programme. It is a non-systemic contact fungicide which disturbs the membrane function of fungi. It controls a wide range of seed-borne diseases of cereals, e.g. seedling blight *(fusarium spp.)*, glume blotch *(septoria)*, common bunt *(tilletia spp.)*, common root rot *(helminthosporium)* and smut *(ustilago)*. On citrus fruit, guazatine is used as a bulk dip after harvest, in the packing line as a spray and in washing installations to disinfect the process water. It controls sour rot *(geotrichum candidum)*, green mould *(penicillium digitatum)* and blue mould *(penicillium italicum)*.

Guazatine is a mixture of reaction products from polyamines, comprising mainly octamethylenediamine, iminodi(octamethylene)diamine, octamethylenebis(iminooctamethylene)diamine, and carbamonitrile. A coding system is used for the compounds that make up guazatine in which 'N' represents any amino group. Thus NN stands for H_2N-$(CH_2)_8$-NH_2 , NNN stands for H_2N-$(CH_2)_8$-NH-$(CH_2)_8$-NH_2 and so on. 'G' stands for any amino group (NH or NH_2) of the above which is guanidated. For example GG stands for H_2N-C(NH)NH-$(CH_2)_8$-NH-C(NH)-NH_2.

The fate of residues has been studied in animals, plants and soil.

Studies on rats and lactating cows showed poor absorption from the gastrointestinal tract, rapid elimination mainly in the faeces (>90%), excretion largely as the unchanged parent mixture and no accumulation in any organs, tissues or milk.

When cows were dosed daily with 0.5 mg/kg bw for 10.5 days, 93% of the administered radioactivity was recovered in the faeces as unchanged guazatine, and the low levels in plasma indicated minimal absorption. ^{14}C in the milk and plasma, expressed as guazatine, reached plateau levels of about 0.02 and 0.015 mg/l respectively by day 3 in milk and day 6 in plasma. Following slaughter after the last dose residues of about 0.08 mg/kg were found in the liver and kidney with only very low levels in other edible tissues (<0.02 mg/kg in skeletal muscle and fat).

Adequate metabolism studies with full characterization of the metabolites in farm animals, an animal transfer study on ruminants and an analytical method for commodities of animal origin were not submitted. The Meeting was therefore unable to establish a definition of the residue of guazatine in animal products and could not estimate maximum residue levels for products of animal origin.

When wheat seeds were dressed with [^{14}C]guazatine at 1.05 g ai/kg seed there was no difference between the total radioactive residue (TRR) levels in the harvested grain, straw or chaff from the treated and the control plots. The method of application was according to GAP.

The foliar application of [^{14}C]guazatine to wheat at 1.1 kg ai/ha, 11 weeks before harvest, resulted in mean TRRs of 29 mg/kg guazatine equivalents in the straw, 18 mg/kg in the chaff, and 0.8 mg/kg in the grain.

When [^{14}C]guazatine was applied to the leaf surface or the fruit of apples (brushing with 0.05 or 0.1 kg ai/hl) its translocation was extremely limited. Autoradiography showed no observable movement in the leaves or fruit and this was confirmed by quantitative determination of the TRR: 87% of the applied radioactivity was recovered from the leaves after 12 weeks, 66% from the surface and 21% from the leaf tissues (61% was identified as the parent mixture). In the fruit 62% of the TRR was located on the surface and 38% in the tissues after 12 weeks, with 81% of the TRR identified as the parent. The remainder comprised a major photodegradation product (4.5%), other extractable compounds (9.7%), and unextractable residues (5.2%).

The uptake of guazatine residues from soil by soya beans and rice plants was investigated by treating soils with 5 mg/kg of [^{14}C]guazatine and planting soya bean and rice plants after 26 weeks. Four weeks after planting, the TRR in soya beans amounted to only 0.08% of the applied radioactivity in the aerial part and 0.12% in the whole plant. The residues expressed as guazatine equivalents on a dry weight basis were 2.8 mg/kg in the aerial part and 3.7 mg/kg in the whole plant. The pods contained 0.052 mg/kg on a dry weight basis 9 weeks after planting.

Guazatine residues taken up from flooded soil were low in the whole rice plant, which absorbed only 0.13% of the applied ^{14}C (0.57 mg/kg on a dry weight basis) during a period of four weeks, with 0.05 % of the applied radioactivity or 0.23 mg/kg (dry weight) in the shoot.

Guazatine has been shown to be metabolized in about 100 days when applied to wheat seeds planted in soil, via deguanidation and subsequent mineralization. The test system had a substantial influence on the degradation time.

When guazatine was applied to wheat seeds which were subsequently planted in soil and the soil leached to simulate rainfall, the guazatine components were found to be associated with the

seeds or the soil surrounding the seeds. The compounds that had moved from the seeds to the soil showed no tendency to migrate. Significant mineralization to carbon dioxide occurred during the leaching period.

The Meeting concluded that these studies were adequate for the use of guazatine for the seed treatment of cereals, and that no further studies on rotational crops were necessary for such uses.

The use of such a complex mixture as guazatine presents a problem in choosing a residue analytical method. It is not considered practical to attempt the determination of all the components so some alternative is necessary. Two approaches may be applicable.

1. Development of a 'total residue' method by conversion to a single compound.

2. The choice of a major component as a 'marker', with the inclusion of a correction factor to give the total residue.

Many of the residue studies used the first approach, involving the hydrolysis of residues to bis(8-amino-octyl)amine (NNN) and its determination either directly or after derivatization. This method was used, e.g., for the analysis of citrus fruits, where the LODs (expressed as guazatine) were 0.05 mg/kg for finisher pulp, 0.2 mg/kg for wet peel and 1 mg/kg for dried peel. The metabolites are determined by the total residue method together with the parent material.

Better results were achieved with cereals, however, by using the marker GG (octane-1,8-diyldiguanidine, H_2N-C(NH)NH-$(CH_2)_8$-NH-C(NH)-NH_2), one of the major guazatine components, for quantification. This method incorporates a correction factor to allow for the fact that GG represents only 30% of the total guazatine. The homologue GG-C6 (1,6-diguanidinohexane, H_2N-C(NH)NH-$(CH_2)_6$-NH-C(NH)-NH_2), is used as an internal standard. The analytical method for grain and straw consists in extraction of samples fortified with the internal standard with hot 1M HCL, clean-up on a cation exchange column, derivatization with hexafluoroacetylacetone (HFAA), clean-up on basic Al_2O_3, and determination of the HFAA derivatives of GG and the internal standard GG-C_6 by GC-MS.

Samples fortified with guazatine showed LODs of 0.05 mg/kg for cereal grains and 0.1 mg/kg for straw with recoveries of 88% and 94% respectively. The lowest fortification levels at the LOD of the marker GG were also 0.05 mg/kg for grain and 0.1 mg/kg for straw (recoveries: grain 97%, straw 82%).

The Meeting concluded that 0.05 mg/kg is a practical limit of determination for GG.

The justification for the choice of GG as representative of the total guazatine residues in cereals has been supported by the following facts.

1. Guazatine shows low uptake and translocation in cereals. This is consistent with the lack of detectable residues reported in crops after seed treatments.

2. Where the material has been applied as a foliar spray on dwarf apples trees there is little evidence of significant metabolism or hence of changes in the proportions of the components of the guazatine mixture.

3. In a situation where metabolism is demonstrably occurring (see below), GG remains a significant component after 29 days.

Evidence for GG still being present under 'metabolizing' conditions comes from an aerobic soil degradation study. In this, a mixture of GG, GN and GGG was applied to seed surfaces, and the seeds were planted in soil in metabolism vessels. Most of the seeds germinated. It was possible to distinguish the seeds from the soil and extract the seeds separately up to 29 days after planting. Analysis of these extracts indicated a change in the profile of components present on the seed with GGG levels decreasing. This is consistent with the generation of $^{14}CO_2$ in the study. However at day 29 GG was still the predominant single compound on the seed, despite the degradation which had been occurring at the seed surface or in the soil in contact with it.

On this basis, it is considered that GG represents a satisfactory marker compound to represent guazatine residues in seed-treated cereals.

The storage stability of analytical samples was investigated by storing analysed samples of wheat grain, ears and straw at -20°C and re-analysing them after two years. The study was not satisfactory as an unvalidated analytical method was used.

Definition of the residue. The metabolism of guazatine in animals has not been fully elucidated, and the Meeting concluded that the residue of guazatine in products of animal origin could not be satisfactorily defined.

The metabolism of guazatine in plants has also not been fully characterized. The main uses of guazatine are for the seed treatment of cereals and the post-harvest protection of citrus fruits. The Meeting concluded that the available studies were adequate only for the seed treatment of cereals. Should further uses (e.g. foliar spray or treatment of plants other than cereals) be planned in future, detailed metabolism studies would be required.

Guazatine has been determined by a total residue method based on conversion to the corresponding triamine, bis(8-amino-octyl)amine, which also occurs as a metabolite. Modern analytical methods using octane-1,8-diyldiguanidine (GG), one of the main components of guazatine, as a marker are more specific.

The Meeting concluded that the residue should be defined for enforcement purposes as "octane-1,8-diyldiguanidine" (GG). Assuming that the content of GG is 30% of the total guazatine content, the GG content should be multiplied by 3 for risk assessment purposes for commodities of plant origin.

Definition of the residue for enforcement purposes: octane-1,8-diyldiguanidine (GG), expressed as octane-1,8-diyldiguanidine.

Definition of the residue for risk assessment purposes: guazatine.

Supervised trials

Citrus fruits. Concentrations of 0.05 to 0.2 kg ai/hl water or 0.3 kg ai/hl wax are registered for

post-harvest treatment.

In Australia, guazatine is registered for the post-harvest treatment of citrus fruits with 0.052 kg ai/hl. Three residue trials according to GAP (one each on oranges, mandarins and lemons) were reported and showed residues of <0.2, 0.3 and 0.5 mg/kg (calculated as guazatine) in the whole fruit.

South African GAP specifies 0.3 kg ai/hl in wax for the treatment of citrus fruits. Five trials (3 on oranges, one each on lemons and grapefruit) at the lower rate of 0.2 kg ai/hl in wax were reported. The residues in the whole fruit ranged from 0.33 to 1.8 mg/kg, calculated as guazatine. These results and the data on the validation of the method were submitted only as summaries.

After dipping oranges in water with 0.2 kg ai/hl guazatine, residues of 5.5 mg/kg were calculated in the whole fruit (2 trials). These results are inconsistent with the results found after waxing and indicate a more critical residue situation. Furthermore, no data were available on residues in small citrus fruits (e.g. mandarins) after treatment with 0.2 kg ai/hl.

The Meeting concluded that the residue data were not adequate for citrus fruits as a major crop and recommended the withdrawal of the existing CXL of 5 mg/kg.

Tomatoes and melons, except watermelons. Post-harvest uses of guazatine exist in Australia but no residue data were received.

No maximum residue level could be estimated for tomatoes, and the Meeting recommended the withdrawal of the existing CXL of 5 mg/kg for melons, except watermelon.

Pineapples and potatoes. Since no residue data or information on GAP were received, the Meeting recommended the withdrawal of the existing CXLs of 0.1* mg/kg for pineapple and potato.

Cereal grains. The use of guazatine for seed treatment is registered in many countries with application rates from 0.05 to 1.05 g ai/kg seed (mainly 0.45-0.6 g ai/kg). A total of 84 supervised trials with treatments at 0.4, 0.6, 0.8, 0.9, 1, 1.2 or 1.5 g ai/kg seed were reported to the Meeting. The samples from 61 trials carried out from 1972 to 1987 were analysed by an unvalidated analytical method and could not be used for evaluation. Valid results from 23 trials carried out in 1994/95 on wheat in France (7), Germany (6) and Italy (10) were submitted. No residues were found above the LOD of 0.05 mg/kg, calculated as guazatine.

In view of the non-systemic character and particular use pattern of guazatine as a seed treatment, the Meeting concluded that the residue in cereal grains was “essentially zero” and estimated an STMR of 0 mg/kg.

The Meeting estimated a maximum residue level of 0.05* mg/kg expressed as GG for cereal grains as a practical limit of determination.

Sugar cane. Guazatine is registered in South Africa for the treatment of plant segments before planting with a solution of 0.08 kg ai/hl water. Only two trials, not complying with GAP, were reported. Sugar cane was treated in Hawaii with solutions of 0.01 or 0.025 kg ai/hl. Residues in

cane, bagasse, molasses and raw sugar were reported as <0.1 mg/kg. The report was submitted only as a summary with little information (e.g. the PHI and analytical method were not stated).

The Meeting recommended the withdrawal of the existing CXL (0.1 mg/kg).

Rape seed. The use of guazatine as a foliar spray is registered in Germany but no residue data were received. No maximum residue level could be estimated.

Straw and fodder of cereal grains. After treatment of wheat with 0.6-0.8 kg ai/kg seed the residues found in 21 trials carried out in 1994/95 in France (7), Germany (6) and Italy (8) were all <0.1 mg/kg calculated as guazatine.

As there was no residue definition for guazatine in animal products, the Meeting did not recommend an MRL for the straw and fodder of cereal grains as a feed item.

Animal products. No transfer study was carried out on ruminants, no definition of the residue in products of animal origin could be proposed, and no maximum residue levels were estimated for any animal feed items.

The Meeting concluded that there was insufficient information to estimate maximum residue levels for guazatine in products of animal origin.

No feeding or metabolism studies were reported for laying hens. As no residues occur in cereal grains after seed treatment, the Meeting concluded that further studies and the estimation of maximum residue levels for residues in poultry commodities resulting from seed treatment were not necessary.

A study of the storage stability of radiolabelled guazatine on oranges after drenching with 0.1 or 0.2 kg ai/hl showed no decrease of the residues after 50 days.

The results of commercial processing studies on citrus fruits indicate that the residues are on the peel surface. Processing factors calculated for dried peel were 4.9, 6.4, 13 and 15, mean 9.8, median 9.7, and for molasses 1, 1.7, 3.6 and 18, mean 6.1, median 2.7. There was a clear reduction of the residue during processing to pulp and juice. The analysis of fresh peel in 15 supervised trials showed ratios of the residues in the peel to those in the whole fruit ("processing factors") of 1.6 (2), 1.8, 2.5, 2.7 (2), 3.1, 3.5 (2), 3.9, 4 (2), 4.3, 6.7 and 10. with a mean of 3.7 and a median of 3.5.

Residues in the edible portions of citrus fruits were low. After treatment according to GAP, most pulp and juice samples contained guazatine residues at or about the LOD (≤0.05 mg/kg) and never more than 0.13 mg/kg.

No information was provided on residues in commodities in commerce or at consumption.

The Meeting estimated the maximum residue level shown in Annex I (Part 2). As the Meeting withdrew the ADI for guazatine this is recorded only as a Guideline Level.

FURTHER WORK OR INFORMATION

Desirable

Any further evaluations for uses apart from the seed treatment of cereals would require the following data.

1. Clarification of the metabolism of all major components in ruminants.

2. Animal transfer studies on ruminants including an analytical method for the determination of residues in products of animal origin.

3. Clarification of the metabolism of all major components in plants.

4.19 LINDANE (gamma-HCH) (048)

TOXICOLOGY

Lindane was evaluated toxicologically by the JMPR in 1963, 1965, 1966, 1970, 1971, 1973, 1977, and 1989. An ADI of 0-0.01 mg/kg bw was established in 1977. On the basis of additional data, the 1989 JMPR allocated an ADI of 0-0.008 mg/kg bw. An Environmental Health Criteria monograph on lindane has been published. Additional short-term studies on toxicity after dermal exposure, long-term toxicity and carcinogenicity, genotoxicity, and reproductive toxicity have become available and were evaluated at the present Meeting.

In all of the studies in rats summarized below, the formation of hyaline droplets in the kidneys of males and the associated renal effects were male-specific and were characterized as so-called 'alpha$_{2i}$-globulin nephropathy'. This type of nephropathy is considered not to be relevant for humans. Therefore, in setting the NOAEL in rat studies these male-specific renal effects were not taken into account.

In a 13-week study of dermal toxicity (evaluated by the 1989 JMPR), rats were exposed to doses of 0, 10, 60, or 400 mg/kg bw per day. At the highest dose, clinical signs of neurological effects (convulsions) were observed. Other targets were the kidney of male animals, and the liver as demonstrated by changes in organ weight and histopathological changes. Since the male-specific renal effects were not taken into account, the NOAEL for dermal exposure was 10 mg/kg bw per day, on the basis of increased liver weight and histopathological changes in the liver.

In another 13-week study of dermal toxicity, rabbits were exposed to doses of 0, 10, 60, or 400 mg/kg bw per day. At the highest dose, clinical neurological effects (convulsions) were observed. The NOAEL for dermal exposure was 10 mg/kg bw per day, on the basis of increased liver and adrenal weights and centrilobular hypertrophy of the liver.

In a two-year study of toxicity and carcinogenicity, rats were exposed to dietary concentrations of lindane of 0, 1, 10, 100, or 400 ppm. At the highest dose neurological effects

(convulsions), reduced body-weight gain, decreased survival rates (also in males at 100 ppm), and changes in erythrocyte parameters were observed. Other changes seen at 400 ppm, and to a lesser extent at 100 ppm, were changes in weight and in the histological appearance of the liver and kidneys. The effects on the kidneys were confined to male rats with a slight increase in hyaline droplet formation that was also observed in male rats at 1 and 10 ppm. Since the male-specific renal effects were not taken into account, the NOAEL was 10 ppm, equal to 0.47 mg/kg bw per day, on the basis of a slight increase in mortality and effects on the liver. There was no evidence of carcinogenicity.

A two-generation study of reproductive toxicity in rats given lindane at dietary concentrations of 0, 1, 20, or 150 ppm did not indicate reproductive toxicity. The main effects found in progeny at 150 ppm were on weight gain, and decreased viability of pups was seen up to day 4 *post-partum*. In the pups of the second generation, there was a slight delay in tooth eruption and hair growth. Pups of the F_2 generation at 150 ppm that died before weaning showed increased incidences of hydronephrosis and hydroureter. The NOAEL for reproductive and developmental toxicity was 20 ppm, equivalent to 1 mg/kg bw per day. Histopathological effects in the kidneys were observed only in male parents at 20 and 150 ppm. Since the male-specific renal effects were not taken into account, the NOAEL for parental toxicity was 20 ppm, equivalent to 1 mg/kg bw per day, on the basis of effects on body-weight gain, liver effects, and increased kidney weights in animals of each sex.

Lindane did not induce chromosomal aberrations or unscheduled DNA synthesis *in vitro*.

Functional effects and histological changes in the immune system were induced by lindane (purity 97% or of unknown purity) in rats, mice, and rabbits. In rats and rabbits, effects were seen at doses equivalent to 1 mg/kg bw per day and above, but not in rats at 0.25 mg/kg bw per day. In mice exposed to doses of 0.012 mg/kg bw per day and above, an initial immunostimulation followed by immunosuppression was observed. It was noted, however, that the purity of the test material used in these studies was lower than that specified by current FAO specifications, namely ≥99% gamma-hexachlorocyclohexane.

The toxicological effects that are relevant for estimating hazard for humans are those on the liver and the central nervous system. In published studies, however, lindane of a purity of 97% or of unknown purity has been found to affect the immune system. As immunotoxic effects were observed at doses close to or even lower than the NOAEL found in the two-year study in rats, the Meeting concluded that additional data on immunotoxicity were required. Further, the Meeting recommended that when the new results become available, a full re-evaluation be performed to consider the validity of the studies that have been reviewed previously and to consider any new information that becomes available.

The Meeting established a temporary ADI at 0-0.001 mg/kg bw on the basis of the NOAEL of 0.5 mg/kg bw per day in the two-year study of toxicity and carcinogenicity in rats, using a safety factor of 500. Pending clarification of the immunotoxicity of lindane that meets FAO specifications, this ADI provides a 10-fold margin of safety over the LOAEL of 0.012 mg/kg bw per day in a study of immunotoxicity in mice.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION
(based on studies from this and earlier JMPR evaluations)

Levels that cause no toxic effect

Mouse: 300 ppm, equivalent to 15 mg/kg bw per day (26-week study of effects on the liver)
50 ppm, equal to 7.8 mg/kg bw per day (80-week study of carcinogenicity)
30 mg/kg bw per day (maternal and developmental toxicity in a study of developmental toxicity)
<0.012 mg/kg bw per day (24-week study of immunotoxicity with 97% pure lindane)

Rat: 10 ppm, equal to 0.75 mg/kg bw per day (13-week study of toxicity)
4 ppm, equal to 0.29 mg/kg bw per day (three-month study of toxicity, LOAEL= 20 ppm)
10 ppm, equal to 0.5 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
20 ppm, equivalent to 1 mg/kg bw per day (two-generation study of reproductive toxicity)
5 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Dog: 50 ppm, equal to 1.6 mg/kg bw per day (two-year study of toxicity)

Rabbit: <5 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Estimate of temporary acceptable daily intake for humans

0-0.001 mg/kg bw

Studies without which the determination of an ADI is impracticable, to be provided by 2000

Confirmatory study of immunotoxicity in mice with lindane that meets the current FAO specification (≥99% gamma-hexachlorocyclohexane).

Studies that would provide information useful for the continued evaluation of the compound

Further observations in humans

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to lindane

Human exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	Oral, toxicity, dog Dermal, toxicity, rabbit Inhalation, 4 h, toxicity, rat Skin, irritation, rabbit Eye, irritation, rabbit Skin, sensitization, guinea-pig	LD_{50} = 40 mg/kg bw LD_{50} = 900 mg/kg bw LC_{50} = 1600 mg/m^3 Not irritating Slightly irritating Not sensitizing
Medium-term (1-26 weeks)	Repeated inhalation, 90 days, toxicity, rat Repeated dermal, 90 days, toxicity, rat/rabbit Repeated oral, 90 days, toxicity, rat Repeated oral, developmental toxicity, rabbit Repeated oral, reproductive toxicity, rat	NOAEL = 0.6 mg/m^3 per day: clinical signs and increased cytochrome P450 enzymes NOAEL = 10 mg/kg bw per day: hepatic effects NOAEL = 0.75 mg/kg bw per day: changes in liver and kidney weight No NOAEL for maternal toxicity NOAEL = 10 mg/kg bw per day: fetuses with 13 ribs NOAEL = 1 mg/kg bw per day: developmental toxicity and hepatic effects
Long-term (one-year)	Repeated oral, 2 years, toxicity/carcinogenicity, rat	NOAEL = 0.5 mg/kg bw per day: hepatic changes and decreased survival; no carcinogenicity.

4.20 MALATHION (049)

TOXICOLOGY

Malathion was evaluated by the JMPR in 1963, 1965, and 1966. An ADI at 0-0.02 mg/kg bw was established in 1963, and confirmed in 1965 and 1966. Malathion is now evaluated in the CCPR periodic review programme.

Malathion is rapidly absorbed, biotransformed, and excreted, predominantly in the urine but also in the faeces, largely as its two monocarboxylic acids and the dicarboxylic acid.

The oral LD_{50} values for malathion in laboratory rodents were 1000-10,000 mg/kg bw, the observed differences probably being due to impurities. The most recent LD_{50} values tend to be higher. The cholinesterase-inhibiting metabolite of malathion, malaoxon, has much lower oral LD_{50} values of 100-220 mg/kg bw. WHO has classified malathion as slightly hazardous.

In a study of acute neurotoxicity in rats receiving doses of 0, 500, 1000, or 2000 mg/kg bw, an NOAEL was not identified, as clinical signs were present at all doses. In a 13-week study of neurotoxicity, also in rats, at dietary concentrations of 0, 50, 5000, or 20,000 ppm, the NOAEL was 5000 ppm, equal to 350 mg/kg bw per day, on the basis of inhibition of brain acetylcholinesterase at the highest dose.

In a 30-day study of toxicity in rats receiving malathion in the diet at concentrations of 0, 50, 100, 500, 10,000, or 20,000 ppm, the NOAEL was 500 ppm, equal to 52 mg/kg bw per day, on the basis of increased liver weight and histopathological changes in the liver (periportal hepatocyte hypertrophy) at the next highest dose.

In a 90-day study of toxicity in rats, malathion was given at dietary concentrations of 0, 100, 500, 5000, 10,000, or 20,000 ppm. The NOAEL was 500 ppm, equal to 34 mg/kg bw per day, on the basis of decreased mean corpuscular volume and mean corpuscular haemoglobin, increased liver weights and relative kidney weights, and chronic nephropathy in males, and decreased mean cell volume, hepatocyte hypertrophy, and increased relative kidney weight in females at the next highest dose.

A 21-day study of dermal toxicity with malathion at doses of 0, 50, 300, or 1000 mg/kg bw per day, 6 h per day, five days per week, was carried out in rabbits. The NOAEL was 300 mg/kg bw per day on the basis of inhibition of brain acetylcholinesterase activity at the highest dose.

In a 28-day study of toxicity in dogs, malathion was fed in gelatin capsules at doses of 0, 125, 250, or 500 mg/kg bw per day for 28 consecutive days. An NOAEL was not identified because of clinical signs at all doses.

In a one-year study of toxicity in dogs, malathion was administered orally in capsules at doses of 0, 62.5, 125, or 250 mg/kg bw per day on seven days per week. The NOAEL was 125 mg/kg bw per day on the basis of body-weight depression and changes in haematological and clinical chemical parameters at the highest dose.

A number of long-term studies of toxicity and carcinogenicity have been carried out on

malathion in both rats and mice. The earlier ones were reviewed by IARC, which concluded that the available data did not provide evidence that malathion was carcinogenic.

In an 18-month study in mice, malathion was administered at dietary concentrations of 0, 100, 800, 8000, or 16,000 ppm. The NOAEL was 800 ppm, equal to 140 mg/kg bw per day, on the basis of inhibition of brain acetylcholinesterase activity at termination and an increased incidence of liver adenomas in animals of each sex at the next highest dose.

In a two-year study in rats, dietary concentrations of 0, 100, 1000, or 5000 ppm were used. The NOAEL was 100 ppm, equivalent to 5 mg/kg bw per day, on the basis of reduced erythrocyte acetylcholinesterase activity and body weight. In another long-term study in rats, malathion was given at doses of 0, 100/50, 500, 6000, or 12,000 ppm for two years. The NOAEL was 500 ppm, equal to 29 mg/kg bw per day, on the basis of decreased survival and body-weight gain, changes in haematological parameters, decreased brain acetylcholinesterase activity, increased ã-glutamyl transpeptidase activity, increased liver, kidney, and thyroid/parathyroid weights, and changes in the olfactory epithelium at the next highest dose.

A number of studies of reproductive toxicity have been carried out, only some of which provided NOAELs. In a study in rats, malathion was administered by gavage to groups of pregnant animals on days 6-15 of gestation at doses of 0, 200, 400, or 800 mg/kg bw per day. The NOAEL was 400 mg/kg bw per day on the basis of maternal toxicity at the highest dose; no fetal toxicity was observed.

Malathion was administered orally at doses of 0, 25, 50, or 100 mg/kg bw per day to groups of pregnant rabbits on days 6-18 of gestation. The NOAELs were 25 mg/kg bw per day for maternal toxicity and 100 mg/kg bw per day for fetal toxicity; teratogenicity was not seen at any dose.

A two-generation study was undertaken in rats in which malathion was given at dietary concentrations of 0, 550, 1700, 5000, or 7500 ppm. The NOAEL was 7500 ppm, equal to 600 mg/kg bw per day, for reproductive toxicity and 1700 ppm, equal to 130 mg/kg bw per day, for developmental toxicity, the latter being based on reduced pup weights.

Numerous tests have been carried out for genotoxicity both *in vitro* and *in vivo*. Most of the evidence indicates that malathion is not genotoxic, although there is some evidence that it can produce chromosomal aberrations and sister chromatid exchange *in vitro*. There was no evidence that malathion induces chromosomal aberrations *in vivo*. Malaoxon did not induce reverse mutation in bacteria, but it caused sister chromatid exchange in two tests in mammalian cells and induced sex-linked recessive lethal mutation in *Drosophila in vivo*. The four common impurities of malathion, isomalathion, *O,O,S*-trimethyl phosphorothioate, *O,S,S*-trimethyl phosphorodithioate, and *O,O,O*-trimethyl phosphorothioate, did not induce reverse mutation in bacteria. The Meeting concluded that malathion is not genotoxic.

Two studies on the neurotoxicity of malathion in hens were reviewed. In neither was there evidence that malathion can cause delayed neuropathy, although some inhibition of neuropathy target esterase was found in the brain at 2000 mg/kg bw.

In a study in volunteers with doses of 8, 16, or 24 mg of malathion per day, the NOAEL was 16 mg per day (equivalent to 0.27 mg/kg bw per day) on the basis of inhibition of plasma and erythrocyte cholinesterase activity. Several cases of exposure to impure malathion have been reported, none of which resulted in delayed neuropathy.

An ADI of 0-0.3 mg/kg bw was established on the basis of the NOAEL of 29 mg/kg bw per day in the two-year study of toxicity and carcinogenicity in rats using a safety factor of 100. This ADI is supported by the NOAEL of 25 mg/kg bw per day in the study of developmental toxicity in rabbits. The alternative approach of basing the ADI on the study in humans was not taken, as the study was old and the material was therefore likely to contain toxic impurities.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 800 ppm, equal to 140 mg/kg bw per day (18-month study of toxicity and carcinogenicity)

Rat: 500 ppm, equal to 29 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
400 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
1700 ppm, equal to 130 mg/kg bw per day (study of reproductive toxicity)

Rabbit: 25 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Dog: 130 mg/kg bw per day (one-year study of toxicity)

Human: 0.3 mg/kg bw per day (47-day study of toxicity)

Estimate of acceptable daily intake for humans

0-0.3 mg/kg bw

Studies that would provide information useful for the continued evaluation of the compound

Further observations in humans.

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to malathion

Human exposure	Relevant route , study type, species	Results, remarks
Short-term (1-7 days)	Oral, toxicity, rat Inhalation, toxicity, rat Dermal irritation, rabbit Ocular irritation, rabbit Dermal sensitization, guinea-pig	LD_{50} = 1000-11 000 mg/kg bw LC_{50} > 5.2 mg/l Mildly irritant Mildly irritant Not sensitizing
Medium-term (1-26 weeks)	Repeated oral, 90 days, rat Repeated dermal, 21 days, rabbit Repeated oral, developmental toxicity, rabbit Repeated oral, reproductive toxicity, rat	NOAEL = 34 mg/kg bw per day: systemic toxicity NOAEL = 300 mg/kg bw per day: decreased brain acetylcholinesterase activity NOAEL = 25 mg/kg bw per day: maternal toxicity NOAEL = 100 mg/kg bw per day: fetal toxicity NOAEL = 600 mg/kg bw per day: no parental toxicity NOAEL = 130 mg/kg bw per day: developmental toxicity
Long-term ($\geq$ 1 year)	Repeated oral, 2 years, rat	NOAEL = 29 mg/kg bw per day: decreased survival, reduced body weight, decreased brain acetylcholinesterase activity

4.21 METHAMIDOPHOS (100)

RESIDUE AND ANALYTICAL ASPECTS

Methamidophos is a widely used organophosphorus insecticide with systemic properties; its residues may also occur as a metabolite of acephate. It was first evaluated in 1976 with further reviews of residue aspects in 1979, 1981, 1984, 1989, 1990, 1994 and 1996. The 1994 JMPR recommended an MRL of 0.5 mg/kg for pome fruit, based on a 21-day PHI. It was held at step 7B by the 29th (1997) Session of the CCPR. The manufacturer has submitted new residue data to support the estimation of a maximum residue level for pome fruit.

The analytical methods employed in supervised trials were based on GLC. Recoveries were >70% and the LOD in all the methods was 0.01 mg/kg.

Studies of the storage stability of residues in several commodities were included in the studies of the stability of acephate residues evaluated in 1996 but no studies of the stability of methamidophos on apples were submitted.

Trials conducted in France and Italy in 1992 on apples and pears were evaluated by the 1994 JMPR and again reviewed by the present Meeting. In three trials on apples according to French GAP (1-2 applications at 0.5 kg ai/ha, 21-day PHI) the residues were 0.01, 0.06 and 0.1 mg/kg. The residue of 0.06 mg/kg was at 28 days; the residue at day 21 was 0.04 mg/kg. Three Italian trials on apples carried out with two applications of methamidophos (Italian GAP allows one) at 0.049 kg ai/hl were evaluated against Greek GAP (1 or 2 applications at 0.045-0.06 kg ai/hl, 21-day PHI). The residues were 0.02, 0.29 and 0.33 mg/kg.

The residues in three trials on apples according to GAP in Greece in 1995/96 were 0.31, 0.4 and 0.49 mg/kg. In similar trials in Spain in 1995 the residues were somewhat lower: 0.08, 0.14 and 0.24 mg/kg at a 21-day PHI. As the application rates were higher than in Spanish GAP the results were evaluated against Greek GAP.

Several of these trials were designed to produce residue decline curves. They showed that when methamidophos was applied twice with an interval of 3 weeks most of the residues resulted from the second application.

Two trials on apples in Israel in 1970 gave residues of 0.04 and 0.23 mg/kg at a 19-day PHI. Since no relevant GAP was reported these results were not considered for the estimation of a maximum residue level.

In a trial in which apples were treated with acephate at an application rate of 1.55-1.6 kg ai/ha the residue of methamidophos at a 15-day PHI was 0.03 mg/kg.

The residues of methamidophos in apples in rank order from the 12 trials according to GAP were 0.01, 0.02, 0.06, 0.08, 0.1, 0.14, 0.24, 0.29, 0.31, 0.33, 0.4 and 0.49 mg/kg.

Pears treated with methamidophos in France in 1992 according to GAP showed residues of 0.15 and 0.21 mg/kg after 21 days.

In view of the identical use patterns on apples and pears the Meeting agreed to evaluate the combined data as applying to pome fruit.

The residues of methamidophos in apples and pears in rank order (median underlined) were 0.01, 0.02, 0.06, 0.08, 0.1, 0.14, <u>0.15</u>, <u>0.21</u>, 0.24, 0.29, 0.31, 0.33, 0.4 and 0.49 mg/kg.

The Meeting agreed to confirm the previously estimated maximum residue level of 0.5 mg/kg, and estimated an STMR of 0.18 mg/kg for methamidophos in pome fruit. The Meeting expressed its concern at the long period of storage of many of the samples and the lack of data on the stability of residues during storage, but noted that methamidophos was scheduled for periodic review in 2002.

FURTHER WORK OR INFORMATION

Desirable

1. Information on methamidophos residues in processed apples.

2. Data on the storage stability of residues of methamidophos for the full duration of studies to be submitted for periodic review in 2002.

4.22 METHIDATHION (051)

TOXICOLOGY

Methidathion was last evaluated toxicologically by the 1992 JMPR when an ADI of 0-0.001 mg/kg bw was established on the basis of an NOAEL of 0.14 mg/kg bw per day in three-month, one-year, and two-year studies in dogs. The ADI was based on a study in which effects on the liver were observed. The CCPR requested the JMPR to establish an acute RfD for methidathion in view of its high acute toxicity. New studies submitted for review were evaluated by the present Meeting.

The NOAEL for behavioural changes in rats after a single oral dose was 3 mg/kg bw. The NOAEL for the inhibition of brain acetylcholinesterase activity measured 4 h after treatment was 1 mg/kg bw in males and 2.5 mg/kg bw in females.

In another study of acute neurotoxicity in rats, changes in clinical signs, the results of a battery of functional observational tests, and maze activity were observed at the time of peak effect (about 2 h after treatment) at 8 mg/kg bw and above in males and at 4 mg/kg bw and above in females. Inhibition of acetylcholinesterase activity in various regions of the brain was found at doses of 4 mg/kg bw and above. Reduced acetylcholinesterase activity in the cortex and hyppocampus of a male treated with 1 mg/kg bw was not considered to be relevant. The overall NOAEL in this study was 1 mg/kg bw.

In a case of methidathion poisoning, the estimated dose was more than 10 times the LD_{50} in rats. The patient recovered from the cholinergic toxicity and developed a mild neuropathy; however, no details were given.

The hepatic changes observed in short-term studies in dogs were not considered relevant for establishing an acute reference dose for humans, as no such changes were observed in the volunteer studies after repeated dosing for up to six weeks. Furthermore, no indication of hepatic toxicity (except slight, transient jaundice in one case) was seen in three cases of massive oral overdose which required atropine and oxime administration and assisted ventilation.

The Meeting established an acute RfD of 0.01 mg/kg bw on the basis of a study reviewed by the 1992 JMPR in which the NOAEL in humans for inhibition of erythrocyte acetylcholinesterase activity was 0.11 mg/kg bw (highest dose tested) and a safety factor of 10. This value is supported by the NOAEL of 1 mg/kg bw in rats for the inhibition of brain acetylcholinesterase activity.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION RELEVANT FOR ESTABLISHING AN ACUTE RfD

Levels that cause no toxic effect

Rat: 1 mg/kg bw (single oral administration, inhibition of brain acetylcholinesterase activity)

Human: 0.11 mg/kg bw per day (six-week study in volunteers, highest dose tested)

Estimate of acute reference dose for humans

0.01 mg/kg bw

4.23 MEVINPHOS (053)

EVALUATION OF EFFECTS ON THE ENVIRONMENT

Mevinphos is a broad-spectrum organophosphate insecticide and acaricide with both contact and systemic activity. It is a mixture of (*E*)- (>60%) and (*Z*)- (<25%) geometrical isomers. The mechanism of pesticidal action is through direct cholinesterase (ChE) inhibition. It is used (except in the USA) to control aphids, mites, grasshoppers, cutworms, leafhoppers, caterpillars and other insects on a variety of vegetable, fruit, and field crops. The available formulations include emulsifiable concentrates, soluble concentrates, ready-to-use liquids, and dusts.

Mevinphos dissipates rapidly in the terrestrial environment. The half-lives of both isomers in soil are less than four days. Biotic degradation is the major means of terrestrial dissipation. The major degradation pathway appears to be the formation of methyl acetoacetate followed by rapid binding to soil and mineralization to carbon dioxide. Under laboratory conditions at 25°C in the dark the aerobic half-lives of the (*E*)- and (*Z*)- isomers were 1.21 and 3.83 hours, respectively.

The hydrolysis half-lives of the (*E*)- and (*Z*)- isomers in sterile aqueous buffered solution are related to the pH (pH 9, 2.8 to 7.5 days; pH 5, 50.8 to 84.6 days). *O*-demethyl- mevinphos is the major product.

The photolysis half-life in aqueous solution was about 27 days for both isomers.

Mevinphos is potentially very mobile in soils because of its high solubility in water (6×10^5 mg/litre) and low soil partition coefficients (K_{ads} values of 0.392-1.92), but rapid degradation of both isomers in the top 15 cm of soil prevents its being leached further.

Mevinphos is toxic to birds. Acute oral LD_{50} values range from 1.34 to 4.6 mg ai/kg bw for sharp-tailed grouse, ring-necked pheasants, and mallards. Dietary LC_{50} values were 236 and 246 ppm ai for Japanese quail and ring-necked pheasants respectively. In reproductive toxicity

studies with bobwhite quail and mallards exposed to mevinphos in their diet for 20 to 22 weeks, chronic NOECs were 1.5 ppm ai and <4 ppm ai respectively. The number of viable embryos and the eggshell thickness of bobwhite quail were significantly reduced at 7.1 ppm ai. The body weights of mallard hens were significantly affected at 4 ppm ai.

The oral LD_{50} value for laboratory rats was 2.2 mg ai/kg bw.

Mevinphos is toxic to a number of insect species. Laboratory-based acute contact and oral LD_{50} values for honeybees were 0.070 ìg/bee and 0.027 ìg/bee, respectively. Mevinphos applied at standard field rates was toxic to predaceous mites, parasitic wasps, and predaceous beetles.

Mevinphos is toxic to fish. The 96-h LC_{50} values for technical mevinphos (60% (*E*)-isomer and 40% related compounds) were 11.9 ìg ai/litre for rainbow trout and 22.5 to 87.0 ìg ai/litre for bluegill sunfish. The 96-h LC_{50} values for the formulated product (30.2-34.6% ai) were 81.4 g ai/litre for bluegill, 41.8 ìg ai/litre for rainbow trout, and 1.46 ìg ai/litre for *Daphnia magna*. The 48-h LC_{50} values of technical material were 0.18 ìg ai/litre for *Daphnia pulex* and 0.42 ìg ai/litre for *Simocephalus serrulatus*. The 96-h LC_{50} values for other invertebrates include 2.8 to

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Pteronarcys californica, 13.5 ìg ai/litre for *Palaemonetes kadiakensis*, and 61 ìg ai/litre for *Asellus brevicaudus*.

For estuarine/marine organisms the 96-h LC_{50} values for the sheepshead minnow were 0.81 mg ai/litre and 0.67 mg ai/litre for total mevinphos and its (*E*)- isomer respectively, and for mysid shrimp 1.3 ìg ai/litre and 1.08 ìg ai/litre respectively. The EC_{50} for the eastern oyster was >1 mg ai/litre, based on a 96-h shell-deposition study.

Chronic studies are not appropriate in view of the rapid degradation of the compound.

Risk Assessment

Terrestrial organisms

Terrestrial organisms may be exposed to mevinphos through consumption of contaminated foods and/or dermal contact with contaminated soil and vegetation.

The risk assessment for foliar sprays is based on comparing dietary LC_{50} values with predicted environmental concentrations (PECs) of mevinphos on potential avian food items (grass, insects, and seeds). PEC values are based on the Kenaga nomogram as modified by Fletcher *et al*. Maximum PECs expected immediately following a direct single application of mevinphos at 1.12 kg ai/ha are 240 mg ai/kg for short grasses, 135 mg ai/kg for small insects, and 15 mg ai/kg for seeds.

For birds, TERs, based on comparing the PECs with the lowest LC_{50} value from avian dietary tests for acute risk, are given in Table 1.

Table 1. Toxicity exposure ratios (TERs) for birds

Risk category	Toxicity value[1]	PEC[2]	TER[3]	Risk classification
Birds, acute	LC_{50} = 236 (Japanese quail)	240 (short grass) 135 (small insects) 15 (seeds)	1.0	very large

[1] Values are for the most sensitive species tested
[2] Maximum PECs from a single application of 1.12 kg ai/ha are used for acute risk
[3] The TER is calculated as the toxicity value divided by the exposure value (i.e. PEC)

This analysis indicates that mevinphos applied at a typical field application rate of 1.12 kg ai/ha presents "very large" to "present" acute risks to herbivorous (TER = 1.0) and insectivorous (TER = 1.7) birds. Acute risk to granivores is expected to be "low" (TER = 15.7). Wildlife mortality from mevinphos exposure has been reported but most incidents involved misuse. Although mevinphos dissipates rapidly and exposure may be brief, its high acute toxicity clearly poses a danger to exposed wildlife.

The Hazard Ratios for risk to honeybees (application rate of 1120g ai/ha) divided by honeybee LD_{50} values (ìg/bee) were 16,000 and 37,333 for contact and oral exposure, respectively, indicating a high risk to honeybees. Mevinphos should not be applied or allowed to drift on to blooming crops or weeds while bees are actively visiting the treatment area. Mevinphos applied at standard field rates was highly toxic to predaceous mites, parasitic wasps, and predaceous beetles in several studies.

Aquatic organisms

Aquatic organisms may be exposed to mevinphos from surface water run-off and soil erosion, and/or drift from treated sites into water bodies.

For mevinphos, risk is assessed using the Generic Expected Environmental Concentration Program (GENEEC) to estimate aquatic PEC values for use in preliminary risk assessments. Acute risk is assessed using peak PEC values from single and/or multiple applications. Because chronic toxicity data are not appropriate for mevinphos, the chronic risk to aquatic organisms was not assessed.

The environmental fate values used in the assessment of mevinphos are soil K_{OC} = 1, solubility = 6 x 10^5 mg/litre, aerobic soil degradation half-life = 1 day, hydrolytic half-life = 16 days, and water photolytic half-life = 27 days.

PEC values after single aerial and ground spray application of mevinphos at rates of 1.12 kg ai/ha and 0.56 kg ai/ha are provided in Table 2.

Table 2. PEC values after single aerial and ground spray applications of mevinphos

Application rate[1] (kg ai/ha)	Application method	Peak PEC (ìg ai/litre)[2]
1.12	aerial spray	16
	ground spray	14
0.56	aerial spray	8
	ground spray	7

[1] Application rates are based on the product label for Phosdrin 4 EC (USEPA registration no. 5481-412, accepted 16/5/94)
[2] PECs are estimated from the USEPA/OPP GENEEC program

As shown in Table 3, TERs for aquatic invertebrates range from 0.01 to 0.08, which indicate that mevinphos applied at a typical field application rate of 1.12 kg ai/ha presents "very large" acute risks to freshwater and estuarine/marine invertebrates. Acute risk to freshwater fish is classified as "large", based on the TER value of 0.74, but is "low" to estuarine/marine fish (TER = 50.6). Although no incidents of fish kills caused by mevinphos have been reported, overspray of freshwaters should be avoided.

Table 3. Risks to aquatic organisms

Risk category	Toxicity value (ìg ai/litre)	PEC[1] (ìg ai/litre)	Toxicity: exposure ratio (TER)[2]	Risk classification
Freshwater fish, acute	11.9	16	0.74	Large
Freshwater invertebrates, acute	0.18	16	0.01	Very large
Estuarine/marine fish, acute	810	16	50.6	Low
Estuarine/marine invertebrates, acute	1.3	16	0.08	Very large

[1] PEC values are calculated from the USEPA/OPP GENEEC screening model; acute exposure is based on peak PEC values for a single aerial application of 1.12 kg ai/ha
[2] TER is calculated as the toxicity value divided by the PEC

RESIDUE AND ANALYTICAL ASPECTS

Mevinphos is a systemic and contact organophosphate insecticide and acaricide used to protect a wide range of crops. It was first evaluated toxicologically in 1965 and for residues in 1972. Since the ADI was established before 1976, it is included in the CCPR periodic review programme (ALINORM 89/24A, para 299; Appendix V). The 1991 CCPR scheduled the review for 1996 (ALINORM 91/24A, para 316; Appendix IV, para 11), but the residue review was postponed to 1997 in 1995 (ALINORM 95/24A, Appendix IV).

The Meeting received information on animal and plant metabolism, environmental fate, analytical methods, updated GAP, supervised residue trials on fruits and vegetables, and residues after storage and processing.

Animal metabolism. The absorption, distribution, metabolism and excretion of mevinphos has been studied in rats, cows, goats and hens. Mevinphos is rapidly absorbed, metabolized and excreted.

Rats. Within 24 hours after oral and intravenous administration approximately 76% of the administered [^{14}C]mevinphos was eliminated as $^{14}CO_2$ and the cumulative excretion in exhaled air and urine accounted for 94% of the total dose in both sexes. Four radioactive peaks were observed in the urine: (*E*)-mevinphos, (*E*)-mevinphos acid, demethyl-(*E*)-mevinphos and unknown.

Cows. Lactating dairy cows were dosed by capsule with unlabelled or ^{32}P-labelled mevinphos at

levels up to the equivalent of 20 ppm in the diet for 12 weeks. The milk, fat, liver, kidney, muscle, heart and brain contained less than 0.03 mg/kg mevinphos-equivalent anticholinestease activity at all dose levels throughout the dosing period. The level of organosoluble radioactivity in milk from a cow which received a single dose of [^{32}P]mevinphos (2.0 mg/kg bw) reached a maximum of 0.062 mg/kg mevinphos equivalents 6 hours after administration and decreased to below 0.007 mg/kg at 96-108 hours. The corresponding level in milk from a cow dosed for 7 successive days with [^{32}P]mevinphos at 1.0 mg/kg bw reached approximately 0.05 mg/kg after 6 h and maintained this level for the remainder of the 7 days. Elimination in the faeces and urine accounted for 77% of the [^{32}P] in the single dose and over half of this was excreted in the urine within the first 12 hours. A similar initial excretion was found with the cow dosed for 7 days.

Goats. Lactating dairy goats were treated with [^{14}C]mevinphos for 6 successive days at the equivalent of 18.0 or 2.9 ppm in the diet. Mevinphos was absorbed from the gastrointestinal tract and eliminated in the urine, mainly in the first 8 hours and decreasingly in the next 16 hours. The patterns of urinary elimination were similar for the low and high doses, and the urinary excretion of both doses was apparently complete within 24 hours. The average proportion of the dose excreted within 24 hours was 24.3% of the low dose and 38.7% of the high dose over the 6-day dosing period.

The faeces were a minor route of elimination with averages of 3.38% and 2.55% of the low and high doses respectively within 24 hours. Radioactivity appeared in the first milk collection, which was 8 hours after the first administration, at levels of 0.47 and 3.84 mg/kg mevinphos equivalent from the low and high doses respectively. By the following morning the levels had decreased to 0.21 and 0.52 mg/kg. The daytime/night-time elimination pattern persisted with the repeated dosing and the levels of eliminated radioactivity in the milk seemed to reach plateaus after the 4th dose. The analysis of milk and tissue fractions showed that the radioactivity was associated with normal endogenous components.

Hens. Laying hens were treated by capsule with [^{14}C]mevinphos for 3 successive days at 23 or 2.3 ppm on a daily feed intake basis. The level of radioactivity in the excreta was fairly constant over the three-day collection period and ranged from 23.0% to 29.6% and 38.5% to 43.1% of the daily dose for the birds in the low and high dose groups respectively. The radioactivity in the egg whites accumulated with repeated dosing in both groups, and reached 0.087 and 0.876 mg/kg after the third treatment in the low and high groups respectively. Radioactivity in the egg yolks was detected after the second administration in both dose groups and increased to 0.104 and 0.393 mg/kg in the low and high groups respectively after the third treatment. The analysis of egg yolk and tissue fractions showed that radioactivity was again associated with normal endogenous components.

Plant metabolism. Studies with lettuce, strawberries and turnips showed that mevinphos is metabolized via two pathways in all three plants. A small proportion of mevinphos is converted to mevinphos acid, while the major path involves cleavage of the P-O-C linkage leading to the formation of methyl acetoacetate. Methyl acetoacetate then undergoes reduction to generate methyl (*R,S*)-3-hydroxybutyrate, which was found conjugated to carbohydrates in plant tissues. The hydroxybutyrate and acetoacetate can undergo hydrolysis to 3-hydroxybutyric acid and acetoacetic acid respectively, which in turn can be conjugated with carbohydrates.

The fate of the phosphorus moiety was not determined because mevinphos was labelled on

the carbon attached to the P-O group, but dimethyl phosphate would presumably be formed when the phosphate ester bond is broken.

Degradation in soil. Studies showed that under aerobic conditions mevinphos is degraded rapidly through the formation of methyl acetoacetate, finally to CO_2 or fragments which bind to fulvic acid, humic acid or humins.

Field dissipation studies to examine the mobility, degradation and dissipation of mevinphos in soil under field conditions showed that the mobility of both mevinphos isomers is minimal. Essentially no residues were detected in any soil layer one day to two months after application, indicating that the use of mevinphos in sandy soils with low organic matter content, which is the "worst case" for potential groundwater contamination, dose not present any risk. This is mainly due to the rapid degradation of both mevinphos isomers in the top six inches of the soil which prevents any further leaching.

Rotational crop studies were conducted to determine the uptake and nature of the residues in plants following the application of [^{14}C]mevinphos to the soil. Thirty two days after application, lettuce, sugar beet and sorghum were planted and harvested at maturity. All samples contained <0.01 mg/kg mevinphos equivalents.

The trials were carried out with several types of formulation (e.g. 10-50% EC, 50% WP, 24% SL and technical grade active ingredient), but the high solubility of this compound in water makes it unlikely that the type of formulation will significantly affect the residue levels in crops.

In the trials before the 1970s the residues were determined by enzymatic methods which relied on the inhibition of acetylcholinesterase activity and showed only the total inhibitory activity. Since the (*E*)- isomer is a stronger inhibitor than the (*Z*)-, and the proportion of the two isomers can be changed by their different dissipation rates in or on crops, the total inhibitory activity does not determine either the individual isomers or their sum. On the other hand, the GLC methods employed in the supervised trials after the 1960s can determine the residues of the two isomers separately, and generally have determination limits of 0.01 mg/kg and recoveries of 80-110% for both the (*E*)- and (*Z*)- isomers.

The Meeting agreed not to evaluate the results obtained by enzymatic methods because they do not determine the correct sum of the two isomers and have other limitations. Such methods are also unsuitable for the regulatory determination of mevinphos residues.

The Meeting also decided not to evaluate the results from trials where the duration or conditions of storage of analytical samples were not reported, because the data on the stability of stored analytical samples show that storage conditions are very important for the preservation of the residues of this pesticide and there is no guarantee that residues would be stable for a 10-month period.

However the studies of the stability of mevinphos residues in analytical samples of lettuce, strawberries and turnips which accompanied the plant metabolism studies showed that mevinphos residues were stable in these crops under frozen conditions (~ -20°C) for at least 10 months.

Since the residues of mevinphos in most crops disappear quickly after application the number of applications will not have a significant effect on the residues at the time of harvest. The number of applications was therefore generally disregarded when trial conditions were compared with GAP.

The plant metabolism studies showed that residual mevinphos would be degraded rapidly through the cleavage of the P-O-C linkage, leading to the formation of methyl acetoacetate, and by a minor pathway to (*E*)-mevinphos acid. Since the level of (*E*)-mevinphos acid is low in relation to the parent compound however, the Meeting considered that it could be excluded from the definition of the residue.

The Meeting concluded that the present definition of the residue (sum of (*E*)-mevinphos and (*Z*)-mevinphos) should be retained both for enforcement and the estimation of dietary intake.

Oranges. Only one supervised trial, carried out in South Africa in 1972, was reported. The trial application (0.04 kg ai/hl) was not comparable with GAP in South Africa (0.015 kg ai/hl, 3 days PHI), and no other information on GAP for citrus fruits was submitted.

There were insufficient data to estimate a maximum residue level for oranges or citrus fruit, and the Meeting recommended the withdrawal of the CXL for citrus fruits (0.2 mg/kg).

Apples and pears. Four supervised trials on apples were carried out in France (1969) and five in the UK (1971 and 1972). Two UK trials at an application rate of 0.25 kg ai/ha complied with French GAP (0.25-0.75 kg ai/ha, 0.05 kg ai/hl, 7 days PHI) and were comparable with Austrian GAP (0.096-0.19 kg ai/ha, 0.0096-0.019 kg ai/hl, 14 days PHI). Two other UK and two French trials at application rates of 0.5 kg ai/ha were also according to French GAP. The other trials were at a higher rate than any GAP reported to the Meeting.

Two supervised trials on pears were carried out in France in 1969, but critical information such as sample storage conditions was not reported.

The Meeting could not estimate a maximum residue level for apples or pears, as there were too few appropriate trials, and recommended the withdrawal of the existing CXLs for apple (0.5 mg/kg) and pear (0.2 mg/kg).

Apricots. Only one supervised trial carried out in the USA in 1958 was reported, with no comparable GAP. The trial samples were analysed by an enzymatic method, and the sample storage period was not reported. The Meeting could not estimate a maximum residue level and recommended the withdrawal of the existing CXL for apricot (0.2 mg/kg).

Cherries. Fourteen supervised trials were carried out in France (4 in 1970 and 4 in 1971), Germany (3 in 1974, 1 in 1982 and 1 in 1983) and the USA (1 in 1958).

The three German trials in 1974 with application at 0.025 kg ai/hl and one in 1983 at 0.24 kg ai/ha and 0.024 kg ai/hl could be compared with Austrian GAP (0.096-0.19 kg ai/ha, 0.0096-0.019 kg ai/hl, 14 days PHI). The 1982 trial was at the same rate as in 1983, but sampling was only up to 10 days whereas the GAP PHI is 14 days. The Meeting concluded that in view of the rapid decline of this compound on crops a PHI of 10 days was not comparable with the GAP

PHI. The residues in the other trials were <0.02-0.09 mg/kg at PHIs of 14-28 days.

The other nine trials were not comparable with any reported GAP. In the US trial the samples were analysed by an enzymatic method and the sample storage period was not reported.

The Meeting could not estimate a maximum residue level from the few adequate trials, and recommended the withdrawal of the CXL for cherries (1 mg/kg).

Peaches. Two supervised trials in France in 1969 could not be evaluated because critical information on such items as sample storage conditions was not reported. Three supervised trials in Germany (1974) at an application rate of 0.025 kg ai/hl were comparable with Austrian GAP (0.0096-0.019 kg ai/hl, 14 days PHI). The residues were <0.02-0.03 mg/kg at 14-21 days. A US trial in 1957 was not comparable with any reported GAP, the samples were analysed by an enzymatic method and the sample storage period was not reported.

There were too few satisfactory trials to estimate a maximum residue level and the Meeting recommended the withdrawal of the CXL for peach (0.5 mg/kg).

Currants. Ten supervised trials were carried out in Germany (1974 and 1975) and the UK (1971) but no information on comparable GAP was reported. The Meeting could not estimate a maximum residue level.

Grapes. Four French trials in 1969 could not be evaluated because sample storage conditions were not reported.

One French trial in 1971 with an application rate of 0.15 kg ai/ha complied with French GAP (0.05-0.25 kg ai/ha, 0.05 kg ai/hl, 7 days PHI). The residue was <0.02 mg/kg at 5 days. Two South African trials and one US trial were not comparable with any reported GAP and the US samples were analysed by an enzymatic method.

The Meeting could not estimate a maximum residue level and recommended the withdrawal of the CXL for grapes (0.5 mg/kg).

Strawberries. Seven supervised trials were carried out in Portugal (1971) and the USA (1957 and 1962), but no comparable GAP was reported. The US samples were analysed by an enzymatic method, and the sample storage period was not reported in the 1957 trial.

The Meeting recommended the withdrawal of the CXL for strawberry (1 mg/kg).

Broccoli. Two supervised trials were carried out in the USA in 1965 but no comparable GAP was reported and the analyses were by an enzymatic method.

The Meeting recommended the withdrawal of the CXL for broccoli (1 mg/kg).

Cauliflower. Eight supervised trials were carried out in France (1969), Germany (1974), and the USA (1972) but no comparable GAP was reported. Sample storage conditions were not reported in the French trials.

The Meeting could not estimate a maximum residue level and recommended the withdrawal of the CXL for cauliflower (1 mg/kg).

Brussels sprouts. Only one supervised trial, which was carried out in South Africa in 1980, was reported. This conformed to South African GAP (Brassica vegetables: 0.11 kg ai/ha, 0.011 kg ai/hl, 4 days PHI), with residues of <0.04 mg/kg at 4-16 days, but was inadequate to estimate a maximum residue level.

The Meeting recommended the withdrawal of the CXL for Brussels sprouts (1 mg/kg).

Head cabbages. Six supervised trials were carried out in Germany (1975, 1982 and 1983), and 14 in the UK (1960, 1970 and 1972).

In the six UK trials in 1960 the samples were analysed by an enzymatic method.

The conditions in three German trials in 1975 with applications at 0.025 kg ai/hl were comparable with French GAP (0.35 kg ai/ha, 0.035 kg ai/hl, 7 days PHI). The highest residues at 7-21 days were 0.02 and 0.03 (2) mg/kg.

Three German trials in 1982 and 1983 were at application rates of 0.43 kg ai/ha and 0.072 kg ai/hl. This is higher than GAP in Austria (0.096 kg ai/ha, 0.0096 kg ai/hl, 14 days PHI), France (0.35 kg ai/ha, 0.035 kg ai/hl, 7 days PHI) and The Netherlands (Brassica vegetables: 0.015-0.11 kg ai/ha, 0.007-0.011 kg ai/hl, 7 days PHI), but the results could be used for residue evaluation because all three residues were below the limit of determination of 0.02 mg/kg at 7-10 days at, effectively, maximum GAP conditions.

The application rate of 0.25 kg ai/ha in five UK trials in 1970 and 1972 was comparable to the GAP rate in France, but in four of them samples were taken only up to 5 days and residues were detected in two. The other three results could be used because the residues were all below the LOD of 0.02 mg/kg.

In three other UK trials in 1970 and 1972 the application rate of 0.5 kg ai/ha was higher than GAP in Austria, France, and The Netherlands, but two results could be used for evaluation because the residues were <0.02 mg/kg at 7-8 days, below the limit of determination.

The Meeting could use six German and five UK trials to estimate a maximum residue level and an STMR. The residues from the eleven trials in rank order were <0.02 (8), 0.02 and 0.03 (2) mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg, to replace the existing CXL of 1 mg/kg, and an STMR level of 0.02 mg/kg for head cabbages.

Kale. Nine supervised trials were carried out in Germany in 1974, 1982 and 1983 but no comparable GAP was reported, so the Meeting could not estimate a maximum residue level and recommended the withdrawal of the existing CXL (1 mg/kg).

Chinese kale. Two supervised trials were reported by the government of Thailand and one was in accord with the national GAP (Brassica vegetables: 0.36-0.48 kg ai/ha, 0.036-0.048 kg ai/hl, 3

days PHI). One trial was not enough to estimate a maximum residue level.

Cucumbers. Three outdoor German trials at 0.025 kg ai/hl were comparable with French GAP (0.35 kg ai/ha, 0.035 kg ai/hl, 7 days PHI) and all the residues were <0.02 mg/kg.

Four outdoor trials in The Netherlands were not comparable with any reported GAP and sample storage conditions were not reported.

Three German glasshouse trials in 1974 at 0.025 kg ai/hl and two in 1983 at 0.29 kg ai/ha and 0.032 kg ai/hl did not accord with any reported GAP. One German glasshouse trial in 1982 (0.14 kg ai/ha, 0.023 kg ai/hl) complied with GAP in The Netherlands (Fruiting vegetables in glasshouse: 0.073-0.22 kg ai/ha, 0.007-0.015 kg ai/hl, 3 days PHI). The residues were 0.02-0.04 mg/kg at 3-7 days.

There were too few trials to estimate a maximum residue level and the Meeting recommended the withdrawal of the CXL for cucumber (0.2 mg/kg).

Melons and watermelons. Three supervised trials on melons and one on watermelons were reported but no information on comparable GAP was available. The samples were analysed by an enzymatic method and two trials lacked information on the conditions or duration of sample storage.

No maximum residue level could be estimated and the Meeting recommended the withdrawal of the CXL for melons except watermelon (0.05 mg/kg).

Tomatoes. Four outdoor trials were carried out in Belgium (1969), two in France (1969) and three in Germany (1975). Two glasshouse trials were conducted in Belgium (1970), four in Germany (1975 and 1982) and two in The Netherlands (1970).

The three German outdoor trials (0.025 kg ai/hl) could be compared to French GAP (0.35 kg ai/ha, 0.035 kg ai/hl, 7 days PHI); all three residues were <0.02 mg/kg at 7-10 days. In the other six outdoor trials the sample storage conditions were not reported.

Three of the four German glasshouse trials were not comparable with any reported GAP. The other (0.14 kg ai/ha, 0.023 kg ai/hl) corresponded to GAP in The Netherlands (Fruiting vegetables in glasshouse: 0.073-0.22 kg ai/ha, 0.007-0.015 kg/l, 3 days PHI) and Belgium and Luxembourg (0.12-0.36 kg ai/ha, 0.012-0.018 kg ai/hl, 7-14 days PHI). The residues were <0.02 mg/kg at 3-7 days.

The Meeting could not estimate a maximum residue level owing to the small number of trials, and recommended withdrawal of the existing CXL for tomato (0.2 mg/kg).

Baby corn. Two supervised trials were reported by the government of Thailand and one, with application at 0.14 kg ai/ha, was close to the national GAP (Sweet corn: 0.06-0.12 kg ai/ha, 0.012-0.024 kg ai/hl, 3 days PHI). No residue was detectable. One trial was not enough to estimate a maximum residue level.

Lettuce. Nineteen outdoor trials were carried out in Belgium (4), France (4), Germany (6), The

Netherlands (2), Spain (1) and the UK (2), and 22 glasshouse trials in Belgium (8), Germany (4), The Netherlands (6), and the USA (4).

There was no information on whether the crops were head or leaf lettuce, and the sample storage conditions were not reported in the Belgian or Dutch outdoor trials or in two of the Dutch glasshouse trials. In the US trials (in 1965) the samples were analysed by an enzymatic method.

The manufacturer informed the Meeting that data on new trials to cover both head and leaf lettuce would be submitted to a future Meeting.

The Meeting could not estimate a maximum residue level because essential information was not available and recommended the withdrawal of the CXL for head lettuce (0.5 mg/kg).

Spinach. Three supervised trials were carried out in Germany (1974), three in the UK (1958) and one each in Belgium (1972 under glass) and South Africa (1980).

The Belgian trial was at an application rate of 0.1 kg ai/hl, but no comparable GAP was reported. The samples in the UK trials were analysed by an enzymatic method. The trial in South Africa at an application rate of 0.11 kg ai/ha with 0.022 kg ai/hl did not comply with South African GAP (0.11 kg ai/ha, 0.011 kg ai/hl, 3 days PHI).

In the German trials the application rate of 0.025 kg ai/hl was comparable to French GAP (0.35 kg ai/ha, 0.035 kg ai/hl, 7 days PHI). The residues at 7 days were 0.03, 0.05 and 0.07 mg/kg.

The Meeting could not estimate a maximum residue level as there were too few trials, and recommended the withdrawal of the CXL for spinach (0.5 mg/kg).

Carrots, celeriac, potatoes and turnips. Three German trials on carrots were at an application concentration of 0.025 kg ai/hl. This is higher than GAP in The Netherlands (root and tuber vegetables: 0.015-0.15 kg ai/ha, 0.007-0.015 kg ai/hl, 7 days PHI), but the results could be used for residue evaluation because all three residues were below the limit of determination of 0.02 mg/kg at 7-14 days. A single US trial was not comparable to any reported GAP and the residues were determined by an enzymatic method.

Three supervised trials were carried out on celeriac in Germany in 1983 at an application rate of 0.16 kg ai/ha at 0.027 kg ai/hl. The spray concentration was higher than GAP in The Netherlands but again all three residues were <0.02 mg/kg at 7 days.

Supervised trials were carried out on turnips and potatoes in the USA in 1956 but no comparable GAP was reported and the residues were determined by an enzymatic method.

The Meeting could not estimate maximum residue levels for carrots, celeriac, potatoes or turnips with so few trials and recommended the withdrawal of the existing CXLs for carrot, potato and garden turnip (all 0.1 mg/kg).

Leeks. Five supervised trials were carried out in Germany (1974, 1982 and 1983) at application rates of 0.025 kg ai/hl or 0.14-0.16 kg ai/ha with 0.023-0.027 kg ai/hl. These rates are higher than

GAP in The Netherlands for stem vegetables (including leeks) of 0.015-0.15 kg ai/ha, 0.007-0.015 kg ai/hl, 7 days PHI, but all five residues were below the limit of determination, <0.02 mg/kg, at 7-14 days.

The Meeting estimated a maximum residue level of 0.02* mg/kg and an STMR of 0.02 mg/kg.

Bulb onions. Only one supervised trial, carried out in the USA in 1956, was reported. There was no comparable GAP, and residues were determined by an enzymatic method.

The Meeting could not estimate a maximum residue level and recommended the withdrawal of the CXL for bulb onions (0.1 mg/kg).

Common beans. Eleven outdoor trials were carried out in Germany (3 in 1974) and the UK (6 in 1960 and 2 in 1971) and four glasshouse trials in Germany in 1974 and 1982, but the samples in the 1960 UK trials were analysed by an enzymatic method.

The three outdoor trials in Germany in 1974 were at an application concentration of 0.025 kg ai/hl. This was higher than GAP in The Netherlands (Legume vegetables: 0.015-0.15 kg ai/ha, 0.007-0.015 kg ai/hl, 7 days PHI) but two of the trials could be used for residue evaluation because all the residues at 7-14 days were <0.02 mg/kg, below the limit of determination.

The two outdoor trials in the UK in 1971 were at application rates of 0.25 and 0.5 kg ai/ha. The lower rate was comparable to French GAP (0.35 kg ai/ha, 0.035 kg ai/hl, 7 days PHI) but exceeded GAP in The Netherlands, and the higher rate exceeded GAP in both countries. The results of both trials could again be evaluated however because the residues were below the limit of determination, <0.02 mg/kg, at 2-7 days. This also applied to two of the three glasshouse trials in Germany in 1974 where the application concentration of 0.025 kg ai/hl was higher than GAP in The Netherlands (Legume vegetables in glasshouse: 0.036-0.15 kg ai/ha, 0.007-0.015 kg ai/hl, 7 days PHI for July).

A glasshouse trial in Germany in 1982 was at a rate of 0.14 kg ai/ha with 0.023 kg ai/hl. The kg ai/ha rate accorded with GAP in The Netherlands and the residue at 7 days was 0.03 mg/kg.

The Meeting agreed to combine the residue data from the outdoor and glasshouse trials because no difference was observed in the residue populations. The residues from the seven relevant trials in rank order were <0.02 (6) and 0.03 mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.02 mg/kg for common beans. The maximum residue level is recommended as an MRL to replace the existing CXL (0.1 mg/kg).

Peas. Four supervised trials were carried out in South Africa (1969) and the UK (1957), but all the samples were analysed by enzymatic methods.

The Meeting could not estimate a maximum residue level and recommended the withdrawal of the CXL for peas (0.1 mg/kg).

Soya beans and peanuts. A supervised trial on soya beans in Brazil and two trials on peanuts in Brazil and South Africa were reported to the Meeting, but relevant GAP was not available.

The Meeting could not estimate maximum residue levels.

Sugar beet. Five supervised trials were carried out in France in 1975 at application rates of 0.24, 0.25 and 0.35 kg ai/ha, but the PHIs (91-98 days) were not comparable with any reported GAP.

In two supervised trials in Germany the application concentration of 0.025 kg ai/hl complied with Austrian GAP (0.12 kg ai/ha, 0.02-0.03 kg ai/hl, 14 days PHI). The residues at 7-14 days were <0.02 mg/kg (4 results) in the roots and <0.02 (2), 0.03 and 0.04 mg/kg in the leaves.

The Meeting could not estimate a maximum residue level for sugar beet or for sugar beet leaves or tops.

Storage

Storage studies were carried out on peaches, strawberries, red cabbage, broccoli, lettuce and spinach at ambient temperature.

Because the number of trials was limited the decline profile of mevinphos residues in or on crops was not clear, but the data showed that the residues declined quickly except in peaches. Half-lives of 29, 3.7-3.9, 3.4, 1.3, 3.4-6.3 and 2.2 days were calculated for peaches, strawberries, red cabbage, broccoli, lettuce and spinach respectively on the assumption that the logarithm of the residue value decreased linearly with time.

Processing

Household. Boiling, washing, and/or peeling studies were carried out on red cabbage, broccoli, cauliflower, spinach and apples but the samples from two of the three broccoli trials and the two cauliflower trials were analysed by enzymatic methods and were not evaluated.

The processing factors were 0.27 and 0.67 for washing cabbage, 0.18 for boiling cabbage, 0.33 for boiling broccoli, 0.26-0.32 for boiling spinach, 0.71-0.95 for peeling apples and 0.53-0.75 for cooking peeled apples.

Industrial. Processing factors for grapes were 0.87 to fresh juice, 1.15 to wet pomace, 0.33 to dry pomace, 0.25 to raisins and 22.2 to raisin waste. Evidently more mevinphos than moisture is lost during drying.

4.24 MYCLOBUTANIL (181)

RESIDUE AND ANALYTICAL ASPECTS

Myclobutanil is a systemic, foliar-applied fungicide. It was first reviewed by the 1992 JMPR. The MRLs recommended for stone fruits are now adopted as CXLs. At the 28th Session of the CCPR the EC delegation questioned the residue evaluation for stone fruits. The manufacturer

provided information on GAP and data on residues for a review of use patterns and a reconsideration of maximum residue levels.

The Meeting received updated information on GAP in EC countries and the USA. The manufacturer provided reports of five supervised trials carried out in the USA on apricots in 1991, and data on residues at a 0-day PHI in cherries, peaches and plums.

The manufacturer also requested the evaluation of data on residues in bananas, blackcurrants, citrus, hops, strawberries and tomatoes. The manufacturer provided data on residues in sweet peppers, but this information was received too late for evaluation.

The analytical methods for determining the residues of myclobutanil and its metabolites in fruits were as described in the 1992 JMPR evaluation.

Studies of the stability of residues in stored analytical samples of soil, apples, grapes, tomatoes, cucurbits and almond meat and hulls were reported to the Meeting. Residues of myclobutanil and its metabolite hydroxy-myclobutanil (RH-9090) were found to be stable in frozen conditions (-15°C) in soil, apples and grapes for at least two years, in cucurbits and tomatoes (at -10°C) for three years and in almond meat and hulls at -10°C for at least two years. It can be concluded that residues of myclobutanil in stored samples are stable in frozen conditions.

Myclobutanil is available as 125 and 240 g/l emulsifiable concentrate, 60 g/l suspension concentrate, 200 g/l emulsion oil in water and 40% wettable powder.

Supervised trials

In all the trials on stone fruits reported to the Meeting the residues were determined in the edible portion of the fruits and the proportional weights of the stones were not given. The average percentage weights of the stones in each of the fruits were reported by the manufacturer and these averages were used to estimate maximum residue levels in the whole fruits.

Apricots. The results of field trials in France, Italy and the USA were provided. The trials from Italy were not considered for the estimation of a maximum residue level as no relevant GAP was reported. Residues from six trials according to GAP in France ranged from 0.01 to 0.08 mg/kg; the residues of the metabolite were not determined. In five trials according to US GAP (7-17 applications at 0.07 to 0.165 kg ai/ha, 0-day PHI), the total residues found were between 0.13 and 0.7 mg/kg in the edible fruit. Residues of the metabolite were between 13 and 26%, and in one trial 46%, of the parent compound. In summary the myclobutanil residues in apricots from trials complying with GAP were 0.01, 0.04, 0.04, 0.04, 0.06 and 0.08 mg/kg in France and 0.11, 0.12, 0.17, 0.23 and 0.62 mg/kg in the USA.

Cherries. Supervised trials on cherries carried out in Germany and the USA which were evaluated by the 1992 JMPR were re-evaluated at the light of new GAP. Total residues (myclobutanil + metabolites) were determined. Myclobutanil residues from four residue decline trials in Germany according to GAP (3 applications at 0.135 kg ai/ha, 21 days PHI) were <0.01 and 0.02 (3) mg/kg. Three of the US trials reported in 1992 which included a 0-day PHI were reviewed. Five other trials reported to the present Meeting complied with US GAP (<9

applications at 0.07-0.16 kg ai/ha, with a maximum of 1.45 kg ai/ha per season, 0-day PHI). The residues of myclobutanil *per se* in the US trials in rank order were 0.2, 0.28, 0.68, 0.85, 0.92, 1.04, 1.12 and 1.44 mg/kg. In two of the trials metabolite residues reached more than 40% of those of the parent compound.

Peaches. Several trials carried out in France, Spain and the USA were reported in 1992. A trial in France was not conducted according to GAP but it could be evaluated against the Spanish use pattern. Residues from two Spanish trials according to GAP (1-4 applications at 0.08-0.1125 kg ai/ha, 15 days PHI) were 0.02 and 0.03 mg/kg; metabolites were not determined. Three US trials reported in 1992 were re-evaluated together with six new trials, all according to new US GAP (<9 applications at 0.07-0.165 kg ai/ha, with a maximum of 1.45 kg ai/ha per season, 0-day PHI). Residues of RH-9090, its conjugate, and the ketone RH-9089 were determined as RH-9090 in all the trials. The total residue in the edible portion in the US trials ranged from 0.35 to 1.53 mg/kg, with residues of myclobutanil from 0.33 to 1.22 mg/kg.

Plums and prunes. Two trials reported to the Meeting complied with US GAP (7 applications at 0.06-0.165 kg ai/ha with a maximum of 1.2 kg ai/ha per season, 0-day PHI). The total residues were 0.1 and 0.73 mg/kg with myclobutanil residues of 0.09 and 0.59 mg/kg. One trial in Italy (4 applications at 0.1-0.15 kg ai/ha, 14-day PHI) was evaluated against Greek GAP (3 applications at 0.055-0.125, 15 days PHI); the total residue was 0.1 mg/kg. There were too few results to estimate a maximum residue level. The existing CXL is 0.2 mg/kg.

In view of the similar use patterns for the individual fruits, the Meeting agreed to evaluate the combined US data as applying to stone fruit, except plums. The myclobutanil residues in stone fruit (edible portion) in rank order (median underlined) were 0.09, 0.11, 0.12, 0.17, 0.2, 0.23, 0.28, 0.33, 0.34, 0.38, 0.59, 0.62, 0.66, 0.68, 0.74, 0.75 (2), 0.85, 0.92, 1.04, 1.12, 1.22 and 1.44 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.62 mg/kg for stone fruit except plums, and recommended the withdrawal of the individual CXLs for apricot, cherries and peach.

Bananas. Several studies were conducted in the USA and Costa Rica according to the proposed use of myclobutanil in banana packing stations in grower countries. All treatments consisted of one application of myclobutanil, and banana hands were sprayed or dipped at various concentrations.

Those trials in which myclobutanil was used at 200 or 400 mg ai/l and residues were calculated on the whole banana were evaluated to estimate a maximum residue level.

Banana samples taken at intervals of 0 to 28 days after treatment showed that the residues in the pulp increase with time. There was also a loss in weight of the banana hands with storage time, mainly from the peel. Storage periods from 7 to 21 or 28 days represent the shipping periods needed to reach different markets.

Residues in samples with 0-7 days storage are most appropriate for estimating maximum residue levels because they are the highest in the whole fruit, but residues after longer storage times are appropriate for assessing dietary exposure because the residues in the pulp increase with time. Residues of the parent compound were predominant in the total residue; those of the sum of the free and conjugated forms of the hydroxy metabolite (RH-9090) were less than 10%

of the total in most of the trials.

The highest residues in whole bananas from each trial at the highest proposed GAP concentration, 400 mg ai/l, from 7 to 28 days ranged from 0.64 to 1.7 mg/kg. Since these results were from trials according only to proposed GAP, the Meeting was unable to estimate a maximum residue level.

Residues of myclobutanil in the edible pulp of the bananas in rank order (median underlined) were 0.1, 0.17, 0.17, 0.19, 0.2, 0.21, 0.22, 0.27, 0.28, 0.35, 0.39 and 0.41 mg/kg.

Citrus fruit. The results of twelve trials in Spain on the post-harvest treatment of mandarins with myclobutanil were reported to the Meeting. The reports lacked critical analytical data such as LOD, recoveries, and chromatograms. The residues of myclobutanil (applied as a water/wax emulsion or emulsifiable concentrate) in samples of whole fruit from trials complying with GAP (0.05 kg ai/hl or 0.01 kg ai/t fruit, 0-day PHI), ranged from 0.94 to 2.9 mg/kg. The residues from treatments with the EC formulation at 0.05 kg ai/hl, 0-day PHI, in rank order were 0.94, 1.15, 1.33, 1.5, 1.56, 1.7 and 2.0 mg/kg. Fruit samples were also analysed at 7 and 14 days after treatment. No decrease in the residue was observed in most of the trials.

Several trials on the post-harvest treatment of various varieties of orange which complied with Spanish GAP were reported to the Meeting. Myclobutanil was used as a water/wax emulsion and an EC formulation. The residues of myclobutanil ranged from 0.87 to 2.66 mg/kg. The myclobutanil residues in the whole fruit from treatment with the EC formulation according to GAP (0.05 kg ai/hl) were 1.06, 1.3, 1.36, 1.49, 1.53 and 1.8 mg/kg.

Since the citrus trials lacked the critical analytical data mentioned above the Meeting could not recommend an MRL.

Whole-fruit samples of the oranges and mandarins in these trials were separated into peel, pulp and juice. Analysis showed that the myclobutanil residue was almost all in the peel and not found in the pulp. The residue in the juice was approximately 10% of that in the whole fruit (0-day PHI). The residues of the metabolite were not determined.

Berries. Several field trials were conducted on blackcurrants in the UK with various myclobutanil formulations. In all the trials blackcurrant samples were analysed for the parent compound and RH-9090. The residues of myclobutanil from trials according to UK GAP (4-6 applications at 0.09 kg ai/ha, 14 days PHI) ranged from 0.04 to 0.43 mg/kg, with total residues (myclobutanil + RH-9090) from 0.08 to 0.47 mg/kg. In three of fifteen trials reflecting GAP, residues of the metabolite were equal to or higher than those of the parent compound.

The residues of myclobutanil in blackcurrants in rank order (median underlined) were 0.04, 0.07, 0.08, 0.19, 0.24, 0.24, 0.26, 0.26, 0.29, 0.3, 0.3, 0.31, 0.35, 0.42, 0.43 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.26 mg/kg for blackcurrants.

Numerous field trials on strawberries have been conducted in the UK, France, Italy and Spain. The residues in seventeen trials in the UK in accordance with GAP (4-6 applications at

0.09 kg ai/ha, 3-day PHI) ranged from 0.1 to 0.5 mg/kg; residues of the metabolite were below the LOD. In one trial in France with more applications than are allowed by GAP, the residue of myclobutanil at 4 days was 0.04 mg/kg. In two trials in Italy which complied with GAP (3 or 4 applications, 0.005 kg ai/hl, 7-day PHI) the residues were 0.05 and 0.09 mg/kg. The residues in strawberries from trials in Spain ranged from 0.02 to 0.15 mg/kg.

The myclobutanil residues in strawberries in rank order (median underlined) were 0.04, 0.05, 0.08, 0.08, 0.09, 0.1, 0.12, 0.15, 0.15, 0.15, 0.17, 0.18, 0.18, 0.19, 0.19, 0.19, 0.19, 0.2, 0.2, 0.22, 0.24, 0.36, 0.48, 0.5 and 0.69 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.18 mg/kg for strawberries.

Tomatoes. The results of a large number of indoor and outdoor trials from several countries were reported to the Meeting. The residues found in Belgian trials (indoors) reflecting GAP (3-6 applications at 0.0075 kg ai/hl, 3 days PHI) ranged from 0.05 to 0.16 mg/kg; metabolites were not detected. Four trials in France (6 applications at <0.12 kg ai/ha, 3 days PHI) were evaluated against Spanish GAP (1-6 applications, <0.112 kg ai/ha, 3 days PHI). The residues were 0.02, 0.03, 0.04 and 0.05 mg/kg. The residues from trials in Spain according to GAP ranged from 0.03 to 0.24 mg/kg; the residues of metabolites determined in two trials were below 20% of those of the parent compound. In one trial in Italy according to GAP the residue was 0.02 mg/kg, with metabolites expressed as RH-9090 below the LOD. Four other trials were carried out in Italy in 1996, but as the Meeting doubted whether the data had been recorded properly the residues from them were not included in the evaluation. In trials according to GAP in Morocco (1-3 applications, 0.00625 kg ai/hl, 7-day PHI), the residues were between 0.02 and 0.06 mg/kg. The residues of the metabolite determined in two trials were below the LOD.

The residues in fifteen US field trials according to GAP on several varieties of tomato (0.07 kg ai/ha/application, with a maximum of 0.4 kg ai/season, 0-day PHI), ranged from 0.01 to 0.22 mg/kg.

The myclobutanil residues in tomatoes in rank order (median underlined) were 0.01, 0.02 (7), 0.03 (3), 0.04 (3), 0.05 (7), 0.06 (2), 0.07, 0.08 (4), 0.09 (2), 0.11, 0.15 (3), 0.16, 0.22 and 0.24 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.05 mg/kg for tomatoes.

Hops. Four of six trials conducted in the UK were according to GAP (6 applications, 0.0045 kg ai/hl, 10 days PHI). The residues of myclobutanil in the dried cones ranged from 0.2 to 1.2 mg/kg. The Meeting considered the database insufficient to estimate a maximum residue level.

The Meeting was informed that a further four trials are in progress in Germany and that they included processing studies.

Processing

Two supervised trials on tomatoes were conducted in the USA, with 4 applications at rates of 0.067 and 0.14 kg ai/ha. Samples harvested 5 days after the last treatment were processed to canned whole tomatoes, juice, purée, pomace and paste. In four processing studies in France, tomatoes treated with 6 applications of myclobutanil (0.107-0.12 kg ai/ha) were harvested 3 days after the last treatment and processed into juice, preserve and purée.

There was no concentration of the residue in tomato juice, canned tomatoes or preserve. The residues in tomato purée were concentrated by factors of 1.0 to 3, with an average of 1.6. The concentration factors for dry pomace were 14 and 17, with an average of 15.5, and for paste 3.7 and 4.2, mean 3.9. In some processed products, residues of the metabolite reached 50% or more of the total residue. On the basis of an STMR of 0.05 mg/kg, the Meeting estimated STMR-Ps of 0.08 mg/kg for tomato purée, 0.78 mg/kg for dry pomace, and 0.2 mg/kg for paste.

Data from three processing trials on blackcurrants in the UK indicated that residues in the juice decreased about 1.5-5 times, with a mean processing factor of 0.35. Canned fruit, in a single trial, showed a decrease in the residue of myclobutanil but a higher concentration of the metabolite, with the same total residue. The Meeting estimated an STMR-P of 0.09 mg/kg for blackcurrant juice from the STMR of 0.26 mg/kg for blackcurrants (whole fruit).

Two processing trials on strawberries in the UK showed that residues do not concentrate in strawberry jam or preserve. The average processing factors were 0.5 for jam and 0.81 for preserve.

The Meeting estimated STMR-Ps of 0.09 mg/kg for jam and 0.15 mg/kg for preserve on the basis of an STMR of 0.18 mg/kg for whole strawberries.

4.25 PARATHION (058)

RESIDUE AND ANALYTICAL ASPECTS

Parathion was first evaluated by the JMPR in 1965 and extensively re-evaluated in 1991 and 1995. The 1991 JMPR recommended an MRL of 0.05 mg/kg for apple. The proposed MRL was advanced to Step 7B by the 1994 Session of the CCPR and subsequently held there, pending re-evaluation by the present Meeting.

The analytical method used in trials reported to the Meeting was based on temperature-programmed GLC with FP detection. Parathion and paraoxon were both determined with LODs of 0.01 mg/kg and recoveries above 80%.

Information on registered uses and national MRLs was recorded in the 1991 JMPR evaluation. New information on registered uses on pome fruits was provided only for France.

Information was submitted on residues from six supervised trials on apples in central and southern France in 1994. These were studies of residue decline and showed that parathion residues decreased from 0.13-0.51 mg/kg at 0 day to <0.01-0.08 mg/kg after 21 days. Residues

of paraoxon were not detected. Since the trials were with a 50% higher application rate than French GAP, the Meeting could not change the previous recommendation.

The Meeting was informed that another eight trials in France and Spain are planned. The Meeting noted that parathion is scheduled for periodic review in 2000.

4.26 PHOSALONE (060)

TOXICOLOGY

Phosalone was evaluated toxicologically in 1972, when an ADI of 0-0.006 mg/kg bw was established, and re-evaluated in 1975 and 1976. In 1993 an ADI of 0-0.001 mg/kg bw was established on the basis of the lowest dose tested (5 ppm), equal to 0.2 mg/kg bw per day, in a two-year study in rats, with a safety factor of 200 because of concern at the possibly significant occurrence of testicular atrophy and reduction in testicular weight. More information on this study was supplied for consideration at the present Meeting.

Dietary concentrations of 0, 5, 50, or 1000 ppm were used, the highest dose being reduced to 500 ppm later in the study. Significant depression of brain acetylcholinesterase activity was found only at the highest dietary concentration. There was a statistically significant increase in the prevalence of testicular atrophy, a reduction in testicular weights in both the high- and middle-dose groups, and a dose-response relationship across all groups for both effects. All testicular weights were within the historical control range of rats at the institute where the study was performed. The slides were re-examined by a consultant, who argued that the apparent dose-response relationship for testicular atrophy was largely a product of an increase in survival among the rats at the highest dose. Furthermore, it was argued that bilateral atrophy is a more reliable indicator of treatment-related change than unilateral atrophy; on this basis there was no clear dose-response relationship. The findings were also re-examined at the laboratory that originally performed the study; no clear dose-response relationship was found. In view of the fact that neither an earlier long-term study in rats nor studies in mice and dogs gave evidence of changes in the male reproductive system, the Meeting considered the NOAEL to be 50 ppm, equal to 1.8 mg/kg bw per day, on the basis of inhibition of brain acetylcholinesterase activity at the highest dose.

The rat remained the most sensitive species examined, and on the basis of the NOAEL of 1.8 mg/kg bw per day in the above study the Meeting established an ADI of 0-0.02 mg/kg bw, using a safety factor of 100.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 150 ppm, equal to 23 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 50 ppm, equal to 1.8 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
50 ppm, equivalent to 2.5 mg/kg bw per day (multigeneration study of reproductive toxicity)

Rabbit: 10 mg/kg bw per day (study of developmental toxicity)

Dog: 200 ppm, equivalent to 5 mg/kg bw per day (several studies)

Estimate of acceptable daily intake for humans

0-0.02 mg/kg bw

Studies that would provide information useful for the continued evaluation of the compound

Observations in humans.

4.27 PHOSMET (103)

RESIDUE AND ANALYTICAL ASPECTS

Phosmet has been evaluated at several Joint Meetings between 1976 and 1988. MRLs were recommended for a number of commodities of plant and animal origin. Updated information on GAP, and reports of supervised trials and studies of processing, metabolism and the stability of residues in stored analytical samples have been made available for evaluation within the CCPR periodic review programme.

Phosmet is a broad-spectrum organophosphorus insecticide used to control a variety of insect and mite pests which attack pome, stone and citrus fruit. It is also used on field, pasture and forage crops. Phosmet is non-systemic and acts by contact and ingestion as a cholinesterase inhibitor. It is registered in a number of countries, mainly for protecting fruits and vegetables. The direct use of phosmet on livestock for the control of warble fly, ticks and lice of cattle, resulting in residues in animal commodities, was not reported to the Meeting.

Carbonyl-labelled [^{14}C]phosmet was used in studies of metabolism and environmental fate.

The absorption, distribution, metabolism and excretion of [^{14}C]phosmet has been studied in rats, goats and hens. The chemical is rapidly absorbed, distributed and excreted, predominantly

in the urine, in all three species. Biotransformation also appeared to be similar in the species studied. Hydrolysis of the phosphorus-containing moiety to yield *N*-mercaptomethylphthalimide is followed by methylation and oxidation at the sulfur atom to give sulfoxides and sulfones. These metabolites, together with *N*-mercaptomethylphthalimide, are hydrolysed to generate a series of phthalamic acids and finally phthalic acid.

The principal metabolites in tissues and milk reflect a single metabolic sequence: hydrolytic displacement of the phosphorus-containing moiety to yield *N*-mercaptomethylphthalimide, followed by methylation and oxidation of the thiol group. Hydrolytic degradation via *N*-hydroxymethylphthalimide also occurred. These reactions generated a series of phthalimide derivatives, which were hydrolysed to the analogous phthalamic acids. Treatment of extracted samples with hydrazine solubilized more than half of the bound residues. Solubilized products of hydrazinolysis consisted mostly of phthalohydrazide. The results indicate that bound residues in tissues and milk contain the *N*-substituted phthalimide moiety, with little or no chemical modification. Residues of phosmet do not accumulate significantly in edible tissues or eggs. Although the rat liver microsomal NADPH enzyme system readily converts phosmet to phosmet oxon, neither phosmet nor its oxygen analogue could be detected in the tissues of the goats or hens.

Lactating goats were dosed with [^{14}C]phosmet at the equivalent of 8-8.8 ppm in the diet for four days. Most of each day's dose was recovered in the urine within the following 24 hours. In total, urinary excretion accounted for 60% of the cumulative dose. Less than 6% remained in the edible tissues at slaughter, 13-14 hours after the final dose. The total radioactivity ranged from 0.006 mg/kg phosmet equivalent in the fat to 0.24 mg/kg in the kidneys. Nine metabolites containing the phthalimide moiety were identified. Neither phosmet nor phosmet oxon was detected in the edible tissues (<0.002-0.003 mg/kg) or milk (<0.0004 mg/kg).

Laying hens dosed for seven days at a level equivalent to 10.5 ppm in the diet excreted 89.6% of the cumulative dose. Edible tissues collected at slaughter and eggs accounted for only 0.3% of the cumulative dose. In egg yolks the highest level of ^{14}C (as phosmet equivalents) was 0.040 mg/kg on day 7, and in whites 0.007 mg/kg on day 4. At slaughter the levels of total radioactivity expressed as phosmet were 0.24 mg/kg in liver, 0.21 mg/kg in kidney, 0.021 mg/kg in breast muscle, 0.015 mg/kg in thigh muscle, 0.005 mg/kg in fat and 0.068 mg/kg in blood. Phosmet itself was not detected (<0.005 mg/kg) in any of the edible tissues, but 0.001 mg/kg was found in egg yolks. None of the metabolites exceeded 0.005 mg/kg in the edible tissues or eggs. The metabolites identified in the edible tissues and egg yolks were phthalimide and phthalic acid.

Plant metabolism studies on sour cherries, cotton, maize and potatoes were reported. Forty four per cent of the applied radioactivity was absorbed by sour cherries within 4 hours. The main surface residue was the parent compound, while 16 or 17 metabolites occurred in the fruit. Phthalic acid was the major metabolite and accounted for 17-21% of the total radioactivity. Several other metabolites accounting for a small fraction of the radioactivity were identified. These included phosmet oxon, phthalimide, and phthalamic acid derivatives. No benzoic acid or ring-hydroxylated products were detected. Related conjugates of *N*-glycosylphthalimide accounted for 27-32% of the total radioactivity, but phthalic acid accounted for 85-90% of the extractable radioactivity after acid hydrolysis.

In maize the major part of the total residue was present in the maize fodder (267 mg/kg

expressed as phosmet equivalent) and forage (31 mg/kg). Cobs (5 mg/kg) and grain (3 mg/kg) contained much lower residues. The metabolism of phosmet in maize involves various hydroxylation (oxidation), hydrolysis and conjugation reactions, giving products that are distinctly more polar than phosmet. The pattern of metabolites was similar in all parts of the plant, but their ratios varied. The parent phosmet amounted to 53% of the total residue in fodder, with the oxon (1.2%) and derivatives of phthalimide and phthalic acid present in small amounts, whereas in the grain phthalic acid was the single identified residue (61%) and the parent compound was not detectable. Most of the radiocarbon in the unidentified metabolites (32.7%) was accounted for as phthalic acid after acid hydrolysis.

In potatoes the foliage contained most of the residue (14-109 mg/kg), and translocation to tubers (1.4-2.1 mg/kg) was limited. Phthalic acid and phthalamic acid were the major metabolites. Phosmet, its oxygen analogue and hydroxylated phthalic acids were not observed in any of the extracts.

The environmental fate of phosmet was studied in soil and water. Degradation in soil was studied under aerobic followed by anaerobic conditions. Under anaerobic conditions the degradation continued, but at a slower rate. The main components of the residue, expressed as phosmet equivalent, found in aerobic soil were phosmet (36.6%), phosmet oxon (0.5%), *N*-methoxymethylphthalimide (5.68%), *N*-methylsulfinylmethylphthalimide (2.59%), *N*-hydroxymethylphthalimic acid (2.44%) and phthalimide (1.53%). In addition, 7 identified metabolites containing the phthalimide moiety (each <1%) and some unidentified intermediate products were also detected. Hydrolysis was shown to be an important factor in limiting the persistence of phosmet in soils, and the initial degradation products were metabolized by soil micro-organisms. After hydrolysis the aryl moiety, with or without a mercapto group depending on the point of cleavage, was further degraded through a variety of reactions including oxidation of the mercapto group to sulfonic acid, its methylation followed by oxidation to the sulfoxide, and imide bond cleavage. Ultimately, mineralization to carbon dioxide occurred. The products under aerobic and anaerobic conditions were largely the same.

Phosmet did not undergo significant photodegradation when exposed on thin layer plates of soil to natural sunlight for a period of 30 days.

Phosmet undergoes fairly rapid hydrolysis at ambient temperatures, with half-lives in water at 25°C of 7.5-9.7 days at pH 5, 9.4 hours at pH 7 and 5.5 minutes at pH 9. Degradation is enhanced by light.

The major hydrolysis products formed at pH 5 in the dark were *O,O*-dimethyl *O*-hydrogen phosphorodithioate (79.4 mol %), *O*-methyl *O,O*-dihydrogen phosphorodithioate, phthalamic acid, phthalimide, and phthalic acid. Following irradiation with a xenon lamp at pH 5, dimethyl hydrogen phosphate, (72.3 mol %), phosphoric acid, methyl dihydrogen phosphate, phthalimide, phthalamic acid and phthalic acid were detected. Other minor products were also detected but not identified.

Residues in rotational crops were studied in radishes, lettuce and wheat which were planted in the soil 30, 120 and 365 days after treatment with [*carbonyl*-^{14}C]phosmet at a rate equivalent to 5.6 kg ai/ha. The total radioactive residue taken up by the plants varied from about 2% to 64% depending on the plant and the time between soil treatment and harvest. Neither phosmet nor its

oxygen analogue were detected in the plant extracts. The radioactive residue consisted of a number of polar metabolites, most of which were characterized by chemical and enzymatic hydrolysis as esters or conjugates of phthalic acid.

The current analytical methods for residues are based on extraction with acetone or ethyl acetate, clean-up on charcoal, silica gel or SX-3 gel columns, and gas-chromatographic determination. Phosmet and its oxon are determined simultaneously. Recoveries are above 70%. The typical limits of determination in plant materials, milk and animal tissues are 0.01-0.05 mg/kg. In most of the supervised trials the LOD reported was 0.05 mg/kg.

Storage stability studies showed that phosmet is stable at -20 ± 10°C in almonds, apples, soya beans, and wheat grain and straw for a minimum of 2½ years and in alfalfa, maize, oranges, peppers and potatoes for a minimum of 2 years.

Definition of the residue

Phosmet is the major residue component; the oxon is either not detected or is less than 10% of the parent compound in most cases. In addition, the other metabolites are water-soluble compounds without the phosphorodithioate group and are less toxic than the parent compound. The significant residue for both regulatory control and dietary intake purposes is therefore the parent compound.

The Meeting noted that phosmet was previously classified as fat-soluble. On the basis of its octanol/water partition coefficient and the distribution of residues between fat and meat, the Meeting concluded that the compound is not fat-soluble.

Definition of the residue for compliance with MRLs and for the estimation of dietary intake: phosmet

Supervised trials

Supervised trials were conducted on oranges in Argentina and Brazil. In the Argentine trials residues were determined in whole fruit, peel and pulp, but in Brazil only the pulp was analysed and the results cannot be used to estimate maximum residue levels. The application rate in the three Argentine orange trials corresponded with the current use pattern and resulted in residues in the whole fruits of 0.07, 0.13 and 0.32 mg/kg. The pulp did not contain detectable residues (<0.05 mg/kg) in any of the trials.

The data were too limited to estimate a maximum residue level for oranges, and since no residue data were provided for other citrus commodities, the Meeting recommended the withdrawal of the existing CXL for citrus fruits (5 mg/kg).

A number of trials were carried out on apples and pears in Brazil, Canada, Germany, The Netherlands, the UK and the USA. No GAP was reported for Germany, The Netherlands or the UK. Trials were according to current GAP in Canada (1.9 kg ai/ha) and the USA (1.7–4.1 kg ai/ha for apples; 1.7-5.6 kg ai/ha for pears) or at somewhat higher rates. The residues in the fruit were generally below 5 mg/kg at 7 days PHI. The residues in pears (1.7, 1.3 and 0.85 mg/kg) were lower than in apples. The Brazilian trials resulted in residues below 0.05 mg/kg in apples

14 days after application at single or double GAP rates. The residues in apples from the Canadian and US trials at approximately maximum GAP rates in rank order were 1.8, 1.8, 2.8, 3.3, 3.4, 3.4, 3.7, 4.2, 4.3 and 7.3 mg/kg.

The Meeting estimated a maximum residue level of 10 mg/kg, and an STMR level of 3.4 mg/kg for apples. Owing to the lack of sufficient data, the Meeting concluded that no maximum residue level could be estimated for pears and recommended the withdrawal of the existing CXL (10 mg/kg).

Field trials on apricots, nectarines and peaches treated at rates up to 1.3 times the US GAP rate resulted in residues up to 6.8 mg/kg at 14 days PHI. The residues in apricots (♦) and peaches treated at 0.7-1.3 times the maximum rates according to Canadian and US GAP in rank order were 0.87 1.2, 1.5, 1.6, 2.9, 4.2♦, 4.7♦, 6.4 and 6.8 mg/kg. The residues in nectarines were lower, 0.45 and 0.55 mg/kg, and could not be combined with those of apricots and peaches.

The Meeting estimated maximum residue levels of 10 mg/kg and STMR levels of 2.9 mg/kg for apricots and peaches, and recommended the withdrawal of the existing CXL for nectarines (5 mg/kg).

Following treatments at about 1-1.3 times current GAP rates, residues in plums of 0.41, 0.55 and 0.48 mg/kg, and in fresh and dried prunes of 2.3 and 2.2 mg/kg were reported. The information was insufficient to estimate a maximum residue level for plums (including prunes).

Grapes were treated at rates of 1.4-2.2 kg ai/ha which accord with GAP for the eastern states of the USA (1.5-2.5 kg ai/ha). Residues up to about 10.2 mg/kg were found 7 days after the last application and up to 9.2 mg/kg after 14 days. The residues from treatments according to GAP in rank order were 0.17, 0.24, 0.61, 2.8, 3.3, 4.0, 4.2 and 9.2 mg/kg.

The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 3.1 mg/kg for grapes.

In supervised trials on olives in France, Italy and Spain the residues declined to <0.02-0.34 mg/kg after PHIs of 28-30 days. The trials in France were evaluated against Spanish and Italian GAP. The residues from GAP applications in rank order were <0.02, 0.09, 0.12, 0.16, 0.24 and 0.34 mg/kg.

The available information indicates that a maximum residue level of 0.5 mg/kg and an STMR of 0.14 mg/kg for olives would be appropriate, but because there was no suitable supporting processing study the Meeting could not make any recommendation.

Of the supervised residue trials on kiwifruit carried out in New Zealand during 1974-76 only one complied with current GAP. The Meeting recommended the withdrawal of the CXL for kiwifruit (15 mg/kg).

In two supervised trials on peas carried out in two states of the USA, phosmet residues were below the limit of determination (<0.05 mg/kg) in succulent peas, <0.05-0.08 mg/kg in dried peas, 0.15-0.51 mg/kg in succulent pods, 2.7-5.6 mg/kg in succulent pea forage and 2.5-17 mg/kg in dry pea hay. Phosmet oxon residues were <0.05 mg/kg in peas and green forage, and

0.06-0.28 mg/kg in hay. The oxon residue was less than 10% of that of the parent compound.

The Meeting concluded that the data were not sufficient to estimate maximum residue levels, and recommended the withdrawal of the existing CXLs for peas (pods and immature seeds), peas (dry), pea hay or fodder (dry) and pea vines (green).

Numerous trials on potatoes in Canada, The Netherlands and the USA indicated that the translocation of the compound to the tuber was limited, and residues in the tubers following applications at recommended and double rates were <0.05 mg/kg. Residues up to 0.11 mg/kg were detected in trials at fivefold rates however, which indicates that this is not a nil residue situation.

The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.05 mg/kg for potatoes. This is the level of the current CXL.

Residues from six supervised trials on cotton in Brazil at 1.5-4.5 times the GAP rate were all below the limit of determination (0.05 mg/kg).

The Meeting concluded that no detectable residue is likely to occur in cotton seed if GAP is followed, and estimated a maximum residue level of 0.05 mg/kg and an STMR level of 0 mg/kg.

Supervised trials were reported on alfalfa, Bermuda grass, lupins, maize forage, peas, rape and soya bean plants used for animal feed. Most of the trials were on alfalfa.

The residue data on forage and fodder crops showed that residues were generally high (commonly 40-80 mg/kg) immediately after application to alfalfa, but declined fairly rapidly. After 14 days they were mainly in the range 0.2-2 mg/kg. The residues of phosmet on lupins, maize, peas and rape were lower and generally below 2.0 mg/kg 7 days after the last application. The residues in fresh alfalfa from applications according to GAP in rank order were 0.13, 0.21, 0.24, 0.26, 0.3, 0.4, 0.77, 0.84, 0.84, 1.2, 1.6, 2.1, 2.1, 2.24 and 3.5 mg/kg. The Meeting did not estimate any maximum residue levels for animal feed items (see "Animal products" below).

The data, if any, were insufficient to estimate maximum residue levels in blueberries, feijoa, maize, maize fodder and forage, pea hay or fodder, sweet corn, sweet potatoes and tree nuts. The Meeting therefore recommended the withdrawal of the existing CXLs for these commodities.

Animal products. Although no detectable residues of phosmet or its oxon occurred in edible animal products in metabolism studies, the Meeting was not able to estimate any maximum residue levels for animal feeds or animal products because of the high residues in animal feed items and the lack of animal transfer studies. Consequently, the Meeting recommended the withdrawal of the existing CXLs for alfalfa fodder and forage, cattle meat and milks.

Processing

Studies have been carried out to determine the effect of processing on residues of phosmet in apples, grapes, peaches, olives, potatoes and prunes.

Field-treated apples containing 12-14 mg/kg phosmet residues were processed to unclarified

and clarified juice and wet and dry pomace, which contained 5.3, 1.4, 29 and 89 mg/kg respectively. The oxon residue was less than 1% of the phosmet residue in all samples. Most of the phosmet residue is evidently in or on the peel, since processing decreased residues about 2.5-10 times in the products which were separated from the peel. Fractions which are normally processed with the peel, such as wet and dry pomace and the combined peels and cores, showed about a 2-6-fold concentration of the residues. The Meeting therefore concluded that maximum residues up to 60 mg/kg might occur in dry apple pomace.

Field-treated grapes were processed to raisins and raisin waste by sun-drying, and into wet and dry pomace. There was no concentration of the residue in the raisins but concentration occurred by factors of 12 in raisin waste, 3 in wet pomace, and about 6 in dry pomace.

Potatoes, treated with excessive amounts of phosmet to obtain detectable residues (0.1 mg/kg), were processed to yield potato chips, potato granules, wet peel and dry peel. There was no detectable residue in potato chips or granules (LOD ≤0.05 mg/kg). Residues in the wet peel were at the same level as in the washed potatoes, but were concentrated about threefold in the dry peel. This was accounted for by an 85% loss of moisture partly offset by the loss of some phosmet during drying (the theoretical residue would be 0.72 mg/kg).

Olives were processed to crude oil and neutralized oil. The residue in the crude oil was about four times that in the original olives, and purification ("neutralization") of the crude oil reduced the residues about threefold. The process used for neutralization was not reported, so the residues in the oil could not be used to estimate those likely to result from industrial processing. The Meeting concluded that the database was not sufficient to estimate maximum residue levels in crude or refined olive oil.

Fresh prunes were processed into dried prunes and both commodities were analysed for phosmet and phosmet oxon. The average phosmet residue in fresh prunes was 2.63 mg/kg, and in dried prunes 0.82 mg/kg. Phosmet oxon was not detectable in any of the samples. The decrease in dried prunes was attributed to the loss of residues during the drying process at 54-60°C, which more than offset the loss of moisture. Since it had not been possible to estimate a maximum residue level for fresh prunes the Meeting could not estimate one for dried prunes.

4.28 TEBUCONAZOLE (189)

RESIDUE AND ANALYTICAL ASPECTS

Tebuconazole is a triazole fungicide used as a seed dressing and spray. It was first evaluated in 1994 when use patterns, methods of residue analysis, results from supervised trials, studies of metabolism and environmental fate, and storage and processing data were reported by the manufacturer. MRLs were recommended for barley, barley straw and fodder, grapes, peanut, peanut fodder, rape seed, rye, rye straw and fodder, summer squash, tomatoes, wheat, wheat straw and fodder, cattle edible offal, meat and milk, and chicken edible offal, eggs and meat. In studies of metabolism in wheat, grapes and peanuts, tebuconazole was the significant residue. Information received since the 1994 evaluation was reviewed by the present Meeting.

New methods of analysis of plant materials and soil were reported. After extraction with

organic solvents and clean-up on Florisil, C-18 or silica columns, and/or gel permeation chromatography, tebuconazole is determined by gas chromatography with a nitrogen-phosphorus detector. In some cases, no clean-up step was required. The limit of determination ranged from 0.01 to 0.05 mg/kg.

Two hundred and eighteen trials were reported to the Meeting, with information on registered uses on the relevant crops. Processing studies were conducted on plums, grapes and peanuts.

The Meeting concluded that the definition of the residue for compliance with MRLs and for estimations of dietary intake should be tebuconazole.

Supervised trials

Pome fruits

GAP is established for the use of tebuconazole on apples in Brazil, France and Indonesia and on apples and pears in Italy, Israel, Turkey and Spain. PHIs vary from 10 to 30 days. There are proposed uses on apples and pears in the USA and apples in Germany in which the recommended PHIs are 75 and 56 days respectively. Results from trials on pome fruits show that residues decrease continuously with time after sprayed applications of tebuconazole.

Apples. In one trial in Brazil, two in Italy and one in Spain according to local GAP (1 to 6 applications of 0.09 to 0.23 mg/kg ai/ha), residues at a PHI of 20-21 or 28 days in rank order were 0.12, 0.13, 0.18 and 0.20 mg/kg. In one further trial in France according to current GAP which was reported to the 1994 Meeting, the residue at a PHI of 21 days was 0.06 mg/kg. In three trials in Brazil, two in France and ten in Korea with more applications and/or higher rates (up to 1.25 kg ai/ha) than recommended GAP, residues varied from 0.04 to 0.5 mg/kg with PHIs of 14 to 35 days.

In two trials in Canada, 18 in the USA and 11 in Germany with applications below, at, or above proposed GAP rates in Germany and the USA (1-6 x 0.1-0.25 kg ai/ha) most residues were below the LOD of 0.01 to 0.02 mg/kg, with 7 values of 0.02-0.04 mg/kg at PHIs of 56 days or longer.

Pears. In one trial in Spain according to GAP (4-6 applications of 0.1-0.15 kg ai/ha) the residue was 0.09 mg/kg at a PHI of 21 days. In six trials in the USA at or below the proposed rates the residues varied from below the LOD (0.01 mg/kg) to 0.03 mg/kg after PHIs of 63 to 106 days.

Three trials in Italy according to GAP (1-4 applications of 0.15-0.28 kg ai/ha, PHI 15 days) and one trial in France according to Spanish GAP were reported in 1994. The residues in Italy were 0.43, 0.12 and 0.20 mg/kg after 14, 10 and 10 days respectively, and in France <0.05 mg/kg after 14 and 30 days. As the residues in the pears appeared to decrease slowly the residues after 10 and 15 days would probably be similar.

As GAP for apples and pears is similar in countries with registrations for both, residues from trials according to GAP in the two crops can be considered to form a single population. The residues from trials according to established GAP in rank order (median underlined) were <0.05, 0.06, 0.09, 0.12 (2) 0.13, 0.18, 0.20 (2) and 0.43 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.12 mg/kg for pome fruits.

Stone fruits

Tebuconazole is registered for use on peaches in Chile, France, Italy and Peru, on plums in Israel and on peaches and cherries in the USA. PHIs vary from 0 in the USA to 35 days in Chile. The results from trials on stone fruit show that residues after spray applications decrease steadily and fairly slowly.

Cherries. Tebuconazole is registered for use on cherries only in the USA. In five trials in Italy at or below proposed Italian GAP (1 or 2 applications of 0.28 kg ai/ha), residues in the fruit with and without stone were 0.18-0.50 mg/kg after 5 to 7 days.

GAP in the USA allows 1-6 applications at a nominal rate of 0.25 kg ai/ha with a 0-day PHI. Twelve trials were carried out at a nominal rate of 0.19 kg ai/ha, the actual rate depending on the size of the trees. The residues at a PHI of 0 days in rank order were 0.09, 0.19, 0.31, 0.40, **0.41**, **0.53**, **0.61**, **0.76** (median), **0.92**, 1.2, **1.4** and **3.1** mg/kg (the last from 7 applications). The residues shown bold were from the highest actual application rates and have been used to estimate an STMR. The residue in another trial at half the application rate was 1.0 mg/kg at a 0-day PHI.

The Meeting estimated a maximum residue level of 5 mg/kg and an STMR of 0.76 mg/kg.

Peaches and nectarines. Two trials on peaches in France and one on peaches and two on nectarines in Italy were according to Italian GAP (1 or 2 x 0.15-0.3 kg ai/ha). The residues ranged from below the LOD (0.02 mg/kg) to 0.17 mg/kg in stoned or whole fruit at a PHI of 7 to 10 days. In four trials on peaches in France according to current GAP, reported in 1994, the residues in stoned and whole fruit at a PHI of 7 days varied from 0.03 to 0.22 mg/kg.

In eight trials on peaches in the USA according to GAP (0.25 kg ai/ha), residues in whole fruit at a PHI of 0 days were 0.20 to 0.81 mg/kg, and in one trial with an application below the GAP rate the residue was 0.04 mg/kg.

Residues from trials according to GAP in whole and stoned peaches in rank order were 0.03, 0.05, 0.11 (2), 0.13, 0.20, 0.21, 0.22, 0.26, 0.34, 0.44, 0.46 and 0.81 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.21 mg/kg for peaches.

Plums. Only Israel has a registered use for tebuconazole on plums. There is a proposed use in France.

In France, residues in the stoned or whole fruit from nine trials at a higher rate or spray concentration than the proposed use (1-3 applications of 0.13-0.15 kg ai/ha) ranged from 0.03 to 0.38 mg/kg at a PHI of 7 days. In ten further trials according to the proposed use, residues ranged from below the LOD (0.01 or 0.02 mg/kg) to 0.1 mg/kg after PHIs of 7 to 79 days.

As no trials according to approved GAP were reported, the Meeting could not estimate a maximum residue level.

Grapes. Tebuconazole is registered for use on grapes in Brazil, Chile, France, Germany, Israel, Italy, Spain and South Africa. The 1994 JMPR recommended an MRL of 2 mg/kg.

In 14 trials in the USA at the use pattern for which registration has been applied and a PHI of 14 days the residues were between 0.10 and 1.7 mg/kg, and in one further trial 4.0 mg/kg at 13 days.

As no additional results from trials according to GAP were reported, the Meeting made no change to the previous recommendation.

Bananas. Tebuconazole is registered for use on bananas in Australia, Cameroon, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Indonesia, the Ivory Coast, Nicaragua, the Philippines and the USA. A PHI of 0 or 1 day is recommended in all these countries.

In one trial in Australia and seven in the USA according to national GAP (5-7 applications of 0.1 kg ai/ha, bagged bananas), residues in the whole fruit were <0.01 (6), 0.01 and 0.03 mg/kg and in the pulp <0.01 (5) and <0.05 mg/kg. Three other trials in Australia, one at a lower and two at a higher rate, gave similar results and could be used to support the results in the trials according to GAP. Two trials on unbagged bananas gave residues of 0.16 mg/kg in the whole fruit at a PHI of 1 day. Two trials in Brazil giving residues in the pulp below the LOD (0.1 mg/kg) after 14 days could not be evaluated owing to the lack of information on GAP.

The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR (based on residues in the pulp) of 0.01 mg/kg for tebuconazole in bananas.

Bulb vegetables

Tebuconazole is registered for use on garlic and onions in Brazil, Israel, and Spain (soil drench) and on onions in New Zealand and South Africa.

Garlic. In one trial in Brazil approximating GAP (1-4 applications of 0.25 kg ai/ha) and three others at a higher rate or with 6 applications, residues were below the LOD (0.05 mg/kg) after the GAP PHI of 14 days. Five trials in France according to proposed GAP gave residues from below the LOD (0.02 mg/kg) to 0.06 mg/kg after a PHI of 21 days.

In seven trials in Korea at various application rates and with spray or soil drench applications, residues ranged from below the LOD after 275 days to 1.4 mg/kg after 51 days. No GAP was available with which to evaluate the trials.

The data from trials according to GAP were insufficient to estimate a maximum residue level.

Onions. In one trial in France, one in Germany, one in Italy and four in The Netherlands, at or close to the proposed German use pattern (1-2 foliar applications of 0.25 kg ai/ha), and in four trials in Brazil which exceeded GAP conditions (1-4 x 0.25 kg ai/ha), residues after 14-28 days

ranged from below the LOD (0.02, 0.05, or 0.1 mg/kg) to 0.3 mg/kg. In Spain, where soil drench application is recommended, two trials with foliar applications gave residues at or below the LOD (0.02 mg/kg) after 14 days.

In two trials in New Zealand according to GAP (2-3 foliar applications of 0.38 kg ai/ha), the residues were 0.14 mg/kg at day 28 and below the LOD (0.05 mg/kg) after 76 days. The GAP PHI is 35 days. In two trials in Australia with 1 or 2 applications of 0.5 kg ai/ha, the residues were below the LOD (0.01 mg/kg) and 0.3 mg/kg after 79 and 154 days respectively.

There were insufficient data from trials according to GAP to estimate a maximum residue level.

Cucumbers. Tebuconazole is registered for use on cucumbers in Chile, Israel and Spain. PHIs vary from 7 to 35 days. There is a proposed use in Italy.

In two trials in Italy according to the proposed rate (1-4 applications of 0.125 kg ai/ha), the residues at a PHI of 7 days were below the LOD (0.02 mg/kg). Eight trials were conducted in Spain according to current GAP (1-3 applications of 0.2-0.3 kg ai/ha), five indoor trials reported to the present Meeting and three field trials reported to the 1994 Meeting. The residues at a PHI of 7 days in rank order were <0.02, 0.02, 0.03 (2), 0.04, 0.08, 0.10 and 0.19 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.035 mg/kg.

Sweet peppers. Tebuconazole is registered for use on sweet peppers only in Spain, with 1-3 applications of 0.2-0.3 kg ai/ha.

In three trials in Spain reported to the present Meeting and four reported in 1994, all according to current GAP, the residues at a PHI of 7 days in rank order were 0.07, 0.13, 0.14 (2), 0.18, 0.23 and 0.36 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.14 mg/kg.

Cereal grains

Tebuconazole is registered for use on barley, oats and/or wheat as a seed or foliar treatment in many countries, including Australia, Spain, South Africa, Germany, the UK and the USA.

Barley. The 1994 JMPR recommended an MRL of 0.2 mg/kg based on residues from foliar applications.

In nine trials in the USA with seed treatment according to GAP, residues in grain samples were below the LOD (<0.01 (4) and 0.02 (5) mg/kg) at harvest (81 to 129 days). In one trial a 12-fold rate gave a residue of <0.01 mg/kg.

The Meeting did not change the 1994 estimate of 0.2 mg/kg as a maximum residue level.

Oats. In eleven trials with seed treatment in the USA according to GAP, all residues in grain samples were below the LOD (0.01 mg/kg) at harvest (78 to 122 days). The residues in straw and

forage were also all below the LOD (0.01, 0.02 or 0.06 mg/kg). Residues in hay, determined in 5 trials, were <0.01 mg/kg in 4 trials and 0.02 mg/kg in the fifth.

Residues in the grain from trials with foliar treatments according to GAP (two in Australia and one in Sweden) reported to the 1994 Meeting were 0.06, 0.09 and 0.12 mg/kg.

On the basis of the US trials and the practical LOD for rye of 0.05 mg/kg indicated by the 1994 JMPR, the Meeting estimated a maximum residue level of 0.05* mg/kg for tebuconazole in oats. As the residues in straw, forage and hay from seed treatments were also below the LOD, except in one sample of hay, the Meeting estimated an STMR of 0 mg/kg for tebuconazole in oats. The Meeting recognized that these estimates would not accommodate foliar applications.

Wheat. The 1994 JMPR recommended an MRL of 0.05 mg/kg on the basis of residues from foliar applications.

In six trials with seed treatment according to GAP in the USA, the residues in grain samples at harvest (81 to 275 days) were below the LOD (0.01 or 0.04 mg/kg). The residues in 13 trials with foliar treatment in Germany and the UK reported to the 1994 JMPR, according to GAP at that time, were <0.05 mg/kg.

The Meeting confirmed the previous recommendation of 0.05 mg/kg as an MRL.

Peanuts. Tebuconazole is registered for use on peanuts in Australia, Argentina, Brazil, Guatemala, Indonesia, Israel, Nicaragua, South Africa and the USA. The 1994 JMPR recommended an MRL of 0.05 mg/kg.

In thirteen US trials with 7 applications, instead of the 4 allowed by GAP, at rates slightly above the authorized 0.23 kg ai/ha, the residues in the kernels at or about the GAP PHI of 14 days in rank order were <0.01 (4), 0.01, 0.03 (3), <0.05 (4) and 0.08 mg/kg.

The Meeting confirmed the the 1994 JMPR recommendation, as it is unlikely that residues would exceed 0.05 mg/kg.

Processing

Plums. Plum trees were treated three times with 0.25 kg ai/ha. In a processing study of samples taken after 7 days residues were reduced by a factor of 0.7 in washed and preserved plums, remained unchanged in jam and were increased by a factor of 4.7 in dried prunes. The Meeting agreed that one study was not sufficient to estimate processing factors.

Grapes. Grapes taken after the last of four applications of 0.25 kg ai/ha were processed. Processing factors were 0.9 and 1.3 for sun- and oven-dried raisins respectively, <0.5 for juice, 4 and 10.6 for sun- and oven-dried raisin waste, 7.5 for wet pomace and 21.9 for dry pomace. Processing studies reviewed by the 1994 JMPR showed processing factors of 1.4 and 1.2 for sun- and oven-dried raisins, 0.04, <0.05, 0.06 and 0.4 for juice, 2.7 and 1.5 for sun- and oven-dried raisin waste, and 1.8 and 5.8 for wet and dry pomace.

Residues in grapes, must and wine were determined in 37 trials reported to the 1994 JMPR (2

to 5 applications of 0.3-0.625 kg ai/ha). In three of these trials juice was also analysed but the results were reported incorrectly by the company in 1994; the correct values were supplied for the present Meeting. The mean and individual processing factors from all the trials were juice <0.21 (0.04, <0.05, 0.06, 0.4, <0.5), raisins 1.2 (0.9, 1.2, 1.3, 1.4), raisin waste 4.7 (4, 10.6, 2.7, 1.5), wet pomace 4.7 (1.8, 7.5), dry pomace 13.9 (5.8, 21.9), must 0.36 (range 0.12-0.78), wine 0.25 (range 0.05-0.78).

On the basis of the draft MRL of 2 mg/kg for grapes and the processing factor of 1.2 for raisins, the Meeting estimated a maximum residue level of 3 mg/kg for tebuconazole in dried grapes.

Peanuts. Plants treated at 5 times the maximum rate gave processing factors of 0.9 for peanut meal, 3.4 for soapstock, 2.0 for crude oil and 0.1 for refined oil. The Meeting agreed that one study was not sufficient to estimate processing factors for peanut products.

4.29 TEBUFENOZIDE (196)

RESIDUE AND ANALYTICAL ASPECTS

Tebufenozide was first evaluated by the 1996 JMPR, which recommended MRLs for grapes, pome fruits, husked rice and walnuts. Trials on kiwifruit could not be related to GAP in New Zealand and no maximum residue level could be estimated.

The New Zealand Government and the manufacturer requested the JMPR to re-evaluate the residue data on kiwifruit in the light of revised New Zealand GAP, in which the PHI has been increased from 21 to 90 days.

The residues in the trials reported in 1996 which reflect the revised New Zealand GAP (median underlined) were 0.05, 0.08, 0.19 and 0.22 mg/kg.

In two trials in the USA with 4 applications at 0.15 kg ai/ha and a 90-day PHI, the residues were 0.09 and 0.15 mg/kg. Although these results cannot be related to the reported GAP, they can be considered as supplementary supporting information.

The Meeting concluded that although the data were limited they were just sufficient to estimate a maximum residue level of 0.5 mg/kg and an STMR of 0.14 mg/kg for kiwifruit.

4.30 THIABENDAZOLE (065)

RESIDUE AND ANALYTICAL ASPECTS

Thiabendazole was evaluated by the Joint Meeting several times from 1970 to 1981, when MRLs were recommended for a number of commodities. The compound was evaluated by the present Meeting under the periodic review programme of the CCPR.

At its 1992 meeting JECFA noted that total residues of thiabendazole and 5-

hydroxythiabendazole were below 0.1 mg/kg in all analysed tissues and milk within a few days of withdrawal and therefore adopted the definition of the residue and the MRLs of 0.1 mg/kg recommended by the 1975 JMPR for animal commodities and milk.

Thiabendazole is registered in many countries for use as a post-harvest and pre-harvest fungicide, veterinary drug and human medicine. The major use for plant protection is the post-harvest application.

The disposition of thiabendazole and its metabolites in humans and farm animals has been extensively studied. Many of the studies have also been published in the open literature. The oral administration of thiabendazole to sheep, cattle, goats, dogs and humans resulted in rapid absorption from the gastrointestinal tract. The time to achieve peak plasma levels varied with species and ranged from about 1 hour in dogs to 7 hours in sheep, goats and cattle. In dogs, goats and cattle, approximately 82% of the dose was excreted in the urine and faeces within the first 72 hours after oral administration. In all the species studied, almost all the recovered ^{14}C (97-99.6%) was in the urine and faeces. The hydroxylation of the benzimidazole ring at the 5-position to form 5-hydroxythiabendazole and subsequent conjugation to form the glucuronide and sulfate are the major metabolic steps. A minor metabolic pathway found in faeces and tissues involves loss of the thiazolyl group to form benzimidazole (BNZ). None of these residues are likely to persist in edible tissues in view of their relatively low concentrations and rapid elimination. Although the magnitude and profile of the residues differ slightly among different animal species (rats, lactating goats and laying hens), and samples (tissues, milk, eggs and excreta) the major metabolic steps and metabolites are the same.

Single gelatine capsules, each containing 120 mg of [^{14}C]thiabendazole, were administered daily to lactating goats for 7 consecutive days. Milk was collected twice daily and tissue samples after slaughter on the 8th day, within 24 hours after the final dose. An average of 74% of the administered dose was accounted for at the end of the study in the excreta (urine + faeces), tissues and milk, nearly all of it in the urine (69%) and faeces (28%). In urine, the residues, expressed as thiabendazole, consisted of unconjugated 5-hydroxythiabendazole (~7.9 mg/kg) and its *O*-sulfate conjugate (~9.5 mg/kg). The residues in the faeces consisted of unconjugated 5-hydroxythiabendazole (2.1 mg/kg), together with lower levels of benzimidazole (~0.4 mg/kg) and unmetabolized thiabendazole (~0.3 mg/kg). About 1% of the dose was found in the tissues. The highest tissue residues were in the liver and consisted of low levels of unmetabolized thiabendazole, unconjugated 5-hydroxythiabendazole and benzimidazole, at maximum concentrations of 0.2, 0.12 and 0.08 mg/kg respectively. Total residues in milk reached a steady state in 3 days and averaged about 1% of the orally administered dose (~1 mg/kg) after the final (7-day) dose. In milk the *O*-sulfate conjugate of 5-hydroxythiabendazole accounted for about 39% of the ^{14}C (0.4 mg/kg). No other individual residue was detectable (≤0.5% of the total radioactivity). Fractionation studies indicated that the unidentified residues were mainly products arising from the extensive degradation of thiabendazole followed by incorporation into proteins (20-60%), lipids (12-14%) and polysaccharides (~1%).

Single gelatine capsules, each containing 3.19 mg of [^{14}C]thiabendazole were orally administered daily to laying hens for 10 consecutive days; eggs and excreta were collected twice and once daily respectively. The hens were killed on the 11th day, within 24 hours after the final dose.

An average of 96.6% of the total administered dose was recovered. About 99.6% of this recovered dose was found in the excreta, and consisted of unconjugated (3.4 mg/kg) and conjugated (4.4 mg/kg) 5-hydroxythiabendazole. Cumulatively, the total residues found in the tissues and eggs accounted for about 0.4% or less of the ^{14}C. The total residues in eggs attained a level of about 0.1 mg/kg by day 2 and remained relatively unchanged throughout the next 8 days. The residues in tissues and eggs consisted mainly of unconjugated 5-hydroxythiabendazole, unmetabolized thiabendazole and benzimidazole at maximum concentrations, in the kidneys, of 0.4, 0.11 and 0.12 mg/kg respectively. The proposed metabolic pathway in poultry is the same as in goats.

Neither thiabendazole nor its related residues are likely to persist in milk, eggs or edible tissues because of their relatively low concentrations and rapid elimination.

The fate of [*phenyl*-^{14}C]thiabendazole was studied in actively growing wheat (2-3 tiller stage), soya beans (late flowering to early pod set) and sugar beet treated at maximum recommended rates (0.8, 0.68 and 2.015 kg ai/ha respectively). Residues were characterized after a combination of solvent (MeOH, MeOH/H_2O) and hydrolytic (KOH/MeOH) extractions, by reversed-phase HPLC and electron-impact GC-MS analyses. The same pattern of metabolites was seen in all three crops.

The total residues were about 0.12 mg/kg in wheat grain, 22 mg/kg in the straw, and 67.5 mg/kg in the foliage. Neither thiabendazole nor any individual metabolite was detectable in grain (≤0.05 mg/kg). The major individual residue found in the shoots was thiabendazole and the highest level, 65.6 mg/kg, was detected in early foliage. In all wheat tissues examined, only low proportions of the applied thiabendazole were converted to benzimidazole, which was subsequently conjugated with sugars. The benzimidazole could be released from the conjugate(s) by treatment with glucosidase. Benzimidazole was detected only in shoot tissues (<0.05 mg/kg in forage and 7.49 mg/kg in straw), either free or as the sugar conjugate(s). The highest level of unextractable residues was found in immature wheat forage (5.77 mg/kg), constituting about 14% of the total radioactive residue. The unextractable residues were distributed in very small amounts throughout several fractions of natural products, all of which were individually at or below the limit of detection (0.05 mg/kg). These results are consistent with findings in residue trials on wheat, including seed dressing and foliar treatments at or higher than the recommended rates with unlabelled thiabendazole, in which no residue (<0.05 mg/kg) was detectable in the grain at harvest. Since thiabendazole was present at higher levels than benzimidazole in growing wheat plants, the expected levels of benzimidazole in grain will also be undetectable (i.e. <0.05 mg/kg).

The aerial parts of actively growing soya bean crops were sprayed twice, at a 14-day interval, with [^{14}C]thiabendazole at a total rate of about 0.68 kg ai/ha. Immature samples (foliage and forage) were taken at intervals of 2 h and 27 days after treatment and mature samples were harvested and separated into grain and straw about 78 days after the first spray. The extractable residues were characterized by both reversed-phase HPLC and GC-MS. The total residues in the seed (~0.9 mg/kg) were less than 10% of those in the straw (~10 mg/kg). At day 27, thiabendazole was the single major residue (59% or 15.12 mg/kg) found in the shoots and benzimidazole-related compounds were present in smaller amounts (1.4% or 0.36 mg/kg). Benzimidazole was released from the conjugate(s) by glucosidase treatment. Thiabendazole (42.9% of the TRR) was the only individual residue detected (≥0.05 mg/kg) in the grain.

The foliage of actively growing sugar beet plants was sprayed five times, at 14-day intervals, with [^{14}C]thiabendazole at a total application rate of about 2.02 kg ai/ha. Immature top and root samples were taken about 2 h after the first and last treatments. About 90 days after the first treatment (35 days after the fifth and final spray) mature samples were harvested and separated into tops and roots. The residues were characterized by HPLC. At day 56 the organo-extractable residue in the roots was about 90% thiabendazole, amounting to 55.8% of the TRR. In the mature roots the total residues (~0.40 mg/kg) were about 4% of those in the tops (~10 mg/kg). The main component was the parent thiabendazole, at about 0.10 mg/kg; no other individual component was detectable (<0.05 mg/kg). A level of 2.7 mg/kg of thiabendazole was present in mature tops, where benzimidazole (1.4 mg/kg) was also present.

The distribution of the residues in wheat, soya beans and sugar beet is consistent with other results showing the predominantly axoplasmic movement of thiabendazole which results in measurable levels of thiabendazole residues in shoot tissues such as leaves and straw, and relatively less in storage tissues (grains and roots). It can be concluded that the profile and distribution of residues of thiabendazole in three representative actively growing crops (small grain, legume and root crops), following foliar applications, are the same.

The uptake, distribution and metabolism of thiabendazole by seed potatoes were studied under post-harvest storage conditions. Potatoes were briefly immersed in solutions of [^{14}C]thiabendazole at concentrations of 50, 100, 200 and 500 mg/kg and pH levels of 2-9. Skin and tissue sections were subsequently analysed. Potato tubers sorbed thiabendazole from aqueous solutions rapidly (within 5 minutes) at all pH levels. Thiabendazole penetrated only about 2 mm into the tubers in 2 weeks and a little more after 12 weeks, most of it (~96%) remaining on the outer skin. Even after 120 days of post-harvest storage, the only radioactive component detected was thiabendazole, accounting for over 80% of the applied ^{14}C. These results are supported by several additional studies indicating that thiabendazole does not penetrate into the fleshy tissues and does not undergo metabolic transformation. Benzimidazole was not detected (<0.05 mg/kg).

The uptake, distribution and residual fate of [^{14}C]thiabendazole under typical post-harvest storage conditions were also examined in Valencia oranges. Virtually all (~95%) of the radioactivity was sorbed by the peel and none penetrated into the inner pulp. Radiometric assays of the orange samples over the 28-day storage period demonstrated that practically all (~95%) of the radioactivity was due to thiabendazole itself although the conditions, at 21°C, were favourable for metabolism.

The post-harvest treatment studies on oranges, potatoes and pears gave similar results, showing sorption of thiabendazole by the outer surface of storage tissues without penetration into the fleshy interior.

The uptake of soil residues was studied in three representative crops: wheat (small grain), turnips (root) and lettuce (leafy vegetable). Three sandy loam plots were sprayed with [^{14}C]thiabendazole once, or twice two weeks apart, at a total application rate of 2.15 kg ai/ha representing the worst case that might occur in practice. The crops were harvested at maturity. After 137, 223 and 398 days, the extractable residues in the soil amounted to 75.3, 88.6, and 78.1% of the TRR respectively and thiabendazole accounted for 69.6, 86.9 and 63.2% of the

TRR at these times. The residues were present in the upper 0–15 cm of the soil; no significant residues were found at 15-30 cm. The major components of the residues in the crops were thiabendazole (0.08–0.23 mg/kg in mature lettuce, 0.08-0.11 mg/kg in turnip roots, 0.63-1.0 mg/kg in turnip tops, <0.05-0.09 mg/kg in wheat grain, 2.61-10.25 mg/kg in wheat straw) and benzimidazole (0.03 mg/kg in mature lettuce, <0.05 mg/kg in turnip roots, 0.05-0.43 in turnip tops, <0.05 mg/kg in wheat grain, and 0.8-2.5 mg/kg in wheat straw), with the benzimidazole both free and as sugar conjugate(s). Lower levels of 5-hydroxythiabendazole (maximum 25-30% of the thiabendazole) were also observed in immature lettuce and wheat forage. Since 5-hydroxythiabendazole is a degradation product in soil, but not a plant metabolite, it is reasonable to conclude that it was produced in the soil and subsequently taken up by the crops. In addition to thiabendazole, benzimidazole, 5-hydroxythiabendazole and the unextractable residues, other radioactive components were also observed in the HPLC radio-chromatograms of various crop extracts, but all of them individually at levels below 0.05 mg/kg. The results demonstrate that the profile and distribution of thiabendazole residues in three representative crops (leafy vegetables, small grains and root crops) planted in treated soil are the same, but the composition of the residue is different from that in actively growing crops following foliar applications.

The fate of thiabendazole in microbially active sandy loam soil was studied under aerobic conditions at 25 ± 1°C. Thiabendazole was degraded with an aerobic half-life of about 737 days. The products consisted of low levels of benzimidazole (<2.5%) and 5-hydroxythiabendazole (<0.5%). Unextractable radiocarbon increased slowly during the study from 1.24% at day 0 to 20.2% at day 120. This increase is consistent with the strong binding of thiabendazole to soil. Volatile material, 96% of which was $^{14}CO_2$, also increased slowly, attaining its highest level after 12 months and accounting for 5.8% of the applied radioactivity. These results indicate that thiabendazole is fairly stable in soil but will eventually be mineralized under aerobic conditions to CO_2. Practically no degradation was observed under anaerobic conditions.

Thiabendazole was found to be photolytically stable on the surface of soil, with a calculated half-life of 933 days. Recoveries of ^{14}C from irradiated and unirradiated soil samples averaged about 98 and 104% respectively, and 90-100% of the radioactivity was due to thiabendazole; no other residue was found.

The adsorption of thiabendazole to soil was studied with silt loam, clay, sandy loam and sand. The results (K_{oc} values ranged from 1,104 to 22,467) indicate that thiabendazole is bound very tightly to soil. Similarly, the desorption of thiabendazole from these soils was also low, with K_{oc} values from about 1,336 to 18,325. Column leaching studies with the parent compound and residues aged on soil surfaces indicated that about 98% of the applied radioactivity remained in the top 2.5 cm of the column. On the basis of the high K_{oc} values and the column leaching studies, thiabendazole is considered to be immobile in soil.

[^{14}C]Thiabendazole was shown to be degraded rapidly in water when exposed to artificial sunlight, with a half-life of approximately 29 hours. The degradation resulted in the formation of benzimidazole-2-carboxamide (~10%), a polar fraction (8.6%) and relatively low levels (~6%) of benzimidazole. A minor degradation product, with HPLC retention properties consistent with a carboxybenzimidazole, was also present in trace amounts.

Analytical methods for determining residues from supervised trials have been validated with all the crops reported in this review. Validated methods are also available for analysing animal

tissues and milk, as well as soil and water. The recoveries in food commodities were above 70% and the typical limits of detection and determination were 0.01-0.05 mg/kg and 0.05-0.1 mg/kg respectively.

Thiabendazole, free and conjugated 5-hydroxythiabendazole, and benzimidazole were found to be stable during frozen storage in crops for periods of 12 to 28 months, and in animal commodities for at least 2 months.

Definition of the residue

The studies carried out with labelled thiabendazole and related studies with the unlabelled material show that the only individual detectable residue (≥0.05 mg/kg) in edible crop commodities is likely to be the parent thiabendazole.

The animal metabolism and transfer studies indicate that thiabendazole and 5-hydroxythiabendazole are the major residue components in meat and eggs, while the sulfate conjugate, which was determined in all reported studies, is the major component in milk. The parent thiabendazole occurred at much lower concentrations in all commodities.

The Meeting concluded that the following definitions of the residue are appropriate.

For compliance with MRLs

For plant products: thiabendazole.
For animal products: sum of thiabendazole and 5-hydroxythiabendazole.

For estimations of dietary intake

For plant products: thiabendazole.
For animal products: sum of thiabendazole, 5-hydroxythiabendazole and its sulfate conjugate.

Post-harvest trials were conducted in the USA and Spain from 1990 to 1994 on oranges, lemons, grapefruit and tangerines. Ten trials were carried out on oranges in Spain with single post-harvest drench applications at 66 g ai/hl and 110 g ai/hl, and eight in the USA on citrus fruit with initial dip applications at 100 g ai/hl, followed by mist applications in wax with 350 or 500 g ai/hl at rates of 8.4 or 12 g ai/t fruit, much higher than the rates of 0.8–5.5 g ai/t specified on the labels. Residues of thiabendazole on unwashed whole fruit from the US trials in rank order were 1.2, 1.8, 2.9, 3.0, 3.8, 3.9, 4.8 and 5.4 mg/kg. The Spanish trials were reported in a summarized form which did not contain essential details and could not be used to estimate maximum residue levels.

Since there were no residue data from treatments according to GAP, the Meeting recommended the withdrawal of the existing CXL of 10 mg/kg.

Post-harvest residue trials were conducted in the USA (10) and Spain (5) in 1990-1991 on apples and pears. In the US trials, initial dip applications at 60 g ai/hl were followed by mist applications at 200 g ai/hl in wax (about twice the GAP concentration). The US labels provided do not include application in wax for pome fruits, however, in contrast to citrus fruits for which

application in wax is specified. The residues on apples and pears (*) in the US trials were 0.89, 1.1* 3.0, 3.2, 3.2, 3.4, 3.4, 3.4, 3.7* and 5.1* mg/kg whole fruit. The trials in Spain were at 110 g ai/hl, the maximum GAP concentration, but were reported in a summarized form which did not contain essential details and they could not be used for the estimation of maximum residue levels.

Pre-harvest foliar applications on apples at four times the Japanese GAP rate gave rise to residues in the range 0.08-0.52 mg/kg.

As the trials were not according to national GAP, the Meeting recommended the withdrawal of the existing CXLs for apples and pears.

Pre-harvest residue trials on strawberries in Mexico, where there is no GAP, and Spain in 1989-1992 were with ground foliar applications of SC and WP formulations. In Mexico four applications were made 7 days apart, at rates of 0.50-2.0 kg ai/ha. In Spain a single application was carried out at 1.2 kg ai/ha (approx. 1.3 times GAP). The residues from the Spanish trials were 0.33 and 1.6 mg/kg at 3 days PHI. The data were insufficient to estimate a maximum residue level.

Residues following the post-harvest treatment of bananas were determined in a number of trials in Hawaii, Honduras and Guadeloupe. Residues in 10-20 replicate samples taken from individual treated lots indicated that the treatments were fairly uniform. The highest residues of the parent thiabendazole in each trial with 0.04 kg ai/hl in rank order were 0.79, 0.88, 1.0, 1.2, 1.4, 1.6, 1.7, 1.8, 2.3 and 3.3 mg/kg. Benzimidazole residues could not be detected in any samples. The dip treatments in Hawaii and Guadeloupe gave higher residues than the spray applications in Honduras. The pulp of ripened bananas from four trials contained average residues in the range 0.011-0.021 mg/kg which amounted to 1.3-2.9% of the residues measured in whole green bananas. The highest residues in individual samples from each trial in rank order were 0.016, 0.028, 0.029 and 0.031 mg/kg.

Since the use patterns (20-40 g ai/100 l) for post-harvest applications are very similar in a number of countries, the Meeting estimated a maximum residue level of 5 mg/kg for banana to replace the current CXL (3 mg/kg) and an STMR level of 0.029 mg/kg for banana pulp.

No information was provided on residues in onions. The Meeting therefore recommended the withdrawal of the CXL for bulb onions.

Four pre-harvest residue trials were conducted on tomatoes grown under plastic in Spain in 1990-1991 with ground spray foliar applications of SC and WP formulations. Two trials in 1990 were with two applications 7 days apart, at 0.50 kg ai/ha, and two trials in 1991 were with single applications at 3.1 kg ai/ha (approximately 3 times the GAP rate). The data were insufficient to estimate a maximum residue level and the Meeting recommended the withdrawal of the CXL for tomatoes.

Single dip or spray applications of SC and SL formulations of thiabendazole were used on chicory roots. Twenty trials were conducted with flowable SC and 20-S formulations at 67-630 g ai/hl. The chicory leaves, hearts and roots were all analysed for thiabendazole residues. Residues in the edible witloof chicory sprouts did not exceed 0.05 mg/kg even when the roots were treated

at a sixfold rate.

The Meeting estimated a maximum residue level, at or about the limit of determination, of 0.05 mg/kg, and an STMR level of 0.05 mg/kg for witloof chicory (sprouts).

Post-harvest residue trials were conducted on potatoes. In seven trials in the UK whole potatoes were treated with a single spray mist application of a flowable formulation at 30-80 g ai/tonne. Potatoes in the US trials were subjected to an initial seed treatment at 2400 g ai/hl (approximately twice the GAP concentration) before cutting and planting, followed by an application of thiabendazole at 6.2 g ai/t (1.1 times the GAP rate) immediately after harvest and before storage, and a similar application about 30 days later. The residues of thiabendazole on unwashed potatoes from both sets of trials in rank order were 1.9, 2.0, 2.2, 2.4, 2.6, 4.2, 5.4, 5.5, 7.3 and 11 mg/kg.

The Meeting estimated a maximum residue level of 15 mg/kg and an STMR of 3.4 mg/kg for potato (adhering soil may be removed by rinsing or gentle brushing, to conform to the commodity to which Codex MRLs apply).

Pre-harvest residue trials on sugar beet were reported from Spain. One or two ground sprays were applied at 480 g ai/ha after development of 4-8 leaves. The residues of thiabendazole were <0.01 mg/kg in all 16 root samples taken from 0 to 91 days after the last application. The leaves and tops contained residues up to 0.41 mg/kg after 59-65 days. Since no GAP or processing studies were reported, the Meeting could not estimate maximum residue levels for sugar beet, sugar beet leaves or tops, molasses or dry pulp, and consequently recommended the withdrawal of the CXLs.

Mushrooms were treated with four applications of an aqueous solution by irrigation at 54-108 g ai/100 m^2 or by direct spray at 9.5-19 g ai/hl. Applications were made after pinning or after the first harvest break and then after the second, third and fourth breaks according to US label instructions. The maximum residues of thiabendazole on mushrooms collected 12 hours after the last application were 1.9, 2.2, 2.4, 2.5, 3.1, 3.2, 3.9, 3.9, 6.0, 6.1, 7.3, 8.0, 9.6, 12 and 13 mg/kg for irrigation and 21, 27, 30, 31, 36, 41 and 52 mg/kg for spray applications. The residues of benzimidazole were <0.01 mg/kg in all samples.

In four residue trials in Japan a WP formulation was applied once to the bed medium at a rate of 0.120 g ai/kg. The residues of thiabendazole were ≤0.25 mg/kg.

The Meeting evaluated the residues from direct spray applications according to US GAP and estimated a maximum residue level of 60 mg/kg and an STMR of 31 mg/kg for mushrooms.

In fourteen pre-harvest trials on wheat a single ground or aerial spray was applied at 620 g ai/ha (US GAP) after development of 2 to 3 tillers but before the first node, and the wheat was grown to harvest. The residues of thiabendazole and benzimidazole were <0.05 mg/kg in all 14 grain samples. The thiabendazole residues in the straw in rank order were <0.05 (11), 0.07, 0.11 and 0.13 mg/kg.

The Meeting noted that wheat readily takes up thiabendazole residues from soil (<0.05-0.09 mg/kg in wheat grain and 2.61-10.25 mg/kg in wheat straw grown in soil treated at 2.15 kg/ha).

Although the pre-harvest use is limited and the application rates (up to 1 kg/ha except onion and garlic 1.4 kg ai/ha) are relatively low, the Meeting concluded that further field-scale rotational crop studies would be required before the pre-harvest use of the compound could be recommendedand accordingly recommended the withdrawal of the CXL for cereal grains.

Animal transfer studies were conducted with poultry and cows. Ten groups of chickens (25 per group, males and females) were treated continuously for 7 weeks with thiabendazole at levels corresponding to 2, 20, 200 and 2000 ppm in the feed. Four males and 4 females at each treatment level were killed within four hours after the last dose and the liver, kidney, fat and muscle analysed for thiabendazole and 5-hydroxythiabendazole, as were eggs from the three highest treatment levels. The sum of thiabendazole and 5-hydroxythiabendazole, including its conjugate released by acid hydrolysis, was 0.02-0.028 mg/kg in fat (taken from different parts of the birds), 0.017-0.023 mg/kg in a 1:1 mixture of breast and leg meat, and 0.06-0.08 mg/kg in liver at the 20 mg/kg feed level (the expected level based on a poultry diet of 70% corn grain, 20% potatoes and waste and 10% wheat grain). At the same feeding level the average residues were 0.023-0.05 mg/kg in egg yolk and 0.007-0.023 mg/kg in egg white.

The Meeting noted the 3.4 mg/kg STMR for potatoes and the processing factor of 17 for processing potatoes to dry potato peel, and concluded that the 20 mg/kg feeding level appropriately covered the residues likely to occur in poultry feed. The Meeting estimated maximum residue and STMR levels of 0.05 mg/kg for poultry meat and 0.1 mg/kg for eggs.

Dairy cattle were treated once daily by capsule for 28 days with thiabendazole at levels corresponding to 25, 75 and 250 ppm in the feed. Milk samples were collected from all cows on days -1, 1, 2, 4, 7, 14, 21, 28, 29, 35, 42 and 56. Tissues and organs from two of the three cows in each treatment group were collected on day 29, and the remaining cow from each group was slaughtered on day 57. All the samples were analysed for thiabendazole and 5-hydroxythiabendazole. The residues in the milk reached plateaus two days after treatment of 0.014 mg/kg thiabendazole and 0.012 mg/kg 5-hydroxythiabendazole in the 25 ppm group and 0.017 mg/kg thiabendazole and 0.11 mg/kg 5-hydroxythiabendazole in the 250 ppm group, but these levels were less than 0.01 mg/kg higher than the control value at the 25 ppm feeding level, and below the limit of determination of the analytical procedure (0.05 mg/kg). The total residues of thiabendazole plus 5-hydroxythiabendazole in the cows of the 25 ppm group were <0.05 mg/kg in the milk and tissues except a single value of 0.05 mg/kg in kidney. At the 250 ppm level the residues were highest in kidney (0.024-0.03 mg/kg thiabendazole, 0.33-0.55 mg/kg 5-hydroxythiabendazole) and liver (0.056-0.08 thiabendazole, 0.12-0.16 mg/kg 5-hydroxythiabendazole), with much lower residues in the muscle and fat (0.014-0.017 mg/kg thiabendazole, 0.004-0.01 mg/kg 5-hydroxythiabendazole). No difference was observed between the thiabendazole residues in various meat tissues. The residues decreased rapidly to control levels when the animals were returned to a thiabendazole-free diet. The level of 25 ppm is a likely maximum rate, based on a diet of 50% maize grain, 25% apple pomace and 25% potato waste.

On the basis of the likely maximum residues in feed items the Meeting estimated maximum residue levels of 0.05 mg/kg for cattle meat and milk and 0.1 mg/kg for cattle edible offal, and STMRs of 0.05 mg/kg for all three commodities.

The metabolism study in goats at a level corresponding to approximately 20 ppm in the feed

indicated much higher total residues of 1.1 mg/kg in milk (0.4 mg/kg 5-hydroxythiabendazole), 4.8 mg/kg in liver, 1.4 mg/kg in kidney and 0.1 mg/kg in meat. The Meeting concluded that further feeding studies would be required to estimate maximum residue levels in the meat, milk and edible offals of other animals, and recommended the withdrawal of the CXLs for milks and the meat and edible offals of goats, horses and sheep.

The effect of cold storage was studied with apples and potatoes after post-harvest treatment. The residues decreased during the first 24 hours but then remained relatively constant for 5 to 6 months.

The effects of processing were studied with post-harvest-treated apples, oranges and potatoes. Apples were treated with a post-harvest dip at 60 g ai/hl followed by a spray mist application in wax at 8.4 g ai/t approximately 30 days after cold storage. Whole fruits were processed into juice, wet pomace and dried pomace. The study could not be used to estimate processing factors, because a wax treatment is not specified on the label and the residues on whole unwashed apples were lower than on washed fruit, which cast doubt on the reliability of the results. Properly planned and executed processing studies representing typical industrial processes would be required before maximum residue levels could be estimated.

Oranges and grapefruit were treated with a post-harvest dip at 12 g ai/t followed by a spray mist application of thiabendazole in wax at 500 g ai/hl. The whole, washed fruits were processed into various fractions. The processing factors were 0.05 for juice and 8 for dried pomace.

The effect of home-processing on residues of thiabendazole in home-made marmalade was studied in the UK in 1993. The processing factors for home-made marmalade prepared in a preserving pan and in a microwave oven were 0.32 and 0.37 respectively.

Since no maximum residue level or STMR could be estimated for citrus fruits, no STMR-P levels could be estimated.

The effect of washing on the thiabendazole residues in potatoes was studied in several trials. The reduction of residues depended mainly on the time which elapsed between treatment and washing, and probably on the efficiency of washing which was not quantified. The processing (i.e. washing) factors calculated from the experiments in rank order were 0.05, 0.09, 0.11, 0.11, 0.12, 0.14, 0.16, 0.16, 0.17, 0.26 and 0.34 with a median of 0.15 and a mean of 0.13. Peeling removed a further substantial proportion of the residues in washed potatoes. The Meeting noted that residues are transferred from the peel to the peeled potatoes during peeling as potatoes peeled before washing contained average residues of 1.54 mg/kg and after washing 0.08 mg/kg. During industrial processing potatoes are always washed before peeling, and in a kitchen operation either before or after peeling or both. The Meeting therefore concluded that it is more appropriate to estimate the effect of peeling washed potatoes. The average ratio of the residue in pulp to that in washed potatoes was 0.045.

Since washing reduced the residues in raw potatoes by an average factor of 0.13 the Meeting estimated STMR-P levels of 0.44 mg/kg (3.4 x 0.13) for washed potatoes, and 0.02 mg/kg (0.44 x 0.045) for washed and peeled potatoes.

In processing trials in the USA seed potatoes were dipped in an aqueous suspension of

thiabendazole containing 2400 g ai/hl before cutting and planting followed by a spray application to the daughter tubers at 6.2 g ai/t immediately after harvest and before cold storage, followed by a second application of 6.2 g ai/t approximately 30 days later. The processing of the potatoes involved washing, abrasive peeling, washing, slicing, washing, frying in vegetable oil at 178-182 ^{o}C, de-oiling, and salting.

The effect of microwave and oven cooking on the residues of thiabendazole in or on potatoes was studied in the UK in 1990. Potatoes were treated post-harvest with a single application at 40 g ai/t. The tubers were stored for 182 days and the raw peel, raw pulp and unpeeled raw potatoes subjected to microwave and oven cooking.

In four trials on the effects of washing, boiling, baking and crisping in the UK in 1976 potatoes were treated post-harvest with single applications at 40 and 80 g ai/t. The tubers were stored for 4 and 21 days after treatment before processing.

The processing factors founs in the US and UK trials were 1.13, 1.16, 1.2 (2) and 1.34, mean 1.2, for baked whole potatoes; 0.044, 0.055 and 0.073, mean 0.06, for potato chips; 0.03 for potato flakes and 17 for dried potato peel.

Since baking and frying do not change the residue content substantially, baked potatoes may be consumed with or without peel, and cooked or fried potatoes may be prepared in widely varying ways, the Meeting recommended the use of STMR-Ps for washed potato (0.44 mg/kg) and washed and peeled potato (0.02 mg/kg) for the assessment of dietary intake.

4.31 TRIFORINE (116)

TOXICOLOGY

Triforine, a fungicide, was evaluated toxicologically by the 1977 JMPR, when no ADI was allocated, and again in 1978, when more toxicological data were made available and an ADI of 0-0.02 mg/kg bw was established. Subsequently, more data have been produced, which were reviewed at the present Meeting within the CCPR periodic review programme.

A battery of tests for acute toxicity with technical-grade triforine showed that it is slightly hazardous by both the oral and dermal routes, with respective LD_{50} values of >5000 and >2000 mg/kg bw. The LC_{50} in rats exposed by inhalation was >5.1 mg/l. Triforine was not irritating or sensitizing to the skin of rodents and was minimally irritating to the eyes of rabbits. WHO has classified triforine as unlikely to present an acute hazard in normal use.

Dietary administration of technical-grade triforine for 4 or 13 weeks showed that the haematopoietic system is a target, as indicated by mild haemolytic anaemia with associated secondary effects in the spleen and liver. Similar results were found in two-year studies of toxicity in mice, rats, and dogs, in which the haematological changes were accompanied by increased weights of the spleen and liver. In addition, in a 105-week dietary study in mice, changes in the large intestine characterized by thickening, enlargement, inflammation, and ulceration were observed; in a two-year dietary study in dogs, increased erythropoiesis and increased haemosiderin deposition were found in the liver and bone marrow. In a four-week

dietary study in rats at 0, 500, 2500, or 12,500 ppm, an NOAEL was not identified. In a four-week study in mice at 0, 200, 1000, or 5000 ppm, the NOAEL was 1000 ppm, equal to 200 mg/kg bw per day. The NOAEL in a 13-week study in rats at 0, 100, or 500 ppm was 500 ppm, equivalent to 25 mg/kg bw per day. In a six-month study in rats fed diets giving 0, 25, 120, 620, or 3100 ppm, the NOAEL was 120 ppm, equivalent to 6 mg/kg bw per day. Two-year dietary studies in rats (0, 200, 2000, or 20,000 ppm), mice (0, 70, 700, or 7000 ppm), and dogs (0, 10, 40, 100, or 1000 ppm) showed NOAELs of 200 ppm, equal to 10 mg/kg bw per day, 70 ppm, equal to 11 mg/kg bw per day, and 100 ppm, equal to 2.4 mg/kg bw per day, respectively.

The major toxic effect observed in the experiments summarized above was anaemia. The effect was mild, occurring in all or many of the exposed animals (depending upon the dose); the effects were reversible in rats and dogs and were characterized by haemosiderin deposition in several organs, the absence of evidence of bone-marrow depression, entry of increased numbers of immature cells into the peripheral circulation, and the absence of effects on organs of the immune system. In dogs, there was actually an increase in erythropoiesis. Oxidative haemolysis in animals with normally functioning erythrocytes would appear to be the most likely mechanism and one that would cease as soon as exposure ceases. Also, there was no evidence of methaemoglobin formation or of any increase in Heinz body-containing cells or deformed erythrocytes in the circulation.

No genotoxic activity was observed in an adequate battery of tests for mutagenicity and clastogenicity *in vitro* and *in vivo*. The Meeting concluded that triforine is not genotoxic.

The results of the studies critical to the derivation of an ADI are shown below; the list does not include an 81-week study in mice treated orally, which was considered inadequate for evaluation since histopathological examination was limited to lesions that were judged at autopsy to be neoplastic.

No carcinogenic effect was observed in rats given dietary concentrations of 0, 25, 125, 625, or 3120 ppm in one study and 0, 200, 2000, or 20,000 ppm in another. Triforine increased the incidence of pulmonary tumours in female mice given 7000 ppm; the NOAEL for carcinogenicity was 700 ppm, equal to 160 mg/kg bw per day. The Meeting concluded that the murine response involves an unidentified non-genotoxic mechanism and that the carcinogenic activity seen in mice was unlikely to be indicative of a human carcinogenic risk at the expected levels of exposure to triforine.

Triforine at dietary concentrations of 0, 500, 3000, or 20,000 ppm did not affect reproductive performance in rats over the course of a two-generation study, with the NOAEL being the highest dose tested, 20,000 ppm, equal to 1500 mg/kg bw per day. The NOAEL for parental toxicity and for the growth and development of the offspring was 500 ppm, equal to 40 mg/kg bw per day, on the basis of decreases in food consumption, body-weight gain, and F_1 pup weight and increases in relative spleen weight at the next highest dose of 3000 ppm.

In a study of developmental toxicity in rabbits given oral doses of 0, 5, 25, or 125 mg/kg bw per day the maternal NOAEL was 5 mg/kg bw per day, on the basis of decreased food consumption and body weight at 25 mg/kg bw per day; the NOAEL for developmental toxicity was 125 mg/kg bw per day. In a later study of rabbits given oral doses of 0, 6, 30, or 150 mg/kg bw per day the NOAEL for maternal toxicity was 30 mg/kg bw per day, on the basis of

decreased food consumption and body-weight gain at 150 mg/kg bw per day; the NOAEL for developmental toxicity was 150 mg/kg bw per day. In two subsequent studies in which triforine was given orally to rabbits at doses of 0, 250, 500, or 1000 mg/kg bw per day and 0 or 1000 mg/kg bw per day, maternal and embryotoxicity (as shown by reduced fetal weight) occurred at 1000 mg/kg bw per day. Decreased fetal weights and delayed ossification were observed in a study of developmental toxicity in rabbits at the maternally toxic dose of 1000 mg/kg bw per day. Thus, developmental toxicity in rabbits occurred only at doses that were also maternally toxic. A study of developmental toxicity in rats given triforine orally at doses of 0, 200, 500, or 1000 mg/kg bw per day did not show adverse effects in either dams or fetuses at doses up to 1000 mg/kg bw per day. The Meeting concluded that triforine has no specific developmental or reproductive toxicity.

The monitoring of workers in three manufacturing plants did not reveal any health effects that might be associated with exposure to triforine.

An ADI of 0-0.02 mg/kg bw was established on the basis of the NOAEL of 2.4 mg/kg bw per day in the two-year study of toxicity in dogs, with a safety factor of 100.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 70 ppm, equal to 11 mg/kg bw per day (105-week study of toxicity and carcinogenicity)

Rat: 200 ppm, equal to 10 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
1000 mg/kg bw per day (study of developmental toxicity)
500 ppm, equal to 40 mg/kg bw per day (parental and fetal toxicity in a study of reproductive toxicity)

Rabbit: 5 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Dog: 100 ppm, equal to 2.4 mg/kg bw per day (two-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.02 mg/kg bw

Studies that would provide information useful for the continued evaluation of the compound

Further observations in humans.

Toxicological criteria for estimation of guidance values for dietary and non-dietary exposure to triforine

Human exposure	Relevant route, study type, species	Results, remarks
Short-term (1-7 days)	Oral, single dose, rat	LD_{50} > 5000 mg/kg bw
	Dermal, single dose, rat	LD_{50} > 2000 mg/kg bw
	Inhalation (4 h), rat	LC_{50} 5.1 mg/l
	Dermal, irritation, rabbit	Not irritating
	Ocular, irritation, rabbit	Minimally irritating
	Dermal, irritation, rat	Not irritating
	Dermal, sensitization, guinea-pig	Non-sensitizing
Medium-term (1-26 weeks)	Dermal, 3 weeks, rat	NOAEL = 1100 mg/kg bw per day (highest dose tested)
	Oral, 13 weeks, dog	NOAEL = 3.6 mg/kg bw per day: haemosiderin deposition
	Oral, two-generation, reproductive toxicity, rat	NOAEL = 1500 mg/kg bw per day: reproductive toxicity NOAEL = 49 mg/kg bw per day: parental and offspring toxicity
	Oral, developmental toxicity, rabbit	NOAEL = 5 mg/kg bw per day: maternal toxicity NOAEL = 125 mg/kg bw per day: fetal and developmental toxicity
Long-term (≥ 1 year)	Oral, 2 years, dog	NOAEL = 2.4 mg/kg bw per day: haematological changes; haemosiderin deposition; haematopoiesis

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 recommended that Joint Meetings on Pesticide Residues should continue to be held annually.

5.2 The Meeting recommended (Section 2.3) that

(1) Maximum Residue Limits for Monitoring (MRLMs) be applied to new or periodic review chemicals reviewed by future FAO Panels of the JMPR, and that they be clearly indicated as such.

(2) the information needed for the JMPR to refine its estimates of dietary intakes continue to be clearly stated in JMPR reports and evaluations.

5.3 In connection with the estimation of residues in animal commodities found in feeding studies the Meeting recommended (Section 2.4) that

(1) reports of future feeding studies should record the feeding levels primarily on a dry weight basis.

(2) worked examples of the derivation of maximum residue and STMR levels should be developed in time for the 1998 JMPR.

5.4 The Meeting recommended (Section 2.5) that

(1) the CCPR request national governments to provide information on situations where extrapolation of residue data to minor crops is considered feasible at the national level.

(2) national governments prepare data submissions for commodities of concern when the specific pesticides are scheduled for review by the JMPR.

5.5 The Meeting recommended (Sections 2.6 and 4.19)

that a full re-evaluation of the toxicological and residue aspects of lindane be undertaken at a future Meeting.

5.6 The Meeting recommended (Sections 3.1 and 4.1) that

(1) Codex MRLs should accommodate the maximum residue levels estimated both by the JMPR and JECFA.

(2) the JMPR and JECFA take note of each other's definitions of residues for enforcement purposes and that these be harmonized to provide definitions suitable for compliance with Codex MRLs.

(3) JECFA be requested to suggest an appropriate maximum residue level in cattle meat, and to consider accepting the broader definition of the residue to accommodate the residues which occur as a result of agricultural as well as veterinary uses.

5.7In order to ensure that appropriate samples of fat are taken in studies of fat-soluble compounds the Meeting recommended (Section 3.2) that

(1) in livestock transfer (feeding) studies with fat-soluble pesticides samples of sub-cutaneous, abdominal (omental, peritoneal, mesenteric) and renal fat should be taken from an animal and analysed separately.

(2) in external animal treatment studies a sample of the fat at the treatment site, in addition to the three fat types required in the feeding studies specified in recommendation 1, should be taken and analysed separately.

(3) in animal studies residue levels should be expressed on the lipid content of the fat (rendered or extracted fat may be assumed to be 100% lipid). The lipid content of the fat in trimmable fat or fatty tissue should also be reported.

(4) the CCPR *ad hoc* Working Group on Methods of Analysis and Sampling should include a more precise description of carcase fat in the tables of "Portion of Commodities to which Codex Maximum Residue Limits Apply and which is Analysed."

(5) in recommending an MRL the JMPR should estimate the maximum residue level which might occur in any fat depot in the animal, recognizing the possibility that a regulatory authority may take a sample of any type of fat.

(6) the recommendations for changed JMPR practices would initially apply only to evaluations of data on new and periodic review compounds.

(7) the content and recommendations of Section 3.2 of the report should be referred to JECFA for information and comment, with the intention of harmonising requirements and procedures relating to the nature of fat samples in studies with fat-soluble compounds.

5.8The Meeting recommended (Section 3.3) that

(1) the chronic dietary risk posed by the two groups of dithiocarbamate pesticides be assessed using STMR levels and other factors, as described in *Guidelines for predicting dietary intake of pesticide residues* (WHO, 1997). For those commodities potentially containing more than one dithiocarbamate pesticide for which residue data have been accepted by the JMPR, the risk assessment should be based on the pesticide that contributes most to the estimated intake in relation to its ADI.

(2) an ADI adjustment approach should be used and that an example of this approach should be developed in 1998.

5.9The Meeting recommended (Section 4.17) that

(1) glyphosate be re-evaluated by the JMPR, as new data have become available since the last JMPR evaluation for toxicity in 1986, and

(2) the significance of the appreciable levels of AMPA which occur in soya beans should be evaluated in a future periodic review, even though they are not believed to pose any risk to consumers.

6. FUTURE WORK

The following items should be considered at the 1998 or 1999 Meeting.
The compounds listed include those recommended for priority attention by the 29th or earlier Sessions of the CCPR, as well as compounds scheduled for re-evaluation in the CCPR periodic review programme.

6.1 1998 Meeting (tentative)

Toxicological evaluations

New compounds

kresoxim-methyl

Periodic review compounds

amitraz (122)
bitertanol (144)
dicloran (083)
diphenylamine (030)
endosulfan (032)
ethoxyquin (035)
methiocarb (132)
pyrethrins (063)
thiometon (076)

Other evaluations

bentazone (172)
dinocap (087)
phosmet (103)
thiophanate-methyl (077)

Residue evaluations

New compounds

kresoxim-methyl

Periodic review compounds

amitrole (079)
benomyl (069)
captan (007)
carbaryl (008)
carbendazim (072)
2,4-D (020)
demeton-S-methyl (073)
dicloran (083)
dimethoate (027)
folpet (041)
formothion (042)
maleic hydrazide (102)
omethoate (055)
oxydemeton-methyl (166)
thiophanate-methyl (077)

Other evaluations

bentazone (172)
dinocap (087)
disulfoton (074)
glufosinate-ammonium (175)
hexythiazox (176)
procymidone (136)
quintozene (064)

6.2 1999 Meeting (tentative)

Toxicological evaluations

New compounds

pyrifenox
pyriproxyfen

Periodic review compounds

chlorpyrifos (017)
dimethipin (151)
ethoprophos (149)
imazalil (110)
permethrin (120)
propargite (113)

Other evaluations

propylenethiourea (PTU, 150)

Residue evaluations

New compounds

pyrifenox
pyriproxyfen

Periodic review compounds

bitertanol (144)
diflubenzuron (130)
ethoxyquin (035)
fenamiphos (085)
malathion (049)
methiocarb (132)
ortho-phenylphenol (056)
piperonyl butoxide (062)
pirimiphos-methyl (086)
pyrethrins (063)

Other evaluations

buprofezin (173)
clethodim (187)
ethion (034)
fenpyroximate (193)
phosalone (060)

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CORRECTIONS TO REPORT OF 1996 JMPR

Additions and changes are shown **bold**. Minor typographical errors are not included.

P. 35 (Section 4.7), para. 2, line 4
Change "13, 38, or 95 mg/kg bw per day for the IPA salt" to "**10, 30, or 75** mg/kg bw per day for the IPA salt".

P. 58 (Section 4.17), para. 2, line 3
Change "equal to 500 mg/kg bw per day" to "equal to **970** mg/kg bw per day".

P. 58 (Section 4.17), para. 2, line 6
Change "equal to 25 mg/kg" to "equal to **29** mg/kg".

P. 58 (Section 4.17), para. 5, lines 6 and 7
Change "equivalent to 750 mg/kg bw per day" to "**equal** to **770** mg/kg bw per day".

P. 59 (Section 4.17), Toxicological evaluation
Under "rat", change "10,000 ppm, equivalent to 750 mg/kg bw per day" to "10,000 ppm, **equal** to **770** mg/kg bw per day".

P. 59 (Section 4.17), Toxicological evaluation
Under "dog", change "750 ppm, equal to 25 mg/kg bw per day" to "750 ppm, equal to **29** mg/kg bw per day".

P. 63 (Section 4.19), para. 1, line 2
Delete "over four days".

P. 70 (Section 4.22), para 1, line 1
Change tebuconazole to **tebufenozide**.

P. 75 (Section 4.25), para. 5, teratogenicity study in hamsters
Delete the paragraph, because the study was performed with thiram.

P. 76 (Section 4.25), Toxicological evaluation
Under "mouse", **move** the study referring to "210 ppm, equal to 10 mg/kg bw per day" to "rat".

P. 76 (Section 4.25), Toxicological evaluation
Under "mouse", **delete** the line referring to "10 mg/kg bw per day (study of reproductive toxicity)".

P. 76 (Section 4.25), Toxicological evaluation
Delete the line referring to the study in hamsters.

P. 78 (Section 4.25) table titled *toxicological criteria for setting guidance values for dietary and*

non-dietary exposure to ziram
Under "medium term", **delete** the entry "repeated oral, developmental toxicity, hamster".

P. 97 (Annex I), Diazinon
(1). **Delete** superscript [1] after Diazinon in column 1.
(2). **Insert** the following STMRs:

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
Diazinon		FP 0009	Pome fruits			0.12
(022)		VO 0448	Tomato			0.12
		VB 0041	Cabbages, Head			0.16

P. 98 (Annex I), Haloxyfop
AM 1051 Fodder beet: **insert STMR 0.02 mg/kg**.

ANNEX I

ACCEPTABLE DAILY INTAKES, ACUTE REFERENCE DOSES, RECOMMENDED MRLs, STMR LEVELS AND GLs RECORDED BY THE 1997 MEETING

The Table of recommendations is in two parts. Part 1 includes maximum Acceptable Daily Intakes (ADIs), Acute Reference Doses (RfDs), recommendations for Maximum Residue Limits (MRLs), and Supervised Trials Median Residue (STMR) levels. Part 2 comprises Guideline Levels (GLs) recorded for guazatine. These were estimates of maximum residue levels, but cannot be recommended for use as MRLs because the Meeting withdrew the ADI for guazatine.

Some ADIs may be temporary: this is indicated by the letter T and the year in which re-evaluation is scheduled in parenthesis below the ADI. All recommended MRLs for compounds with temporary ADIs are necessarily temporary, but some recommendations are designated as temporary (TMRLs) until required information has been provided and evaluated, irrespective of the status of the ADI. Such recommendations are followed by the letter T in the table. (See also the list of qualifications and abbreviations below.)

In general, the MRLs recommended for compounds which have been reviewed previously are additional to, or amend, those recorded in the reports of earlier Meetings. If a recommended MRL is an amendment the previous value is also recorded. All recommendations for compounds re-evaluated in the CCPR periodic review programme are listed however (even if identical to existing CXLs or draft MRLs) because such re-evaluations replace the original evaluation rather than supplement it.

STMR levels were introduced in 1996 in response to recommendations of a Joint FAO/WHO Consultation on Guidelines for Predicting the Dietary Intake of Pesticide Residues held in York, UK, in 1995.The 1996 JMPR report explains the reasons for their introduction and gives details of the procedures used in their calculation (Sections 2.2.1, 2.2.3, Annex IV and the introduction to Annex I).

The Table includes the Codex reference numbers of the compounds and the Codex Classification Numbers (CCNs) of the commodities, to facilitate reference to the Guide to Codex Maximum Limits for Pesticide Residues and other Codex documents.

Commodities are listed in alphabetical order. This is a change from earlier practice where commodities were listed in the order of the "Types" in the Codex Classification of Foods and Animal Feeds, and in alphabetical order within each Type. The change has been made to facilitate checking and comparison with the CCPR Tables of MRLs, which are in alphabetical order.

The following qualifications and abbreviations are used. Some of the abbreviations are included in the list on pp. xv-xviii, but are repeated here for convenience.

* following recommended MRL	At or about the limit of determination
* following name of pesticide	New compound
** following name of pesticide	Compound reviewed in CCPR periodic review programme
E	Extraneous Residue Limit (ERL).
F following recommendations 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 II of the Codex Alimentarius.
(fat) following recommendations for meat	The recommendation applies to the fat of the meat.
P following an STMR	An STMR for a processed commodity calculated by applying the level mean processing (concentration or reduction) factor for the process to the STMR calculated for the raw agricultural commodity.
Po	The recommendation accommodates post-harvest treatment of the commodity.
PoP following recommendations for processed foods (classes D and E in the Codex Classification)	The recommendation accommodates post-harvest treatment of the primary food commodity.
STMR	Supervised Trials Median Residue.
T following ADIs	The ADI is temporary, and due for re-evaluation in the year indicated.
T following MRLs	The MRL is temporary, irrespective of the status of the ADI, until required information has been provided and evaluated.
V following recommendations for commodities of animal origin	The recommendation accommodates veterinary uses.
W in place of a	The previous recommendation is withdrawn, or withdrawal of a

recommended MRL CXL or draft MRL is recommended.

PART 1. ACCEPTABLE DAILY INTAKES (ADIs), RECOMMENDED MRLs AND SUPERVISED TRIALS MEDIAN RESIDUES (STMRs)

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
Abamectin (177)	0.002[1]	TN 0660	Almond	0.01*	-	0
		AM 0660	Almond hulls	0.1	-	0.040
		FP 0226	Apple	0.02	-	0.003
		JF 0226	Apple juice			0.00019 P
		MO 0812	Cattle, Edible offal of	W	0.05	
		MF 0812	Cattle fat	0.1 V	-	
		MO 1289	Cattle kidney	0.05 V	Note[2]	
		MO 1281	Cattle liver	0.1 V	Note[2]	
		VC 0424	Cucumber	0.01	0.05	0.005
		DH 1100	Hops, dry	0.1	-	0.016
		VL 0482	Lettuce, Head	0.05	-	0.020
		VC 0046	Melons, except Watermelon	0.01*	-	0.002
		FP 0230	Pear	0.02	0.01*	0.005
		VR 0589	Potato	0.01*	-	0
		VC 0431	Squash, Summer	0.01*	-	0.002
		VO 0448	Tomato	0.02	0.02	0.0085
		TN 0678	Walnut	0.01*	-	0
		VC 0432	Watermelon	0.01*	-	0.002
			Apple sauce			0.00036 P
			Canned pears			0.00023 P
			Pear purée			0.00024
		(for MRLs and STMRs): sum of avermectin B_{1a}, avermectin B_{1b}, 8,9-*Z*-avermectin B_{1a} and 8,9-*Z*-avermectin B_{1b} [1]For sum of abamectin and 8,9-*Z* isomer. Previous ADIs were 0.001 mg/kg bw for abamectin n of abamectin and the 8,9-*Z* isomer. [2]Previous recommendation for cattle edible offal is replaced by recommendation for cattle mmodate JECFA recommendations arising from veterinary uses of abamectin				
Aminomethylphos-phonic acid (AMPA)	0.3[1]	GC 0645	Maize	2		
		AS 0645	Maize fodder	5		
(198)		AF 0645	Maize forage	2		
		for MRLs: aminomethylphosphonic acid (AMPA)				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
		for STMRs: see glyphosate [1]for sum of glyphosate and aminomethylphosphonic acid See also recommendations for glyphosate. AMPA is the main residue resulting from the ed maize with glyphosate.				
Amitrole (079)	0.002	Previous Temporary ADI 0.0005 mg/kg bw				
Captan	0.1	FP 0226	Apple	20	10	4.05
(007)		AB 0226	Apple pomace, dry	2	-	0.26 P
		FS 0013	Cherries	40	20	15
		DF 0269	Dried grapes (currants, raisins and sultanas)	50	-	10.4 P
		FB 0269	Grapes	25	20	6.1
		FB 0275	Strawberry	30	15	4.8
			Apple juice (unheated)			1.2 P
			Apple juice (heated)			0 P
			Apple sauce			0 P
			Grape juice			7.3 P
		(for MRLs and STMRs): captan				
Carbofuran**	0.002	AL 1020	Alfalfa fodder	10	20	1.6
(096)		AL 1021	Alfalfa forage (green)	10	5	0.93
		FI 0327	Banana	0.1*	0.1*	0.1
		GC 0640	Barley	W	0.1*	
		VB 0402	Brussels sprouts	W	2	
		VB 0041	Cabbages, Head	W	0.5	
		VC 4199	Cantaloupe	0.2	-	0.02
		VR 0577	Carrot	W	0.5	
		MF 0812	Cattle fat	0.05*	0.05*	0.05
		VB 0404	Cauliflower	W	0.2	
		DM 0001	Citrus molasses[1]			0.11 P
		AB 0001	Citrus pulp, dry[1]	2	-	0.29
		SB 0716	Coffee beans	1	0.1*	0.1
			Coffee, Instant			0.005 P[1]
		SM 0716	Coffee, Roast			0.005 P
		VC 0424	Cucumber	0.3	-	0.05
		MO 0096	Edible offal of cattle, goats, horses, pigs and sheep	0.05*	0.05*	0.05
		VO 0440	Egg plant	W	0.1*	
		MF 0814	Goat fat	0.05*	0.05*	0.05
		DH 1100	Hops, dry	W	5	
		MF 0816	Horse fat	0.05*	0.05*	0.05

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
		VB 0405	Kohlrabi	W	0.1*	
		VL 0482	Lettuce, Head	W	0.1*	
		GC 0645	Maize	W	0.1*	
		AS 0645	Maize fodder	W	5	
		MM 0096	Meat of cattle, goats, horses, pigs and sheep	0.05*	0.05*	0.05
		ML 0106	Milks	0.05*	0.05*	0.05
		SO 0090	Mustard seed	W	0.1*	
		GC 0647	Oats	W	0.1*	
		SO 0088	Oilseed	W	0.1*	
		VA 0385	Onion, Bulb	W	0.1*	
		FC 0004	Oranges, Sweet, Sour[1]	0.5	-	0.1
		JF 0004	Orange juice[1]			0.001
		FS 0247	Peach	W	0.1*	
		FP 0230	Pear	W	0.1*	
		MF 0818	Pig fat	0.05*	0.05*	0.05
		VR 0589	Potato	0.1	0.5	0.03
		CM 0649	Rice, Husked	W	0.2	
		MF 0822	Sheep fat	0.05*	0.05*	0.05
		GC 0651	Sorghum	0.1*	0.1*	0.01
		AF 0651	Sorghum forage (green)	2	-	0.065
		AS 0651	Sorghum straw and fodder, dry	0.5	-	0.055
		VD 0541	Soya bean, dry	W	0.2	
		VC 0431	Squash, Summer	0.3	-	0.05
		FB 0275	Strawberry	W	0.1*	
		VR 0596	Sugar beet	W	0.1*	
		AV 0596	Sugar beet leaves or tops	W	0.2	
		GS 0659	Sugar cane	0.1*	0.1*	0.1
		SO 0702	Sunflower seed	0.1*	0.1*[2]	0.1
		VO 1275	Sweet corn (kernels)	W	0.1*	
		VO 0447	Sweet corn (corn-on-the -cob)	0.1	-	0.03
		VO 0448	Tomato	W	0.1*	
		GC 0654	Wheat	W	0.1*	
		for MRLs: sum of carbofuran and 3-hydroxy-carbofuran expressed as carbofuran for STMRs: sum of carbofuran and 3-hydroxy-carbofuran, free and conjugated, expressed as carbofuran [1]Residues are from the use of carbosulfan [2]Previously included with Oilseeds (SO 0088) Periodic review was for residues only				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
Carbosulfan**	0.01	DM 0001	Citrus molasses			0.0012 P
(145)		AB 0001	Citrus pulp, dry	0.1	-	0.0082 P
		JF 0004	Orange juice			0 P
		FC 0004	Oranges, Sweet, Sour	0.1	-	0.01
		(for MRLs and STMRs): carbosulfan Periodic review was for residues only				
Chlormequat	0.05	GC 0640	Barley	0.5	-	
(015)		AS O640	Barley straw and fodder, dry	20	50	
		SO 0691	Cotton seed	0.5	-	
		DF 0269	Dried grapes	W	1	
		FB 0269	Grapes	W	1	
		ML 0107	Milk of cattle, goats and sheep	W	0.1*	
			Milk products	W	0.1*	
		GC 0647	Oats	10	10	
		AF 0647	Oat forage (green)	20	-	
		AS 0647	Oat straw and fodder, dry	20	50	
		FP 0230	Pear	10	3	
		SO 0495	Rape seed	5	-	
		OC 0495	Rape seed oil, crude	0.1*	-	
		GC 0650	Rye	3	5	
		CM 0650	Rye bran, unprocessed	10	-	
		AF 0650	Rye forage (green)	20	-	
		AS 0650	Rye straw and fodder, dry	20	50	
		CF 1251	Rye wholemeal	3	-	
		GC 0654	Wheat	2	5	
		CM 0654	Wheat bran, unprocessed	5	-	
		CF 1211	Wheat flour	0.5	-	
		AS 0654	Wheat straw and fodder, dry	20	50	
		CF 1212	Wheat wholemeal	2	-	
		chlormequat cation (usually used as the chloride) Chlormequat was reviewed in the periodic review programme in 1994. The 1994 Meeting isted above, but they were recorded only as GLs because the ADI was withdrawn. As an ADI has he 1994 estimates are now recommended for use as MRLs.				
Chlorothalonil	0.03	FI 0327	Banana	0.01*[1]	W[2]	0
(081)		VD 0071	Beans, dry	0.2	-	0.02
		VB 0400	Broccoli	5	W[2]	2.25
		HH 0624	Celery leaves	3	-	1.95
		FB 0021	Currants, Black, Red and White	5	W[2]	1.7

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
		HH 0740	Parsley	3	-	1.95
		FS 0247	Peach	0.2	1	0.01
		VO 0445	Peppers, Sweet	7	W[2]	1.5
		VO 0447	Sweet corn (corn-on-the-cob)	0.01*	W[2]	0.01
		for MRLs: chlorothalonil for STMRs, plant products: chlorothalonil for STMRs, animal products: sum of chlorothalonil and 4-hydroxy-2,5,6-trichloroisophthalonitrile, expressed as chlorothalonil [1]Based on trials with bagged bananas [2]Withdrawal of existing MRL or CXL was recommended by 1993 JMPR Note changed definition of residue for STMRs for animal products				
Clethodim	0.01	AL 1020	Alfalfa fodder	10	-	1.6
(187)		VD 0071	Beans (dry)	W	0.1	0.05
		VP 0061	Beans, except broad bean and soya bean	0.5*	-	0.05
		MO 1280	Cattle kidney	0.2*	0.1	-
		MO 1281	Cattle liver	0.2*	0.1	-
		MM 0812	Cattle meat	0.5*	0.05*	-
		ML 0812	Cattle milk	0.1*	0.05*	-
		PE 0840	Chicken eggs	0.5*	0.05*	-
		PM 0840	Chicken meat	0.5*	0.05*	-
		OC 0691	Cotton seed oil, crude	0.5*	0.1	-
		OR 0691	Cotton seed oil, edible	0.5*	0 05	-
		VD 0561	Field pea (dry)	2	0.1	0.08
		AM 1051	Fodder beet	0.1*	-	0.03
		VA 0381	Garlic	0.5	-	0.1
		VA 0385	Onion, Bulb	0.5	-	0.1
		SO 0697	Peanut	5	-	1.3
		OC 0495	Rape seed oil, crude	0.5*	0.05	-
		OR 0495	Rape seed oil, edible	0.5*	0.05	-
		OR 0541	Soya bean oil, refined	0.5*	0.1	-
		VR 0596	Sugar beet	0.1	0.2	-
		SO 0702	Sunflower seed	W	0.2	-
		OC 0702	Sunflower seed oil, crude	W	0.05	-
		OR 5702	Sunflower seed oil, edible	W	0.05	-
		VO 0448	Tomato	1	-	0.35
		(for MRLs and STMRs): sum of clethodim and its metabolites containing the 5-(2-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulfoxides and n				
Ethephon	0.05	ADI unchanged				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
(106)						
Fenamiphos** (085)	0.0008	Previous ADI 0.0005 mg/kg bw. Periodic review was for toxicology only				
Fenbuconazole*	0.03	FS 0240	Apricot	0.5	-	0.25
(197)		FI 0327	Banana	0.05	-	0.01
		GC 0640	Barley	0.2	-	0.03
		AS 0640	Barley straw and fodder, dry	3	-	0.94
		MF 0812	Cattle fat	0.05*	-	0
		MO 1280	Cattle kidney	0.05*	-	0
		MO 1281	Cattle liver	0.05	-	0.01
		MM 0812	Cattle meat	0.05*	-	0.01
		ML 0812	Cattle milk	0.05*	-	0.01
		FS 0013	Cherries	1	-	0.36
		VC 0424	Cucumber	0.2	-	0.02
		PE 0112	Eggs	0.05*	-	0
		JF 0269	Grape juice	-	-	0.03 P
		FB 0269	Grapes	1	-	0.3
		VC 0046	Melons, except watermelon	0.2	-	0.025
		FS 0247	Peach	0.5	-	0.25
		TN 0672	Pecan	0.05*	-	0.01
		FP 0009	Pome fruits	0.1	-	0.025
		PO 0111	Poultry, Edible offal of	0.05*	-	0
		PF 0111	Poultry fats	0.05*	-	0
		PM 0110	Poultry meat	0.05*	-	0
		SO 0495	Rape seed	0.05*	-	0.05
		GC 0650	Rye	0.1	-	0.02
		VC 0431	Squash, Summer	0.05	-	0.02
		SO 0702	Sunflower seed	0.05*	-	0.02
		GC 0654	Wheat	0.1	-	0.02
		CM 0654	Wheat bran, unprocessed	-	-	0.052 P
		CF 1211	Wheat flour	-	-	0.005 P
		AS 0654	Wheat straw and fodder, dry	3	-	0.79
		CP 1211	White bread	-	-	0.0092 P
			Wine	-	-	0.018 P
		(for MRLs and STMRs): fenbuconazole				
Fenthion (039)	0.007	Acute RfD: 0.01 mg/kg bw. Previous acute RfD was 0.007 mg/kg bw				
Fipronil*	0.0002	Acute RfD 0.003 mg/kg bw Evaluation was for toxicology only				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
Fipronil-desulfinyl	0.00003 T (2000)	Acute RfD 0.003 mg/kg bw				
Folpet	0.1	FP 0226	Apple	10	-	1.8
(041)		JF 0226	Apple juice			0.063 P
		DF 0269	Dried grapes (currants, raisins and sultanas)	40	-	7.0 P
		JF 0269	Grape juice			0.0066 P
		FB 0269	Grapes	10	2	2.2
		VC 0046	Melons (except Watermelon)	3	-	0.41
		VO 0448	Tomato	3	-	1.15
			Apple pomace, wet			4.7 P
			Must			0.64 P
			Raisins, hydrated			4.2 P
			Tomato paste			0.032 P
			Tomato purée			0.032 P
			Wine			0 P
		(for MRLs and STMRs): folpet				
Glyphosate	0.3	SO 0691	Cotton seed	10	0.5	2.0
(158)			Cotton seed, delinted			0.38 P
			Cotton seed, kernels			0.17 P
			Cotton seed hulls			0.68 P
			Cotton seed meal			0.24 P
		OC 0691	Cotton seed oil, crude	0.05*		0 P
		OR 0691	Cotton seed oil, edible	0.05*		0 P
		GC 0645	Maize	1	0.1*	0.47
		AF 0645	Maize forage	1		0.81
		GC 0651	Sorghum	20	0.1*	5.8
			Sorghum, cleaned			7.0 P
			Sorghum bran			27 P
			Sorghum flour			2.1 P
			Sorghum grain dust			27 P
			Sorghum grits (medium)			2.8 P
			Sorghum germ			0 P
			Sorghum starch			0 P
		for MRLs: glyphosate See also recommendations for aminomethylphosphonic acid. AMPA is the main nent of genetically-modified maize with glyphosate.				
Guazatine**	**ADI**	Maximum residue levels estimated by the present Meeting are recorded as GLs. See Part 2 of the				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
(114)	**withdrawn**					
Lindane (048)	0.001 T (2000)	Previous ADI 0.008 mg/kg bw				
Malathion** (049)	0.3	Previous ADI 0.02 mg/kg bw Periodic review was for toxicology only				
Methamidophos	0.004	FP 0009	Pome fruits	0.5	0.5	0.18
(100)		(for MRLs and STMRs): methamidophos methamidophos is a metabolite of acephate for which separate MRLs are recommended				
Methidathion (051)	0.001	Acute RfD 0.01 mg/kg bw				
Mevinphos**	0.0008	FP 0226	Apple	W	0.5	
(053)		FS 0240	Apricot	W	0.2	
		VB 0400	Broccoli	W	1	
		VB 0402	Brussels sprouts	W	1	
		VB 0041	Cabbages, Head	0.05	1	0.02
		VR 0577	Carrot	W	0.1	
		VB 0404	Cauliflower	W	1	
		FS 0013	Cherries	W	1	
		FC 0001	Citrus fruits	W	0.2	
		VP 0526	Common bean (pods and/or immature seeds)	0.05	0.1	0.02
		VC 0424	Cucumber	W	0.2	
		FB 0269	Grapes	W	0.5	
		VL 0480	Kale	W	1	
		VA 0384	Leek	0.02*	-	0.02
		VL 0482	Lettuce, Head	W	0.5	
		VC 0046	Melons, except watermelon	W	0.05	
		VA 0385	Onion, Bulb	W	0.1	
		FS 0247	Peach	W	0.5	
		FP 0230	Pear	W	0.2	
		VP 0063	Peas (pods and succulent = immature seeds)	W	0.1	
		VR 0589	Potato	W	0.1	
		VL 0502	Spinach	W	0.5	
		FB 0275	Strawberry	W	1	
		VO 0448	Tomato	W	0.2	
		VR 0506	Turnip, Garden	W	0.1	
		(for MRLs and STMRs): sum of (*E*)- and (*Z*)-mevinphos Periodic review was for residues only				

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
Myclobutanil	0.03	FS 0240	Apricot	W	0.2	
(181)		FB 0278	Blackcurrant	0.5	-	0.26
		JF 1140	Blackcurrant juice			0.09 P
		FS 0013	Cherries	W	1	
		FS 0247	Peach	W	0.5	
		FS 0012	Stone fruits, except plums	2	-	0.62
		FB 0275	Strawberry	1	-	0.18
		VO 0448	Tomato	0.3	-	0.05
		JF 0448	Tomato juice			0.05 P
			Strawberry jam			0.09 P
			Strawberry preserve			0.15 P
			Tomato, canned			0.05 P
			Tomato, dry pomace			0.78 P
			Tomato paste			0.2 P
			Tomato purée			0.08 P
		(for MRLs and STMRs): myclobutanil				
Phosalone (060)	0.02	Previous ADI 0.001 mg/kg bw				
Phosmet**	0.01	AL 1020	Alfalfa fodder	W	40	
(103)		AL 1021	Alfalfa forage (green)	W	40	
		FP 0226	Apple	10	10	3.4
		FS 0240	Apricot	10	5	2.9
		FB 0020	Blueberries	W	10	
		MM 0812	Cattle meat	W	1 (fat) V	
		FC 0001	Citrus fruits	W	5	
		SO0691	Cotton seed	0.05	-	0
		FI 0335	Feijoa	W	2	
		FB 0269	Grapes	10	10	3.1
		FI 0341	Kiwifruit	W	15	
		GC 0645	Maize	W	0.05	
		AS 0645	Maize fodder	W	10	
		AF O645	Maize forage	W	10	
		ML 0106	Milks	W	0.02 V	
		FS 0245	Nectarine	W	5	
		AL 0072	Pea hay or fodder (dry)	W	10	
		AL 0528	Pea vines (green)	W	10	
		FS 0247	Peach	10	10	2.9
		FP 0230	Pear	W	10	
		VP 0063	Peas (pods and succulent =	W	0.2	

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
			immature seeds)			
		VD 0063	Peas (dry)	W	0.02*	
		VR 0589	Potato	0.05*	0.05	0.05
		VO 0447	Sweet corn (corn-on-the-cob	W	0.05	
		VR 0508	Sweet potato	W	10 Po	
		TN 0085	Tree nuts	W	0.1	
		(for MRLs and STMRs): phosmet Changed definition of residue Periodic review was for residues only				
Tebuconazole	0.003	FI 0327	Banana	0.05	-	0.01[1]
(189)		FS 0013	Cherries	5	-	0.76
		VC 0424	Cucumber	0.2	-	0.035
		DF 0269	Dried grapes (currants, raisins and sultanas)	3	-	
		GC 0647	Oats	0.05*	-	0
		FS 0247	Peach	1	-	0.21
		VO 0445	Peppers, Sweet	0.5	-	0.14
		FP 0009	Pome fruits	0.5	-	0.12
		(for MRLs and STMRs): tebuconazole [1]In the edible portion				
Tebufenozide	0.02	FI 0341	Kiwifruit	0.5	-	0.14
(196)		(for MRLs and STMRs): tebufenozide (fat-soluble residue)				
Thiabendazole**	0.1	FP 0226	Apple	w	10	
(065)		FI 0327	Banana	5 Po	3	0.029[1]
		GC 0080	Cereal grains	w	0.2	
		FC 0001	Citrus fruits	w	10 Po	
		MO 0812	Cattle, Edible offal of	0.1		0.05
		MM 0812	Cattle meat	0.05		0.05
		ML 0812	Cattle milk	0.05		0.05
		MO 0096	Edible offal of cattle, goats, horses, pigs & sheep	w	0.1*	
		PE 0112	Eggs	0.1	0.1	0.1
		MM 0096	Meat of of cattle, goats, horses, pigs & sheep	w	0.1*	
		ML 0106	Milks	W	0.1*	
		VO 0450	Mushroom	60		31
		VA 0385	Onion, Bulb	w	0.1	
		FP 0230	Pear	w	10	

Pesticide (Codex ref. No.)	ADI (mg/kg bw)	Commodity		Recommended MRL or ERL (mg/kg)		STMR (mg/kg)
		CCN	Name	New	Previous	
		VR 0589	Potato	15	5 Po[2]	3.4
		PM 0110	Poultry meat	0.05	0.1	0.05
		FB 0275	Strawberry	w	3	
		VR 0596	Sugar beet	w	5	
		AV 0596	Sugar beet leaves and tops	w	10	
		DM 0596	Sugar beet molasses	w	1	
		AB 0596	Sugar beet pulp, dry	w	5	
		VO 0448	Tomato	w	2	
		VS0469	Witloof chicory (sprouts)	0.05*		0.05
			Potato,washed			0.44 P
			Potato, washed and peeled			0.02 P
		for MRLs, plant products: thiabendazole [1]for banana pulp Periodic review was for residues only				
Triforine** (116)	0.02	ADI unchanged Periodic review was for toxicology only				

PART 2. GUIDELINE LEVELS RECORDED FOR COMPOUNDS WITHOUT ADIs

Pesticide (Codex ref. no.)	Commodity		GL, mg/kg	Previous MRL, mg/kg	STMR, mg/kg
	CCN	Name			
Guazatine	FC 0001	Citrus fruits	W	5 Po	
(114)	FI 0353	Pineapple	W	0.1*	
	GC 0080	Cereal grains	0.05*	0.1*	0
	GS 0659	Sugar cane	W	0.1*	
	VC 0046	Melons (except Watermelon)	W	5 Po	
	VR 0589	Potato	W	0.1*	
	for GLs: octane-1,8-diyldiguanidine ("GG"), expressed as				

ANNEX II

INDEX OF REPORTS AND EVALUATIONS

Numbers in parentheses are Codex Classification Numbers.

ABAMECTIN (177) 1992 (T,R), 1994 (T,R), 1995 (T), 1997 (T,R)

ACEPHATE (095) 1976 (T,R), 1979 (R), 1981 (R), 1982 (T), 1984 (T,R), 1987 (T), 1988 (T), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1994 (R), 1996 (R)

ACRYLONITRILE 1965 (T,R)

ALDICARB (117) 1979 (T,R), 1982 (T,R), 1985 (R), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation), 1992 (T), 1993 (R), 1994 (R), 1996 (R)

ALDRIN (001) 1965 (T), 1966 (T,R), 1967 (R), 1974 (R), 1975 (R), 1977 (T), 1990 (R), 1992 (R)

ALLETHRIN 1965 (T,R)

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

AMINOMETHYLPHOS-PHONIC ACID (AMPA, 198) 1997 (T,R)

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

AMITROLE (079) 1974 (T,R), 1977 (T), 1993 (T,R), 1997 (T)

ANILAZINE (163) 1989 (T,R), 1992 (R)

AZINPHOS-ETHYL (068) 1973 (T,R), 1983 (R)

AZINPHOS-METHYL (002) 1965 (T), 1968 (T,R), 1972 (R), 1973 (T), 1974 (R), 1991 (T,R), 1992 (corr. to 1991 rpt), 1993 (R), 1995 (R)

AZOCYCLOTIN (129) 1979 (R), 1981 (T), 1982 (R),1983 (R), 1985 (R), 1989 (T,R), 1991 (R), 1994 (T)

BENALAXYL (155) 1986 (R), 1987 (T), 1988 (R), 1992 (R), 1993 (R)

BENDIOCARB (137) 1982 (T,R), 1984 (T,R), 1989 (R), 1990 (R)

BENOMYL (069) 1973 (T,R), 1975 (T,R), 1978 (T,R), 1983 (T,R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E)

BENTAZONE (172) 1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R), 1995 (R)

BHC (technical) 1965 (T), 1968 (T,R), 1973 (T,R) (see also lindane)

BIFENTHRIN (178) 1992 (T,R), 1995 (R), 1996 (R), 1997 (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), 1993 (T,R)

BUTOCARBOXIM (139) 1983 (R), 1984 (T), 1985 (T), 1986 (R)

BUPROFEZIN (173) 1991 (T,R), 1995 (R), 1996 (corr.to 1995 rpt.)

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), 1994 (R), 1995 (T), 1997 (R)

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), 1996 (T)

CARBENDAZIM (072) 1973 (T,R), 1976 (R), 1977 (T), 1978 (R), 1983 (T,R), 1985 (T,R), 1987 (R), 1988 (R), 1990 (R), 1994 (R), 1995 (T,E)

CARBOFURAN (096) 1976 (T,R), 1979 (T,R), 1980 (T), 1982 (T), 1991 (R), 1993 (R), 1996 (T), 1997 (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), 1993 (R), 1997 (R)

CARTAP (097) 1976 (T,R), 1978 (T,R), 1995 (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), 1994 (T), 1996 (R)

CHLORMEQUAT (015) 1970 (T,R), 1972 (T,R), 1976 (R), 1985 (R), 1994 (T,R), 1997 (T)

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 (T,R), 1991 (corr. to 1990 evaluation), 1992 (T), 1993 (R), 1997 (R)

CHLORPROPHAM 1965 (T)

CHLORPYRIFOS (017) 1972 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1981 (R), 1982(T,R), 1983 (R), 1989 (R), 1995 (R)

CHLORPYRIFOS-METHYL (090) 1975 (T,R), 1976 (R, Annex I only), 1979 (R), 1990 (R), 1991 (T,R), 1992 (T) and corr. to 1991, 1993 (R), 1994 (R)

CHLORTHION 1965 (T)

CLETHODIM (187)	1994 (T,R), 1997 (R)
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), 1993 (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	1970 (T,R), 1973 (T,R), 1974 (R), 1975(R), 1977 (T), 1978 (T,R),
TRICYCLOHEXYLTIN	1980 (T), 1981 (T), 1982 (R), 1983 (R), 1985 (R), 1988 (T),
HYDROXIDE) (067)	1989 (T), 1991 (T,R), 1992 (R), 1994 (T)
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), 1996 (T), 1997 (E)
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), 1993 (R), 1994 (R), 1996 (R)
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),

1993 (T,R), 1994 (R), 1996 (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), 1993 (T,R)

DICLORAN (083) 1974 (T,R), 1977 (T,R)

DICOFOL (026) 1968 (T,R), 1970 (R), 1974 (R), 1992 (T,R), 1994 (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), 1994 (R), 1996 (T)

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), 1994 (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), 1994 (R), 1996 (T)

DITHIANON (180) 1992 (T,R), 1995 (R), 1996 (corr. to 1995 rpt.)

DITHIOCARBAMATES (105) 1965 (T), 1967 (T,R), 1970 (T,R), 1983 (R propineb, thiram), 1984 (R propineb), 1985 (R), 1987 (T thiram), 1988 (R thiram), 1990 (R), 1991 (corr. to 1990 evaluation), 1992 (T thiram), 1993 (T,R), 1995 (R), 1996 (T,R ferbam, ziram; R 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), 1993 (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), 1993 (T), 1994 (R), 1995 (T), 1997 (T)

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), 1994 (R)

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), 1993 (T,R)

ETOFENPROX (184) 1993 (T,R)

ETRIMFOS (123) 1980 (T,R), 1982 (T,R[5]), 1986 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R)

FENAMIPHOS (085) 1974 (T,R), 1977 (R), 1978 (R), 1980 (R), 1985 (T), 1987 (T), 1997 (T)

FENARIMOL (192) 1995 (T,R,E), 1996 (R & corr. to 1995 rpt.)

FENBUCONAZOLE (197) 1997 (T,R)

FENBUTATIN OXIDE (109) 1977 (T,R), 1979 (R), 1992 (T), 1993 (R)

FENCHLORPHOS (036) 1968 (T,R), 1972 (R), 1983 (R)

FENITROTHION (037) 1969 (T,R), 1974 (T,R), 1976 (R), 1977 (T,R), 1979 (R), 1982, (T) 1983 (R), 1984 (T,R), 1986 (T,R), 1987 (R and corr. to 1986 R evaluation), 1988 (T), 1989 (R)

[5]R evaluation omitted. Published 1986.

FENPROPATHRIN (185) 1993 (T,R)

FENPROPIMORPH (188) 1994 (T), 1995 (R)

FENPYROXIMATE (193) 1995 (T,R), 1996 (corr. to 1995 rpt.)

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), 1995 (T,R,E), 1996 (corr. to 1995 rpt.), 1997 (T)

FENTIN COMPOUNDS (040) 1965 (T), 1970 (T,R), 1972 (R), 1986 (R), 1991 (T,R), 1993 (R), 1994 (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), 1996 (T,R)

FIPRONIL 1997 (T)

FIPRONIL-DESULFINYL 1997 (T)

FLUCYTHRINATE (152) 1985 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1993 (R)

FLUMETHRIN (195) 1996 (T,R)

FLUSILAZOLE (165) 1989 (T,R), 1990 (R), 1991 (R), 1993 (R), 1995 (T)

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), 1993 (T,R), 1994 (R), 1995 (T), 1997 (R)

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), 1994 (R)

GLYPHOSATE (158) 1986 (T,R), 1987 (R and corr. to 1986 rpt), 1988 (R), 1994 (R), 1997 (T,R)

GUAZATINE (114) 1978 (T.R), 1980 (R), 1997 (T,R)

HALOXYFOP (194) 1995 (T,R), 1996 (R & corr. to 1995 rpt.)

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), 1993 (R), 1994 (R)

HEXACHLOROBENZENE (044) 1969 (T,R), 1973 (T,R), 1974 (T,R), 1978(T), 1985 (R)

HEXACONAZOLE (170)	1990 (T,R), 1991 (R and corr. to 1990 R evaluation), 1993 (R)
HEXYTHIAZOX (176)	1991 (T,R), 1994 (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), 1994 (R)
IPRODIONE (111)	1977 (T,R), 1980 (R), 1992 (T), 1994 (R), 1995 (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) (publ. as Annex VI to 1971 evaluations), 1973 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1978 (R), 1979 (R), 1989 (T,R), 1997 (T)
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), 1997 (T)
MALEIC HYDRAZIDE (102)	1976 (T,R), 1977 (T,R), 1980 (T), 1984 (T,R), 1996 (T)
MANCOZEB (050)	1967 (T,R), 1970 (T,R), 1974 (R), 1977 (R), 1980 (T,R), 1993 (T,R)
MANEB	see dithiocarbamates, 1965 (T), 1967 (T,R), 1987 (T), 1993 (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), 1995 (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[6]), 1984 (R), 1985 (T), 1989 (R), 1990 (T,R), 1994 (R), 1996 (R), 1997 (R)

[6]R evaluation omitted. Published 1989.

METHIDATHION (051)	1972 (T,R), 1975 (T,R), 1979 (R), 1992 (T,R), 1994 (R), 1997 (T)
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)
METHOXYCHLOR	1965 (T), 1977 (T)
METHYL BROMIDE (052)	See bromomethane
METIRAM (186)	1993 (T), 1995 (R)
MEVINPHOS (053)	1965 (T), 1972 (T,R), 1996 (T), 1997 (E,R)
MGK 264	1967 (T,R)
MONOCROTOPHOS (054)	1972 (T,R), 1975 (T,R), 1991 (T,R), 1993 (T), 1994 (R)
MYCLOBUTANIL (181)	1992 (T,R), 1997 (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), 1995 (T,R),

1997 (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), 1994 (R), 1995 (T)

PENCONAZOLE (182) 1992 (T,R), 1995 (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), 1993 (T), 1994 (T), 1996 (T)

PHOSALONE (060) 1972 (T,R), 1975 (R), 1976 (R), 1993 (T), 1994 (R), 1997 (T)

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), 1994 (T), 1997 (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), 1995 (T)

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), 1994 (R)

PROCHLORAZ (142) 1983 (T,R), 1985 (R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1991 (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), 1993 (R)

PROFENOFOS (171) 1990 (T,R), 1992 (R), 1994 (R), 1995 (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), 1994 (R)

PROPINEB 1977 (T,R), 1980 (T), 1983 (T), 1984 (R), 1985 (T,R), 1993 (T,R)

PROPOXUR (075) 1973 (T,R), 1977 (R), 1981 (R), 1983 (R), 1989 (T), 1991 (R), 1996 (R)

PROPYLENETHIOUREA (PTU) (150) 1993 (T,R), 1994 (R)

PYRAZOPHOS (153) 1985 (T,R), 1987 (R), 1992 (T,R), 1993 (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), 1995 (T,R)

2,4,5-T (121) 1970 (T,R), 1979 (T,R), 1981 (T)

TEBUCONAZOLE (189) 1994 (T,R), 1996 (corr. to Annex II of 1995 rpt.), 1997 (R)

TEBUFENOZIDE (196) 1996 (T,R), 1997 (R)

TECNAZENE (115) 1974 (T,R), 1978 (T,R), 1981 (R), 1983 (T), 1987 (R), 1989 (R), 1994 (T,R)

TEFLUBENZURON (190) 1994 (T), 1996 (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), 1997 (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), 1994 (R), 1995 (T,E)

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), 1996 (R)

TOLCLOFOS-METHYL (191) 1994 (T,R) 1996 (corr. to Annex II of 1995 rpt.)

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), 1995 (R)

TRIADIMENOL (168) 1989 (T,R), 1992 (R), 1995 (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), 1993 (T,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), 1997 (T)

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), 1995 (T)

ZINEB (105) see dithiocarbamates, 1965 (T), 1967 (T,R), 1993 (T)

ZIRAM (105) see dithiocarbamates, 1965 (T), 1967 (T,R), 1996 (T,R)

ANNEX III

INTAKE PREDICTIONS

At the request of the Meeting, WHO(GEMS/Food) calculated the predicted intakes of residues on the agenda of the Joint Meeting, based on the methods described in *Guidelines for Predicting Dietary Intake of Pesticide Residues* (WHO, 1997).

Detailed TMDI (Theoretical Maximum Daily Intake) calculations and, where information was available, IEDI (International Estimated Daily Intake) calculations were performed on those pesticides considered by the JMPR. These calculations were based on the ADIs and MRLs proposed by the Meeting and existing and pending MRLs in the Codex system. For IEDI calculations, Supervised Trials Median Residue (STMR) levels were available for newly evaluated pesticides and for some pesticide/commodity combinations for previously considered pesticides. In a few cases, processing data was also available to refine the exposure assessment calculations. Dietary intakes were not estimated for amitrole and fipronil because no MRLs exist or have been proposed.

For the following compounds, the TMDI and/or IEDI did not exceed the ADI:

abamectin, amitrole, AMPA, bifenthrin, captan, carbofuran, carbosulfan, chlormequat, chlorothalonil, clethodim, fenbuconazole, folpet, glyphosate, malathion, methamidophos, mevinphos, mycobutanil, phosalone phosmet, tebuconzole, tebufenozide, thiabendazole and triforine.

The TMDI exceeded the ADI for lindane and fenamiphos, but information on STMRs and processing factors was not available to calculate the IEDI.

It should be noted that the TMDIs calculated over-estimate the true pesticide residue intake. It should, therefore, not be concluded that the MRLs for lindane and fenamiphos are unacceptable when the TMDI exceeds the ADI. Instead, TMDI calculations may be used as a screening tool and the IEDI should be calculated where data are available to allow refinement of the intake calculation.

References

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FAO/WHO, 1995. *Recommendations for the revision of the guidelines for predicting dietary intake of pesticide residues*, Report of a FAO/WHO Consultation, York, United Kingdom, 2-6 May 1995, Document WHO/FNU/FOS/95.11, World Health Organization, Geneva.

FAO/WHO, 1997. *Food consumption and exposure assessment to chemicals*, Report of a FAO/WHO Consultation, Geneva, 10-14 Febraury 1997, Document WHO/FSF/FOS/97.5, World Health Organization, Geneva.

[i] International Programme on Chemical Safety. *Joint Meeting on Pesticides: Report of the 1997 meeting of the Core Assessment Group*, Geneva, in preparation.

[ii] Maximum residue levels for use by government laboratories in their monitoring and/or enforcement activities. The JMPR estimates of dietary exposure based on these residue levels exceed the ADI.

[iii] Anon 1996. Report of an informal workshop on data evaluation in the estimation of dietary intake of pesticide residues for the JMPR. The Hague, Netherlands, April 1996.

[iv] JMPR Residue Evaluations, 1993, pages 354-5.

WHO (1994) *Glyphosate* (Environmental Health Criteria 159), Geneva

WHO (1991) *Lindane* (Environmental Health Criteria 124), Geneva

T = Evaluation of toxicology

R = Evaluation of residue and analytical aspects

E = Evaluation of effects on the environment